FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE (AAC) MEETING

Tuesday, July 12, 2016

7:29 a.m. to 4:44 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Room 1503)

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

(7:29 a.m.)

Call to Order

Introduction of Committee

DR. SOLOMON: We're going to go ahead and get started. Good morning, everyone. I'd like to first 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. She's in the back.

My name is Daniel Solomon; I'm the acting chairperson of the Arthritis Advisory Committee, and I will be chairing this meeting. I will now call the Arthritis Advisory Committee meeting to order, and we'll start by going around the table and introducing ourselves. Let's start on my right with Mara.

DR. BECKER: Hi. I'm Mara Becker. I am a pediatric rheumatologist at Children's Mercy, Kansas City, the division director of rheumatology,

and in the Division of Clinical Pharmacology and Medical Toxicology.

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

DR. OLIVER: Alyce Oliver, adult rheumatologist at the Medical College of Georgia, and program director for the Rheumatology Fellowship.

DR. HORONJEFF: Jennifer Horonjeff, researcher at Columbia University Medical Center in adolescent rheumatology and also serving as the consumer representative with the history of juvenile arthritis.

MS. ARONSON: Good morning. I'm Diane Aronson. I'm the patient representative.

DR. GELLER: Good morning. I'm Nancy Geller. I'm from the Office of Biostatistics Research at the National Heart, Lung, and Blood Institute.

DR. MARGOLIS: Hi. I'm David Margolis. I'm a professor of dermatology and a professor of epidemiology from the University of Pennsylvania.

DR. ROBINSON: June Robinson, research professor of dermatology, Northwestern University, Chicago.

DR. BERGFELD: Wilma Bergfeld, professor of dermatology and pathology, dermatologist, Cleveland Clinic.

DR. ADLER: Jeremy Adler, pediatric gastroenterologist and health services researcher at the University of Michigan. I'm also the director of the Pediatric Inflammatory Bowel Disease Program.

DR. STREETT: Sarah Streett, from Stanford University, associate professor and director of the clinical IBD program for adult medicine.

DR. FEAGINS: Hi. I'm Linda Feagins. I'm a gastroenterologist at UT Southwestern and the Dallas VA.

DR. SOLGA: I'm Steve Solga, a solo, independent, private practice gastroenterologist from Bethlehem, Pennsylvania.

DR. NATHANSON: Good morning. Jeff Nathanson, gastroenterologist at North Shore

University Health Systems and affiliated with the University of Chicago.

DR. CURTIS: Good morning. Sean Curtis. I'm head of scientific affairs at Merck, and I'm the acting industry representative today.

DR. CHRISTL: Leah Christl, associate director for Therapeutic Biologics in the Office of New Drugs in CDER.

DR. CHOWDHURY: Hi. I'm Badrul Chowdhury, division director, Division of Pulmonary, Allergy, and Rheumatology Products, FDA.

DR. NIKOLOV: Good morning. My name is Nikolay Nikolov. I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA.

DR. KOZLOWSKI: Steven Kozlowski. I'm the director of the Office of Biotechnology Products at CDER.

DR. WELCH: Joel Welch, product quality team leader, Office of Biotechnology Products in CDER.

DR. MAGER: Don Mager, professor of pharmaceutical sciences at the University of

Buffalo.

DR. WALDMAN: Scott Waldman, professor of internal medicine and chair of pharmacology and experimental therapeutics, Thomas Jefferson University in Philadelphia. I'm a clinical pharmacologist.

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

DR. HOHMAN: I'm Bob Hohman. I'm associate director for research technologies at the National Institute of Allergy and Infectious Diseases at NIH.

DR. HANCOCK: William Hancock, professor in bioanalytical chemistry, Northeastern University, Barnett Institute.

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

DR. SCHER: Jose Scher. I'm an adult rheumatologist in New York University, and I'm also the director of the Psoriatic Arthritis Center there.

DR. WOLPAW: I'm Therese Wolpaw. I'm a professor of medicine at Penn State University and adult rheumatologist, and the vice dean for educational affairs.

DR. REIMHOLD: Andreas Reimhold. I'm a rheumatologist at the Dallas VA and the University of Texas Southwestern Medical Center.

DR. JONAS: I'm Beth Jonas. I'm associate professor of medicine in the Division of Rheumatology and director of the Rheumatology Fellowship Training Programming at the University of North Carolina, Chapel Hill.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. SOLOMON: Great. Thanks, everyone, for those introductions.

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

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Moon Hee Choi, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Arthritis

Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is

determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C., Section 208, their employers.

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

Today's agenda involves biologic license application BLA 761024 for ABP 501, a proposed biosimilar to AbbVie's Humira, adalimumab, submitted by Amgen.

The proposed indications and uses for this product are:

1) Reducing signs and symptoms, inducing major clinical response, inhibiting the progression

of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis, alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs, DMARDs;

2) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older, alone or in combination with methotrexate;

3) Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis, alone or in combination with non-biologic DMARDs;

4) Reducing signs and symptoms in adult patients with active ankylosing spondylitis;

5) Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. ABP 501 would be indicated

for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab;

6) Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine. The effectiveness of ABP 501 would not be established in patients who have lost response to or were intolerant to TNF blockers; and

7) Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systematic therapy or phototherapy , and when other systemic therapies are medically less appropriate, only to be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

This is a particular matters meeting, during which specific matters related to Amgen's BLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the

participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

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

FDA Opening Remarks – Janet Woodcock

DR. WOODCOCK: Good morning. I'd like to thank the members of the advisory committee, the presenting staff at FDA and other FDA staff who are supporting this meeting, the sponsors, and all the attendees of the meeting.

We are continuing to write, basically, the early history of a new class or set of products regulated by FDA, the biosimilar products. These are the third and then tomorrow will be the fourth application under the biosimilar pathway to be discussed at advisory committee.

Amgen's adalimumab will be discussed today

and etanercept, from Sandoz, a biosimilar, to be discussed tomorrow. This will be the first application to be discussed for proposed biosimilar to adalimumab, a monoclonal antibody to TNF alpha. Tomorrow will be the first application to be discussed in an AC for a proposed biosimilar to etanercept, a TNF receptor fusion protein.

Of course, as you all know, the TNF inhibitors helped revolutionize treatment for rheumatic diseases, and biologics, in general, have become really a mainstay of the therapeutic armamentarium for rheumatic diseases. And a total of 14 biologics have been approved for rheumatic or other autoimmune indications since 1988.

Acknowledging these molecules are very important, and they're used in a wide variety of conditions, in inflammatory as well as conditions such as rheumatoid arthritis and psoriasis. These proposed biosimilars are also very complex molecules, and therefore, it's very important that they're evaluated extremely carefully to ensure they're highly similar to the reference product and

that there are no clinically meaningful differences.

This will be discussed extensively, what the statutory standard is and how FDA has approached the evaluation of biosimilars, in the next several presentations by FDA.

These evaluations are based on an extensive set of data, comparative data, on the structural and functional characteristics of the molecules. When done correctly and acceptably, they should provide a high degree of confidence that the biosimilar reference product and the biosimilar would be expected to have similar efficacy and safety.

We have developed an algorithm, more or less, for this comparative set of comparisons that will be done for structural comparisons, functional comparisons, pharmacokinetic comparisons, and then some limited clinical comparisons.

What we'll be asking the advisory committee today and tomorrow is how do you view the adequacy of these comparisons for the determination of a

high degree of similarity?

Now, the reason this is important is that the biosimilar pathway is a really key mechanism to provide affordable treatments for our patients and to improve access since these are extremely important therapeutic molecules in the various subspecialty areas that are represented here today. But we know there is limited access for patients in some cases.

Congress has created this pathway to enable more competition in this space. However, it's really contingent upon us, both the advisory committee, the FDA, and all of us, to ensure that when these products are evaluated, that they undergo a very thorough evaluation so that treating clinicians and patients can have the confidence they deserve that any FDA-approved product would deliver the safety and efficacy that is represented in the label of that product.

Good luck today. As I said, you're continuing to write history on this, and I think it'll be very informative. Thank you very much for

participating.

DR. SOLOMON: Thank you, Dr. Woodcock.

Dr. Leah Christl will now give us an overview of the 351(k) regulatory pathway.

(Pause.)

DR. SOLOMON: Minor technical issues.

(Pause.)

Presentation - Leah Christl

DR. CHRISTL: Good morning, everyone. Thank you for your patience. My name is Leah Christl. I am the associate director for therapeutic biologics in the Office of New Drugs in CDER at FDA.

Before we begin the product-specific discussion for today's meeting, we wanted to take an opportunity to orient the committee and to orient the audience a little bit about the biosimilar pathway and the scientific approach that FDA has outlined in several guidance documents to the development and approval of biosimilar products in the U.S.

I'll begin with an overview, providing you with a little bit of background about the

biosimilar pathway, some definitions, and talk about some of the general requirements for these applications.

Then I will talk about the development of biosimilar; the development of the data to support biosimilarity, including the approach to development; and I will go over some very specific development concepts as well.

The Biologics Price Competition and Innovation Act of 2009, or the BPCI Act, was passed as a part of health reform under the Affordable Care Act, and that was signed into law on March 23, 2010.

The BPCI Act created an abbreviated licensure pathway for biological products that are shown to be biosimilar to or interchangeable with an FDA-licensed reference product. And we'll spend the next couple of slides going through several of the terms in that second bullet on the slide to give you a bit more information there.

What do we mean in terms of an abbreviated licensure pathway? The BPCI Act states that a

biological product that is demonstrated to be highly similar to an FDA-licensed biological product, which is referred to as the reference product, may rely for licensure on, among other things, publicly available information regarding FDA's previous determination that the reference product is safe, pure, and potent.

This licensure pathway permits a biosimilar biological product to be licensed under the Public Health Service Act under Section 351(k) based on less than a full complement of product-specific preclinical, and clinical data. This is what we mean by an abbreviated licensure pathway.

We'll talk about the data components that are a part of the data package that would support the approval of a biosimilar product. But what we mean by the abbreviated licensure pathway is again you have product-specific data, comparative data with the reference product, but then also this ability to rely for licensure on publicly available information about what's known about the reference product. So the data package for a biosimilar

product is actually quite extensive. It's the approval pathway that's abbreviated, not the data package.

What do we mean by biosimilarity? Again, this is defined in the Act to mean that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Both of these aspects need to be met to support a demonstration of biosimilarity. So again, the product must be highly similar and have no clinically meaningful differences in comparison to the reference product.

You couldn't have a lack of a demonstration of highly similar but see no clinically meaningful differences in any of your clinical data and say that it was biosimilar or vice versa. Again, both of these prongs need to be met to support a

demonstration of biosimilarity.

We've talked about that the product can be biosimilar to or interchangeable with a reference product. The reference product is defined in the act to mean a single biological product licensed under 351(a) of the Public Health Service Act against which the proposed biological product is evaluated in an application submitted under a 351(k) of the Public Health Service Act.

Since I'm sure (a)s and (k)s are not all that familiar to folks, an application that's submitted under Section 351(a) of the Public Health Service Act is a "stand-alone" application that contains all the information and data necessary to demonstrate that the proposed product is safe, pure, and potent. So that application would have a full complement of product-specific preclinical and clinical data. It's a stand-alone application.

In contrast, an application that's submitted under Section 351(k), which is for a biosimilar or interchangeable product, needs to demonstrate that the proposed product is biosimilar to the reference

product. For licensure, the proposed biosimilar relies on, among other things, comparative data with the reference product, as well as publicly available information regarding FDA's previous determination that the reference product is safe, pure, and potent.

As was noted, the product can be biosimilar to or interchangeable with a reference product. While the subject of today's meeting is for ABP 501 as a proposed biosimilar to US-licensed Humira, we did want to provide the definition for interchangeability. However, I do want to note that the product before you today is not seeking licensure as an interchangeable product; it is seeking licensure as a biosimilar.

Interchangeability is defined in the Act to mean that the biological product is biosimilar to the reference product so it meets that same biosimilarity standard of highly similar with no clinically meaningful differences, and it can be expected to produce the same clinical result as the reference product in any given patient.

For a product that is administered more than once to an individual, the risk, in terms of safety or diminished efficacy of alternating or switching between the use of the product and its reference product, is not greater than the risk of using the reference product without such alternation or switch.

The Act goes on to state that an interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. Again, this is specific to interchangeable products. The concept of substitution for products does not apply to biosimilar products according to the BPCI Act.

The Act describes, in general, requirements for a biosimilar product. The application needs to include information demonstrating that the proposed product is biosimilar to the reference product -- again, it meets that biosimilarity standard; it utilizes the same mechanism or mechanisms of action for the proposed conditions of

use but only to the extent that those are known for the reference product.

The conditions of use proposed in labeling, such as indications, populations, have been previously approved for the reference product. It has the same route of administration, dosage form, and strength as the reference product.

The product is manufactured, processed, packed or held in a facility that meets the appropriate standards for a biological product to ensure that that product continues to be safe, pure, and potent through its life.

The Act goes on to state that the types of data that would be expected to be submitted in a 351(k) application include analytical studies, animal studies, and clinical studies.

The analytical studies would be demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; animal studies, which could include an assessment of toxicity, and a clinical study or

studies that could include the assessment of immunogenicity and pharmacokinetics or pharmacodynamics that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

The BPCI Act does state that FDA may determine, in its discretion, that one of these data elements described above is unnecessary to support a 351(k) application. And we'll talk a little bit more when we talk about the development approach of these products as to how that may come about.

It's important to note that FDA has taken a scientific approach in guidance that we've issued about the use of a non-US-licensed comparator product. So as was previously noted, the PHS Act defines reference product as the single biological product that's licensed by FDA under Section 351(a) against which a biological product is evaluated.

However, data from animal studies and

certain clinical studies comparing the proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product.

However, sponsors should provide adequate data or information to scientifically justify the relevance of those data to an assessment of biosimilarity and to establish an acceptable bridge to the US-licensed reference product. And you'll hear today in the product-specific presentations more about how this bridge is established.

The type of bridging data that would be included, it includes direct physicochemical comparison of all three products, likely include a three-way bridging clinical PK and/or PD study, if relevant, and all three pairwise comparisons need to meet the prespecified acceptance criteria for similarity.

Again, the sponsor needs to justify the extent of the comparative data needed to establish the bridge to the US-licensed reference product and again to justify the relevance of the data

generated using a non-US-licensed comparator to the demonstration of biosimilarity with the U.S. reference product.

Now, I'll move to an overview of FDA's approach to the development of biosimilars. We find that it's a little easier to move through some of these concepts by targeting key development concepts instead of walking through the guidances in general.

The first key concept that's important to understand is that the goals of a stand-alone and a biosimilar development program are different. First, stand-alone development program -- again, this would be application that would be under 351(a) of the Public Health Service Act -- the goal is to establish the safety and efficacy of the new product.

Drug development starts with preclinical research, moves to phase 1, phase 2, and then culminates in phase 3 pivotal trials that are to show safety and efficacy of the proposed product in each of the conditions of use. This is the model

of drug development that most individuals are familiar with.

In contrast, the abbreviated development program for a biosimilar product, the goal there is to demonstrate biosimilarity or interchangeability But again, today we're focusing on biosimilarity.

The abbreviated pathway, again, means that the biosimilar product can be approved based on less than a full complement of product-specific preclinical and clinical data because the FDA can rely on certain existing scientific knowledge about the safety and effectiveness of the reference product.

The types of data that you would see in this package, again, involve analytical, nonclinical, clinical pharmacology, and possibly additional clinical studies, though they're the same types of data in terms of the scientific areas. But this is going to be comparative data that's comparing the proposed product to the reference product, and the foundation of this data is the analytical similarity assessment, which we'll talk more about.

This approach avoids unnecessary, expensive, and unethical duplication of studies and allows safe and effective products to be made available to patients, hopefully, faster and at potentially lower cost.

The next key concept is that of stepwise evidence development. Again, if you remember that diagram looking like a triangle or a pyramid, where the base of that is the analytical similarity assessment and then it goes up to those additional clinical studies at that peak, FDA has outlined a stepwise approach to generating that data to support a demonstration of biosimilarity.

It involves the evaluation of residual uncertainty at each step, and it's the totality of the evidence that supports a demonstration of biosimilarity. So whereas for stand-alone development we talked about those pivotal phase 3 clinical trials to demonstrate safety and effectiveness, here we're talking about a totality of the evidence. There's no one study that demonstrates biosimilarity.

We apply this stepwise approach to data generation and this evaluation of residual uncertainty about biosimilarity. Beginning with those analytical studies as the foundation, comparing the proposed product and the reference product on a structural and functional level, what differences are observed and what's the potential impact of those differences on clinical performance? What residual uncertainty do you have, and what are the studies that will address the residual uncertainty? So it's a very targeted development program and targeted data generation.

Again, there's no one pivotal study that demonstrates biosimilarity, and there's also no one-size-fits-all assessment because we do look at the totality of the evidence and evaluating residual uncertainty at each step.

The next key concept is that of analytical similarity data, which again is the foundation of a biosimilar development program of the extensive structural and functional characterization.

When assessing analytical similarity, we

look at comparative assessment of the attributes that can include a number of things, including amino acid, heterogeneity, glycosylation, bioactivity, impurities. These are just a subset of the list, and for each product, you will hear more about the specific attributes that were evaluated for that product-specific program.

If a molecule is known to have multiple biological activities, where feasible, each should be demonstrated to be highly similar between the proposed product and the reference product.

It's critical to understand the molecule and function and identify the critical quality attributes so that those can be assessed and make sure that they are highly similar between the two products.

In terms of that stepwise data generation, again, beginning with the analytical similarity assessment, the sponsor would characterize the reference product quality characteristics and product variability.

Then the manufacturing process for the

proposed biosimilar product would be designed to produce a product with minimal or no differences in product quality characteristics as compared to the reference product.

The sponsor would identify and evaluate the potential impact of any differences that are observed and determine what study or studies will be needed to address the residual uncertainty about biosimilarity.

Again, it's key to understand the relationship between the quality attributes and the clinical safety and efficacy profile because this aids in the ability to determine residual uncertainty about biosimilarity and to predict expected clinical similarity based on the quality data.

FDA has taken a scientific approach in terms of applying a statistical analysis of analytical similarity data. The statistical analysis is conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product.

It's not a pass/fail system. Again, it's an analysis that supports the demonstration of highly similar. It's one analysis in a very large armamentarium of scientific tools that are used to demonstrate biosimilarity.

With this, the quality attributes are ranked based on criticality with regard to their potential impact on biological activity, functional activity, PK/PD, safety, immunogenicity, and other factors that would be important to the function of the product.

Data are then analyzed by various testing methodologies, which could include equivalence testing, a quality range testing, and raw or graphical comparisons for attributes with low criticality or those which are not amenable to other testing methodologies.

For example, amino acid sequence has a highly critical attribute. You want that to be the same, but it doesn't lend itself to an equivalence test or even a quality range testing.

Something that's in that category of a raw

or graphical comparison doesn't necessarily mean it's any less critical, so there is a balance with that. So it's not that things that are critical are always in the equivalence testing. Again, this is just a tool that's applied, and it does involve the ranking of attributes and then appropriate testing.

As was noted, there may be animal data that's a part of the data package for a biosimilar program. Animal toxicity data can be useful when there are uncertainties about the safety of the proposed product prior to initiating clinical studies.

The scope and extend of animal studies, including toxicity studies, will depend on the publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed product in the extent of known similarities or differences between the two.

In some circumstances, a comparison of PK or PD in an animal model may also be useful. This is

one place where you may see that the FDA does determine its discretion that a particular data element talking about animal studies, particularly the animal toxicity data, may not be needed. And this depends on the robustness of the analytical similarity data, whether you're observing any differences, and how much uncertainty that you have about the similarity of the two products before proceeding with clinical studies.

The next key concept is around the role of clinical studies in a biosimilar development program. The nature and scope of the clinical studies will depend on the extent of residual uncertainty about biosimilarity of the two products after conducting structural and functional characterization and, where relevant, animal studies.

As a scientific matter, FDA does expect an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar and the US-licensed reference product. Also, as a scientific matter, at least one clinical study that

includes a comparison of the immunogenicity of the proposed and reference product generally will be expected.

It's important to note that when we talk about clinical data in the context of a biosimilar application, we refer to any clinical data, so that could include a PK/PD study or a more traditional clinical efficacy or safety study. So within this clinical data, you would have an adequate comparison of immunogenicity, but it could come in any of the clinical studies.

Also, as a scientific matter, a comparative clinical study would be necessary to support a demonstration of biosimilarity if there are residual uncertainties about whether there are clinically meaningful differences between the proposed and reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

So again, it's moving through that stepwise evidence development, and at the top of that

pyramid were the additional clinical studies. We look at all the data that's generated in that program, all the comparative data, and then make an assessment about residual uncertainty and whether additional clinical data in a comparative clinical study would be necessary.

Specifically focusing on the types of clinical data, so around comparative human PK and PD data, it's generally considered to be the most sensitive clinical study or assay in which to assess for differences between the products, should they exist.

For PK, it's important to demonstrate PK similarity in an adequately sensitive population to detect any differences, should they exist. Similar PD, using PD measure or measures that reflect the mechanism of action or reflects biological effects of the drug, can be important.

The PK and PD similarity data would support a demonstration of biosimilarity. And in this context, no clinically meaningful differences, with the assumption that similar exposure and

pharmacodynamic response, if applicable, will provide similar efficacy and safety. So an exposure-response relationship exists.

When thinking about additional clinical data in the form of a comparative clinical study, the comparative clinical study, if it's determined to be necessary based on residual uncertainty, should be designed to investigate whether there are clinically meaningful differences between the products in terms of safety and efficacy.

Therefore, the population, endpoint, sample size, and study duration need to be adequately sensitive to detect differences, should they exist. Typically, FDA has looked for an equivalence design to be used, but other designs may be justified, depending on the product-specific and program-specific considerations.

Again, we would expect that there's an assessment of safety and immunogenicity in an adequate clinical study. So if a comparative clinical study does need to be done, we would expect that an assessment of safety and

immunogenicity would be a part of this comparative clinical study.

The potential does exist for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed, based on extrapolation of data that is intended to support a demonstration of biosimilarity in one condition of use, such as an indication to other conditions of use. However, there needs to be sufficient scientific justification for extrapolating data.

FDA has outlined in the guidance a number of factors or issues that should be considered when providing scientific justification for extrapolation. Some of the examples are listed here, including the mechanism of action or actions in each condition of use for which licensure is sought, the PK and biodistribution of the product in different patient populations, and the immunogenicity of the product in different patient populations; also, differences in expected toxicity in each condition of use and patient population.

It's important to note that differences between these conditions do not necessarily preclude extrapolation. What it means is that these factors need to be addressed, discussed, and then any data or information that's necessary to address them would need to be a part of the application and a part of the justification to support extrapolation.

The sponsor needs to ensure that the totality of the evidence in the application, including the scientific justification for extrapolation, supports their approach to demonstrating biosimilarity.

In summary, the content of a biosimilar development program is based on the stepwise evidence development and the evaluation of residual uncertainty about biosimilarity between the proposed product and the reference product.

The approval of a proposed biosimilar product is based on the integration of various information and the totality of the evidence that is submitted by the sponsor to provide an overall

assessment that the proposed product is biosimilar to the reference product.

With that, I thank you for your attention, and I'm happy to take any general, non-product-specific questions from the committee at this time about the background.

Clarifying Questions to FDA

DR. SOLOMON: Thanks very much for that presentation. Are there any clarifying questions? Robert?

DR. HOHMAN: Could you just go over again the difference between biosimilar and interchangeable?

DR. CHRISTL: Yes. So a biosimilar product, the definition is that that is highly similar with no clinically meaningful differences as compared to the reference product.

Interchangeability is an additional standard. It compasses biosimilarity, so an interchangeable product would need to demonstrate that it's biosimilar; but then also that it can be expected to produce the same clinical result in any

given patient. And that for a product that's administered more than once, that you look at the risk in terms of safety or efficacy of switching between the proposed product and the reference product versus not switching and staying on the reference product.

The Act does state that an interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the product.

The Act ties that to an interchangeability demonstration, not a biosimilarity demonstration. So the FDA would expect that while a prescriber can prescribe a biosimilar or an interchangeable product, as a prescribing decision, that only the interchangeable product could be substituted at the pharmacy level without the intervention of the healthcare provider.

DR. SOLOMON: Could people state their name before they ask questions? Dr. Gellar?

DR. GELLER: Nancy Geller. I'm concerned about the exchangeability. There's no mention of

exchangeability when extrapolating to juveniles. Could you comment on that, please?

DR. CHRISTL: So again, we're looking at a different development paradigm. So the concept is, as a part of biosimilarity, there's an expectation that there are no clinically meaningful differences and that the biosimilar product can rely on what's known about the reference product.

When we talk about extrapolation in the context of a biosimilar product, you're extrapolating what's known about the reference product to the biosimilar, not from adults to pediatrics the way that you would in a stand-alone development program.

You're extrapolating from the reference product to the biosimilar product regarding the indications, populations, or other conditions of use based on the data.

DR. SOLOMON: Dr. Adler?

DR. ADLER: Thank you. Jeremy Adler here. I also had a question about the extrapolation. When you mentioned sufficient scientific

justification for extrapolating is necessary, is there a requirement for a sufficient justification for each of the conditions to which this --

DR. CHRISTL: Yes. The scientific justification would need to address each of the conditions of use for which the biosimilar applicant would be seeking licensure.

If they have a comparative clinical study or other data that's demonstrating biosimilarity in one or more conditions of use but then they want to extrapolate to other conditions of use and seek licensure -- and again, those would have to be conditions of use previously approved for the reference product -- their scientific justification would need to specifically address each of those additional indications for which they would be seeking licensure.

DR. ADLER: Thank you.

DR. SOLOMON: I saw a question down this way. Steven?

DR. SOLGA: Steve Solga. Thank you for the excellent presentation. I understand this is a

pre-approval committee meeting, and I understand the definitions between biosimilar and interchangeable are quite different.

However, there seems to be overwhelming public concern, and I agree with and share this concern, appropriate concern, that post-approval, payers in pharmacies are going to manage biosimilars and interchangeables as the same.

You can talk about a different definition now, but later, it's just going to be switched, and patients and doctors are going to be powerless to prevent that.

So I'm wondering, in the pre-approval process, what is the FDA's post-approval regulatory plan to prevent this from happening?

DR. SOLOMON: Could I maybe cut this off? We're going to have plenty of time for discussion, and I think we want to focus on clarifying questions about the presentation. These are important concerns, so we'll come back to these.

Diane Aronson?

MS. ARONSON: I note in some of the public

testimony that I've read, we've been asked to consider reasonable proof. Does the FDA use that term, "reasonable proof," or not?

DR. CHRISTL: I wouldn't say that we use the term "reasonable proof." Again, we expect that the data package, the totality of the evidence, supports a demonstration of biosimilarity. That would include the demonstration of highly similar and no clinically meaningful differences, but then also that it has the same mechanism or mechanisms of action, and as much as they're known, same dosage form, route of administration, strength, and so forth.

So we do expect that that total data package does address the statutory and legal requirements that are outlined, and then the scientific recommendations that FDA has articulated, in terms of the data package.

We would look at that and say -- we would make an assessment, does that total data package support the demonstration of biosimilarity based on the definition of biosimilarity? So if we don't

think the data package provided adequate proof, adequate scientific proof, in that data package to support a demonstration of biosimilarity, then we wouldn't license it as a biosimilar product.

DR. SOLOMON: Dr. Scher?

DR. SCHER: Jose Scher here. One clarification point on definition. When you look at a highly similar biological product, the definition is that you have to have only minor differences in clinically inactive components. How do we define minor differences?

DR. CHRISTL: Right. So again, I don't want to delve too much into the product-specific issues that are here. But for each product, we would consider based on what we know scientifically about that product.

As I said, for that evidence generation, the sponsor would conduct an analysis of the reference product looking at the various quality attributes and ranking them as highly critical, critical, less critical, so on and so forth, and looking at those, so understanding what's important about that

product.

So based on their testing of the reference product and then also the statistical analysis that we apply, there are acceptance criteria for each of those attributes that are generated. And again, that is derived from the sponsor's analysis of the reference product.

You're looking at acceptance criteria for each attribute that's generated based on the data from the sponsor, so that's product-specific within that package. But then it is bound, again, around the statistical analysis that we talk about, which again is in pass/fail system.

There may be scientific justifications as to why it might be a little outside the acceptance criteria, based on what we know about the product. But that's really that starting point of how we look at what's going to be the definition of highly similar for an attribute.

Then we would look at the same type of information, although we don't have specific acceptance criteria, for those minor differences in

clinically inactive components. But we look at what clinically inactive components are on a product-specific basis based on what we know about the function of the molecule, the biological activity of the molecule.

DR. SOLOMON: Okay. I see no more clarifying questions, so why don't we move on. Thank you very much.

We'll now proceed with additional introductory FDA remarks from Dr. Nikolay Nikolov.

FDA Introductory Remarks - Nikolay Nikolov

DR. NIKOLOV: Good morning, everyone. I would like to welcome you to the Arthritis Advisory Committee meeting for the 351(k) biologics license application for ABP 501, a proposed biosimilar to US-licensed Humira.

My name is Nikolay Nikolov. I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products. I'm also an adult rheumatologist.

Before I begin, I would like to thank the members of this advisory committee for taking the

time off your busy schedules to come in and provide your expertise. I would also like to thank and acknowledge the attendance in the room, which is indicative of the importance of this meeting to the community.

In the next few slides, I will provide an overview of ABP 501 development program in the context of the abbreviated licensure pathway that was just discussed by Dr. Leah Christl.

The applicant, Amgen, has submitted the biologics license application, or a BLA, under 351(k) section of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira.

In this application, Amgen is seeking a licensure of ABP 501 for the indications listed on this slide for which U.S. Humira is also licensed. To support this application, Amgen provided extensive analytical data intended to support:

1) A demonstration that ABP 501 and US-licensed Humira are highly similar; and

2) A demonstration that ABP 501 can be

manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet required quality standards.

To support the demonstration of no clinically meaningful difference between ABP 501 and US-licensed Humira, Amgen provided data intended to demonstrate:

1) Similarity in exposure or PK, pharmacokinetics, in healthy subjects;

2) Similarity in efficacy and safety in patients with rheumatoid arthritis and plaque psoriasis; and

3) Similarity in immunogenicity between ABP 501 and Humira comparator products in patients with rheumatoid arthritis, plaque psoriasis, and healthy subjects, as well as in patients who underwent a single transition from EU-approved Humira to ABP 501.

This slide summarizes the clinical development program of ABP 501 and key design aspects of the clinical studies supporting the application.

These studies provide data on similarity in exposure, efficacy, safety, and immunogenicity between ABP 501 and Humira comparator products. The first study, study 217, provided data on similarity of exposure to support the finding of biosimilarity between ABP 501 and US-licensed Humira, and to also establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using European Union or EU-approved Humira in study 263.

Studies 262 and 263 were comparative clinical studies in two distinct patient populations, rheumatoid arthritis and plaque psoriasis, using two approved dosing regimens, either in combination with background immunosuppression with methotrexate in study 262 in the rheumatoid arthritis, or as monotherapy in study 263 in patients with plaque psoriasis.

Of note, study 263 also provided safety and immunogenicity data in the setting of patients undergoing a single transition from EU-approved Humira to ABP 501.

This information is relevant and important to ensure that if approved as a biosimilar, ABP 501 could be administered safely to patients who may have been previously exposed to Humira.

As discussed by Dr. Leah Christl, an applicant needs to provide information to demonstrate biosimilarity based on a comparison between the proposed biosimilar product and the reference product.

As was detailed in the previous slides, part of the ABP 501 clinical development program used a non-US-licensed comparator, specifically, European Union-approved Humira.

The FDA has determined that in cases like this, the applicant should, as a scientific matter, provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

Consistent with this guidance, to justify the relevance of the data generated using the

unknown US-licensed comparator, Amgen provided extensive analytical bridging data that directly compared all three products and conducted a clinical study to demonstrate a three-way similarity in exposure between ABP 501, US-licensed Humira, and EU-approved Humira in healthy subjects.

The agency has also determined that it may be appropriate for a biosimilar product to be licensed for one or more additional indications for which the reference product is licensed based on extrapolation of data in the biosimilars program.

The justification for such extrapolation should address issues like potential differences in mechanism of action, PK, and biodistribution; immunogenicity; and safety for each of the sought indications.

Consistent with these principles outlined in the FDA guidance documents and previously discussed by Dr. Christl, the applicant provided scientific justification for extrapolation of data to support that there would be no clinically meaningful differences for the additional indications sought

for licensure.

Later this afternoon, we will be asking the committee's thoughts on the following questions:

1) Whether the evidence from analytical studies supports demonstration that ABP 501 is highly similar to US-licensed Humira;

2) Whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the studied indications of rheumatoid arthritis and plaque psoriasis; and

3) Whether the data provides sufficient scientific justification to support the demonstration of no clinically meaningful differences, and respectively biosimilarity, between ABP 501 and US-licensed Humira for the additional indications for which U.S. Humira is licensed and Amgen is seeking licensure of ABP 501.

Following this discussion, the committee will be asked to vote on one question, namely: Does the totality of the evidence support licensure of ABP 501 as a biosimilar product to US-licensed

Humira for the following indications for which U.S. Humira is licensed and for which Amgen is seeking licensure? These are the ones listed on the slide.

I would like to note that in light of the nature of this advisory committee and discussion topics, the agency has made every effort to invite a panel of diverse expertise relevant to the product quality, clinical pharmacology, immunology, biostatistics, gastroenterology, and dermatology, in addition to the standing Arthritis Advisory Committee, which we believe will foster a very productive discussion today.

Thank you for your attention, and I will turn the podium back to Dr. Solomon.

DR. SOLOMON: Thanks very much.

Dr. Richard Siegel had entered. I just want to give him a chance to introduce himself.

DR. SIEGEL: Sure. Hello. I'm Richard Siegel. I am a rheumatologist and immunologist, and studied the TNF family of cytokines in mouse models and translational areas for the last

20 years. And I work at NIH and the NIAMS. Thank you.

DR. SOLOMON: Dr. Margolis, did you have another clarifying question?

DR. MARGOLIS: Yes. The question I have is getting back to the biosimilar interchangeability issue in the U.S., is the EU-approved Humira considered interchangeable, biosimilar, or neither?

DR. CHRISTL: So it's neither. The reason that we ask sponsors to provide a justification regarding the relevance of that data and demonstrating an adequate level of similarity between the U.S. reference product and the non-US-licensed comparator is because of that reason.

The product that's approved ex-U.S. is not the US-licensed reference product, but there are a lot of global development programs. And it's important as an agency, and other global regulatory agencies have taken the same approach, in terms of, in certain studies, a non-regionally- approved product could be used as a comparator if the

sponsor justifies the relevance of that data.

So again, they need to make that three-way bridge between the proposed product, the US-licensed reference product, and the non-US-licensed comparator to support the relevance of that data.

We strictly view whatever it is, even if it's an EU-approved product with a non-US-licensed comparator, as an active comparator in that study. But then the sponsor needs to justify the relevance of that data to a demonstration of biosimilarity with the U.S. reference product.

DR. MARGOLIS: So right now, the EU --

DR. SOLOMON: You know what? I think that we should probably hold some of these discussion points to later on. Okay? So I'm going to move now to the applicant presentation.

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

presentation.

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

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

We will now proceed with Amgen's presentations.

Applicant Presentation - Richard Markus

DR. MARKUS: Good morning. I'm Richard Markus. I'm vice president of development for Amgen's biosimilars division, and I'd like to thank

the FDA and the advisors for all your effort and preparation that has led up to this day. It's an important day for Amgen but also for patients, as this is the first advisory committee hearing for a biosimilar to adalimumab.

Our presentation today will follow this agenda: I will provide some background on the development program for ABP 501. We designed the program according to the FDA guidance and with many agency meetings.

Simon Hotchin is head of regulatory affairs for Amgen's biosimilars, and he has an extensive background in regulatory sciences for CMC -- that's chemistry, manufacturing, and control -- and he will share our development process and data for creating, testing, and manufacturing ABP 501, and also the nonclinical similarity data. Importantly, the comprehensive analytical comparisons show the product to be highly similar to the reference product.

I will then share the results of the clinical development program, which confirms there

are no clinically meaningful differences between ABP 501 and adalimumab. I will also highlight the scientific considerations for extrapolation to all the indications.

Finally, Steven Galson, head of regulatory affairs and safety at Amgen, will conclude the presentation. The experts listed on this slide are also available to answer your questions.

Amgen is a biotechnology pioneer with more than 35 years of experience developing and manufacturing complex biologics, including products for the treatment of inflammatory diseases.

In addition to the pipeline of innovative medicines, Amgen has a broad pipeline of biosimilars in development. Amgen biosimilars and innovative medicines are created by the same scientists and in the same laboratories, and we use the same manufacturing network and the same quality systems to produce our biosimilars.

I would now like to briefly orient everyone to ABP 501, which was developed as a biosimilar to adalimumab.

ABP 501 and adalimumab are IgG1 human monoclonal antibodies that bind with high affinity to tumor necrosis factor, or TNF alpha. The primary mechanism of action for ABP 501 and for adalimumab is the binding and neutralization of soluble TNF. This blocks the inflammatory signals induced by TNF, thereby inhibiting functions that contribute to disease such as apoptosis, proliferation, cytokine and chemokine release, adhesion molecule expression, dendritic cell maturation, and cell death.

Today, we will discuss the functional assays, which demonstrate similarity between ABP 501 and adalimumab with respect to the neutralization of proinflammatory TNF activities. Additional activities of ABP 501 and adalimumab are possible, although the exact contribution to clinical benefit is still in question.

Because the antibody is able to bind to membrane-bound TNF, it can induce activities such as cellular cytotoxicity through ADCC or CDC, apoptosis through reverse signaling, or the

inhibition of immune cell proliferation through the induction of regulatory macrophages.

Again, today's discussion will include data demonstrating the similarity of ABP 501 and adalimumab in mediating several of these responses, which are different than the primary mechanism of action but may be important in some of the indications.

Now, moving on to the development process, there are four major steps to drug development, including for biosimilars, and these are conducted in a stepwise manner to establish the totality of evidence.

The first step is analytical characterization. In this step, we assess the quality profile of the product, including its critical attributes, and we ensure that the biosimilar is structurally similar and also functionally similar to the reference product. This forms the foundation for the remainder of the biosimilar development. The nonclinical assessment of biosimilar is focused on demonstrating a similar

toxicology profile compared to the reference product.

Clinical pharmacology for a biosimilar is not used to determine the half-life or the kinetics in specific uses. Instead, its purpose is to assess the PK equivalence with the reference product, and this allows for progression on the abbreviated pathway.

Finally, the clinical program for a biosimilar is conducted to confirm equivalent efficacy and similar safety and immunogenicity. If conducted in a sensitive population to inform the other indications of use, then along with scientific justification, the biosimilar can be approved for all indications.

When all steps are conducted with rigor and state-of-the-art sensitive assays, then the totality of evidence can demonstrate the biosimilar to be highly similar to the reference product.

Amgen followed the regulatory pathway for the development of ABP 501, and I would like to briefly touch on each step, which will then be

presented in detail in the following presentations.

Looking at the first step, analytical characterization, we will share data demonstrating that ABP 501 is highly similar to adalimumab. All biosimilars must have the same amino acid sequence as the reference product, and this is the case for ABP 501. And it also has the same potency and strength as required.

We will show you that while ABP 501 has similar structure and only minor differences compared to adalimumab, as expected for a biosimilar, the nature and the low levels of these differences are not meaningful because the functional activities of ABP 501 are equivalent with those of the reference product.

This includes the binding to soluble and membrane-bound TNF binding to Fc gamma receptors and the effector functions, ADCC and CDC.

The next step is nonclinical assessments. We conducted a four-week study in cynomolgus monkeys where we evaluated the toxicokinetics of ABP 501 compared to adalimumab. And importantly,

the toxicology showed the expected lymphatic changes were similar to adalimumab. There were no new safety findings, and as a result, the nonclinical assessments support similarity.

For the clinical pharmacology step, we will show you that the pharmacology study demonstrates ABP 501 pharmacokinetics are equivalent to adalimumab.

You will see the equivalent PK, based on a study using the standard methodology for bioequivalence. Of note, there are no specific pharmacodynamic markers predictive of efficacy for the TNF inhibitors.

You will also see that ABP 501 has a similar immunogenicity profile to adalimumab, and the clinical pharmacology shows similar drug exposure between ABP 501 and adalimumab.

In the final step of our development, the clinical studies confirm equivalent efficacy and that the safety and immunogenicity are similar to the reference product.

We conducted the clinical program in two

sensitive populations: a six-month study in rheumatoid arthritis, and a one-year study in plaque psoriasis, thus evaluating populations with and without methotrexate. Both studies were randomized, double-blind, active-controlled studies comparing ABP 501 to adalimumab.

The psoriasis study also includes a randomized, double-blind assessment of a single switch for subjects stable on adalimumab and then switched to ABP 501. Both clinical studies confirm equivalent efficacy and similar safety and immunogenicity. There are no clinically meaningful differences between ABP 501 and adalimumab.

Extrapolation of indications is not a new regulatory concept, but it is applied with a different approach for biosimilars. Extrapolation is generally thought of as understanding the clinical risks and benefits in one population and applying them to a similar population.

For biosimilars, the FDA has issued guidance outlining the elements of the scientific justification required to support extrapolation.

Specifically, the following elements should be considered: the mechanisms of action in each condition of use, the PK and biodistribution of the product in different patient populations, the immunogenicity of the product in different patient populations, and differences in expected toxicities in each condition of use, as well as any other factor that could impact efficacy or safety of the product in a patient population.

For ABP 501, based on the knowledge of the different disease states and the totality of evidence for similarity, these factors were all considered in order to conclude that ABP 501 will behave similarly to adalimumab in each patient population.

Since ABP 501 is expected to perform comparably in all of the indications of use, Amgen is seeking approval for all the indications that are not protected by regulatory exclusivity. The proposed indications are all shown here.

I now would like to introduce Mr. Hotchin, who will review the analytical and nonclinical

similarity data for ABP 501.

Applicant Presentation - Simon Hotchin

MR. HOTCHIN: Good morning. My name is Simon Hotchin, executive director of Regulatory Affairs at Amgen, with responsibility for the Amgen biosimilar programs.

I will present the analytical and nonclinical similarity data supporting the approval of ABP 501 as a biosimilar to the reference product.

First I will provide the background on Amgen's approach to product and process design for ABP 501. I will then discuss our approach to assessing analytical similarity, before reviewing the data and the conclusions. And finally, I will review the results of the nonclinical program.

Let's begin by discussing the development of the ABP 501 cell line manufacturing process and formulation. This background is important because these factors can influence the degree of similarity achieved between a biosimilar and its reference product.

With regard to the cell line, each new biosimilar requires a new transfection, and because of this, the selection of the cell line is a critical aspect of achieving similarity targets.

We undertook a careful process to create the ABP 501 cell line, screened a large number of clones, before creating the cell bank. This ensured that ABP 501 matched the amino acid sequence and other similarity targets of the reference product.

With the ABP 501 cell line in place, we then focused on the development of the manufacturing process. Our aim was to establish a process that consistently delivers similar product.

The ABP 501 commercial manufacturing process was developed prior to the initiation of clinical trials, and we minimized changes throughout development to reduce the potential for shifts in product quality. Additionally, the same cell line was used throughout development.

Now, let's briefly address the development of the presentations and the formulation. We

developed three comparable drug product presentations, shown here. All use the same formulation and the same primary container.

We selected the ABP 501 formulation based on Amgen's experience with other antibodies, using excipients that are common in injectable products. The formulation is different to that of the reference product, but the combined results of the analytical, nonclinical, and clinical similarity assessment show that this difference does not impact similarity.

I will now turn to the design and the execution of the analytical similarity exercise. An important first step in the design of any similarity plan is the identification of the structural attributes and the functional activities of the molecule that drive the safety and efficacy in each indication. These were identified for ABP 501 based on a thorough review of the literature and the comprehensive characterization of the reference product.

Adalimumab and ABP 501 are human monoclonal

antibodies of the IgG1 isotype. They have the characteristic structure of an IgG antibody, consisting of two heavy chains and two light chains. These are linked by disulfide bonds, and each heavy chain contains an end-link glycan.

The fragment antigen binding or Fab region of the molecule is responsible for binding to the antigen target. In this case, the target is the soluble and membrane-bound forms of trimeric TNF.

The fragment crystallizable or Fc region of the molecule is responsible for binding to Fc receptors on various cell types, as well as binding to complement component C1q.

When the Fab region binds to target expressed on cells, and the Fc region engages an Fc gamma receptor or C1q, an effector response may be triggered. Additionally, cell-mediated immune responses may be triggered, as observed in a mixed lymphocyte reaction, or MLR.

Because biological products are made in a living system, they typically show a degree of structural variation. Depending on the location

and the level of these variants, an impact to potency, safety, or immunogenicity may be observed.

An example is glycosylation. As noted by the green circles, glycosylation occurs in the Fc portion of the molecule, and variations in glycosylation can impact binding of the antibody to Fc receptors and the related functions. Knowledge of such relationships between structure and function was an important consideration when selecting the assays to be performed.

Lot-to-lot variability can be observed in some attributes, and so an important element of the similarity assessment is understanding the variability of the reference product over time.

We procured adalimumab lots on a regular basis, covering a period of six years and totaling 24 lots of adalimumab from the U.S. and 18 lots of adalimumab from the EU. These were compared with 10 ABP 501 lots manufactured over approximately the same period.

With regards to the testing of the lots, at least 10 lots were typically tested for attributes

that could be influenced by the manufacturing process such as purity test, glycosylation, and associated effector functions. And for other attributes, a reduced number of lots were sometimes tested.

Although our focus today is on the similarity of ABP 501 and the U.S. reference product, our development program also included the use of adalimumab lots procured in the EU.

Therefore, we needed to establish a scientific bridge between the U.S. reference product and adalimumab procured in the EU. We achieved this by including three pairwise comparisons for each test in the testing plan.

These data, when combined with the results of the 3-arm PK similarity study, which will be discussed shortly, establish the requisite scientific bridge.

The final piece of the similarity plan was to establish the assessment criteria. Amgen engaged with the FDA on this topic throughout the development of ABP 501, ultimately implementing the

tier-based statistical assessment approach recommended by the agency.

Under this approach, each similarity attribute was assigned to one of three tiers based on the relevance of the given attribute to clinical outcomes.

Tier 1 attributes have the highest risk to clinical outcomes and were assessed by demonstration of statistical equivalence. The panel on the right shows an example of a passing outcome where the confidence interval for the difference in means, represented by the blue bar, is fully contained within the equivalent acceptance criteria, or EAC. That's represented by the red lines.

The EAC is set at plus or minus 1.5 times the standard deviation of the U.S. reference product data set and represents a stringent limit, requiring the difference in means between the products to be small relative to the observed variability of the reference product.

The tier 1 attributes for ABP 501 were

agreed with the FDA prior to the submission of the marketing application and corresponds to the primary mechanism of action, binding, and neutralization of soluble TNF.

Tier 2 attributes are those with the lower risk to clinical outcomes and are concluded to be similar when 90 percent of the ABP 501 lots are within a predefined quality range of the U.S. reference product mean plus or minus 3 times a standard deviation. This range is considered reasonable since it's based on well-established practices for statistical process control and establishing product specifications.

The right panel shows an example when 90 percent of the lots fall within the U.S. quality range denoted by the dashed lines. Each point represents the reported result for a given lot.

The remainder of the attributes were assessed in tier 3, including attributes with the lowest risk to clinical outcomes and those that do not deliver quantitative results. Similarity of tier 3 attributes is based on qualitative

comparisons.

Now, I will discuss the results starting with the structural and purity attributes of ABP 501. Throughout this section, a check mark indicates that the predefined assessment criteria were met. Where minor differences were observed, this is noted and discussed further.

The first category of product attributes is primary structure. The primary structure analysis included assays to assess the amino acid sequence and glycosylation.

The results show that ABP 501 has the same amino acid sequence as the reference product. Shown on the right are the results of the reduced peptide mapping analysis.

In this method, the protein is enzymatically digested and the resulting mixture of peptides is then analyzed by HPLC. The similar profile of the peptide peaks supports the conclusion that the products have the same amino acid sequence, which is a requirement to be consider biosimilar.

Given the importance of glycosylation

profile in achieving similarity in effector functions, we expended significant efforts to develop a sensitive and highly resolving glycan map method. This method has the limits of quantitation of 0.1 percent for individual glycan peaks, and allows for the quantitation of over 20 individual glycan structures.

Shown here, the glycosylation profile was similar between the products, but we did observe some quantitative differences. These are small differences and thus difficult to see in the figure. But specifically, ABP 501 had a higher level of galactosylation and sialylation and small differences in high mannose in afucosylated species. However, as will be discussed shortly, none of these differences impacted PK or functional similarity.

Next, we assessed higher order structure and particles in aggregates. For higher order structure, we performed a number of techniques to assess the similarity of the secondary and tertiary structures. No differences were observed.

As an example, here are the results of the near-UV circular dichroism assessment. This method provides information on the overall 3dimensional confirmation of the protein. And the overlapping spectra, as shown here, indicate that the products have similar higher order structure.

We used a variety of methods to assess aggregates, as well as particles of different size ranges and morphologies. No differences were observed.

Shown here are the results for the micro flow imaging of proteinaceous particles greater than or equal to 5 microns. And as can be seen, ABP 501 and the reference product contain similar levels of these particles.

Let's now turn to product-related substances and impurities.

The main product-related substances and impurities for ABP 501 are size variants and charge variants. We assess these attributes using highly sensitive chromatographic techniques, confirming the presence of the same species in both products,

but noting some small quantitative differences in individual species.

The differences that were observed in the reduced and the non-reduced CE-SDS methods were considered unlikely to be clinically meaningful because of the small magnitude of the differences, approximately 1 percent.

Focusing now on the charge variants, presented on the right are the results the cation exchange chromatography analysis. This method separates proteins according to their surface charge, which can be influenced by the presence of variants such as deamidation, glycation, oxidation, and C-terminal lysine.

As can be seen, the overall peak profiles were similar, although there were differences in the acidic and basic peak areas. We therefore performed additional characterization to identify the variants driving these differences.

Based on the characterization, we determined that the differences observed in the basic peak resulted from differences in C-terminal lysine

variants. And the differences in the acidic peak were the result of quantitative differences in two deamidated species, both of which are also present in the reference product.

These modifications are not within the region of the molecule responsible for antigen binding, binding to Fc receptors, or C1q, and no impacts to functional activity were observed. Overall, these differences in charge variants were considered unlikely to impact PK, efficacy, safety, or immunogenicity.

We also assessed the similarity of the product in comparative thermal forced degradation experiments. We did this because the degradation behavior of a molecule may highlight structural differences that may not be apparent from other testing. As illustrated by the plot, the rate of change shows that the products have similar force degradation behavior.

We observed similarity in all of the general pharmaceutical properties of the formulation. Notably, the volume and protein concentration

results support the conclusion that ABP 501 and the reference product have the same strength.

Finally, we assessed process-related impurities. Since ABP 501 and the reference product are manufactured using different cell lines and processes, we sought to show that there were no meaningful differences between the levels of process-related impurities.

As expected, based on the use of Amgen's well-established manufacturing platform, the results demonstrated that these impurities are reduced to lower levels and, importantly, are no worse than those of adalimumab.

With the assessment of structural impurity attributes concluded, I will now present the results of the functional similarity assessment. These data play an important role in informing the potential clinical relevance of the minor structural differences and are also important to support extrapolation.

As for the assessment of structural impurity attributes, the similarity assessment for

functional activities was comprehensive, covering Fab and Fc-related activities that are known or suspected to contribute to the mechanism of action in each of the indications of the reference product. We extensively assessed mechanisms of action mediated by the binding and neutralization of soluble TNF since this is the primary mechanism of action for all indications.

Regarding additional mechanisms of action that may contribute to efficacy and IBD, Amgen assessed binding to membrane-bound TNF, effector functions, and inhibition of proliferation in an MLR. We consider this appropriate to elucidate all mechanisms of action mediated by membrane-bound TNF, including reverse signaling.

As noted by the FDA in their briefing materials, a specific functional readout of reverse signaling was recently requested. These data are being generated and will be provided to the FDA for review to supplement the comprehensive package already provided. However, we do not expect to see differences in this attribute based on the

overwhelming demonstration of similarity provided by the other testing already completed.

I will focus on a few of the key functional attributes today, but importantly, all of these functions demonstrated similarity.

The primary mechanism of action is binding to soluble TNF, which prevents its interaction with TNF receptors and downstream signaling. A comparison of the binding to soluble TNF is therefore the most critical assessment for functional similarity. Shown here, the results clearly demonstrate the similarity of TNF binding between ABP 501 and the reference product.

We also assessed the results of this assay using the tier 1 statistical methodology recommended by the FDA. And on the right, the confidence interval for the difference in means between ABP 501 and the reference product is fully contained within the EAC, demonstrating equivalence, and establishing similarity.

In addition to assessing binding to soluble TNF, we evaluated the ability to inhibit binding

and subsequent cellular responses using an apoptosis inhibition assay. The data clearly established similarity, with the ABP 501 data tightly grouped, and as shown on the right, equivalence was also demonstrated according to the tier 1 criteria.

We also assessed similarity and activities mediated by the Fc region of the molecule. The first of these was Fc gamma RIIIa binding. The results demonstrate that ABP 501 binds Fc gamma RIIIa similarly to the reference product, meeting the tier 2 quality range derived from the U.S. reference product data set, and represented by the dotted lines on the figure.

FcRN binding was assessed because it provides information on the overall integrity of the Fc region as well as informing PK. Once again, the data demonstrates similarity in FcRN binding, meeting the quality range criteria.

Showing similarity in effector functions is relevant since these functions may play a role in the IBD indications, here are the ADCC data.

Similarity of ABP 501 and the reference product was established for ADCC activity meeting the quality range.

We also established similarity with respect to CDC. These data support a conclusion that the ABP 501 process is well-controlled with respect to the functional activities that may be impacted by variations in the level of different glycans.

Finally, we evaluated similarity binding to membrane-bound TNF as well as the modulation of immune cells in an MLR. The ABP 501 demonstrated similar binding to membrane-bound TNF in a cell-based competition assay. Also, ABP 501 demonstrated similar inhibition of proliferation in an MLR.

As mentioned earlier, the analytical similarity assessment was designed to catch the known or suspected mechanisms of action of the product in each of the authorized indications.

Overall, similarity was established for the functional activities assessed by Amgen, including those mediated through binding to soluble TNF and

membrane-bound TNF.

The primary mechanism of action for all indications is the binding and neutralization of soluble TNF, and functional similarity has been demonstrated using multiple assays.

Mechanisms of action mediated by membrane-bound TNF have been proposed to contribute to efficacy in IBD. With regards to these mechanisms of action, functional similarity has been demonstrated in assays for both membrane-bound TNF binding, effector functions, and modulation of immune cells expressing membrane-bound TNF. The functional similarity results therefore form the foundation of the scientific justification for extrapolation.

In conclusion, Amgen performed a comprehensive analytical assessment based on an in-depth review of the structural and functional characteristics of the reference product. The results of the analysis established the similarity of ABP 501 and the reference product.

Importantly, similarity was demonstrated in

all functional activities, including assays that address the known or suspected mechanisms of action in each of the indications of the reference product.

Therefore, we conclude that ABP 501 is highly analytically similarity to the reference product, and the results support scientific extrapolation to all proposed indications.

I will now briefly discuss the nonclinical similarity assessment. The species selection, dose regimen, and duration for the comparative toxicology study were selected to provide a meaningful toxicological comparison between ABP 501 and the reference product.

With FDA feedback, we conducted a toxicology study in male and female cynomolgus monkeys comparing ABP 501, the reference product, and a vehicle control.

The dose of 157 milligrams per kilogram per week was the maximum toxicology dose from studies of similar duration in the reference product development program.

We conducted a four-week study in order to allow sufficient exposure to assess toxicokinetics and the expected toxicology. As shown, ABP 501 and the reference product had similar toxicokinetics. Both products induced the expected lymphoid changes in the cynomolgus monkey, with no unexpected toxicities observed.

Overall, the nonclinical data supports biosimilarity. The kinetic profiles in the nonclinical study were similar to that of adalimumab, and the toxicology results were comparable, with no new findings for ABP 501.

This, in addition to the structural and functional similarity shown earlier, now leads us to the clinical pharmacology evaluation. And now Dr. Markus will continue our presentation.

Applicant Presentation - Richard Markus

DR. MARKUS: Thank you. I'll now review the clinical development program of the next step, being clinical pharmacology.

The first study in the clinical development program was a pharmacokinetics, or PK, similarity

study in healthy volunteers. Then we conducted two clinical studies to assess efficacy, safety, and immunogenicity.

One study was in subjects with rheumatoid arthritis, or RA, and that was a randomized, double-blind, head-to-head study in 526 subjects, comparing ABP 501 and US-sourced adalimumab. The primary endpoint was the clinical endpoint of ACR20 measured at week 24.

We also included an extension study for all those who completed the RA study and wished to continue treatment with ABP 501. 467 subjects enrolled in the open label extension study, and the study just completed and will now be analyzed.

The other study was in subjects with plaque psoriasis, and this was a one-year study in 350 subjects, comparing ABP 501 to EU-sourced adalimumab, with the primary endpoint of PASI percent improvement at week 16.

I will now review the pharmacology data, starting with the study in healthy volunteers. The objective of this study was to demonstrate PK

similarity.

We conducted this study in adult male and female healthy volunteers, as this is a sensitive population to detect a difference in PK if a difference exists. The healthy volunteers provide a homogeneous population without concomitant medications or other disease factors that could increase PK variability, and such an increase in PK variability would decrease the ability to detect the difference if it exists.

The study included a single dose of 40 milligrams administered subcutaneously, and then 63 days of extensive PK follow-up. The key endpoints were the Cmax -- that's maximum serum concentration -- and the AUC, or the concentration time area under the curve.

The prespecified equivalence margin was a standard bioequivalence margin and consistent with FDA guidance; namely, the 90 percent confidence interval for the ratio of geometric means must fall entirely within a range of 80 percent to 125 percent.

The study was designed as a 3-arm study, comparing ABP 501 to adalimumab sourced from both the U.S. and the EU. This three-way comparison additionally supports the scientific bridge such that studies with comparators sourced from either region are relevant for the U.S.

The primary results are shown here. You can see ABP 501 is both absorbed and cleared from healthy subjects in an almost identical fashion to adalimumab. All comparisons of ABP 501 to US- or EU-sourced adalimumab met the prespecified equivalence margin to allow us to conclude PK similarity.

The figure on the right shows the ratio of geometric means and the 90 percent confidence interval for ABP 501 compared to US- and to EU-sourced adalimumab. All comparisons are within the predefined equivalence margin of 80 percent to 125 percent. You can also see in blue that the US- and EU-sourced comparator were bioequivalent to each other. This, along with the analytical comparisons previously discussed, completes the

scientific bridge of US- and EU-sourced adalimumab.

In this table, you see the adverse events that were reported in at least 5 percent of the subjects from any group. Observations were comparable across the treatment groups.

The safety findings from the study were as expected for a healthy population when they're followed for two months. There was only one SAE reported on study, and this was a ruptured dermoid cyst in a subject receiving adalimumab from the EU, and this was considered not related to study drug.

Shown here are the percentage of the healthy subjects who developed antidrug antibodies by the end of the study. I will start with a comment that Amgen created new assays using techniques that were not available at the time adalimumab was developed.

These new assays are both very sensitive and drug-tolerant, meaning they can detect antidrug antibodies even in the presence of adalimumab or ABP 501. Therefore we expect to detect a relatively high incidence of antidrug antibodies compared to historical studies.

On the left are subjects who developed binding antidrug antibodies. The rates were comparable across the three treatment groups. Approximately 43 percent of subjects receiving ABP 501 and 50 percent of subjects receiving adalimumab formed binding antibodies.

On the right, you can see the subset of subjects whose antidrug antibodies were neutralizing. And this was also similar across the three treatment groups.

Finally, we looked at the pharmacokinetics across the three different clinical populations we studied. First, you see the healthy volunteer population we just went through. However, those results were used to model the steady-state concentration, represented here in the box-and-whisker plots.

The boxes represent the 25th to 75th percentiles, and the whiskers represent the range of observations, except where there are individual dots that outliers. The solid lines represent the mean, and the dashed lines represent the median.

In the RA and psoriasis clinical trials, we intermittently evaluated the trough PK. And here you see that result with the RA study at week 12 and the psoriasis study at week 16. Of note, the mean and the median in the RA study are equal, and hence the dash line and solid lines are overlapping.

The data show similar PK comparing ABP 501 to adalimumab in each population. Additionally, the steady-state drug concentration is consistent between the three different populations.

In summary, we have demonstrated pharmacokinetic similarity, adding clinical pharmacology to the totality of evidence. Now, we will move to the next step, clinical confirmation of biosimilarity, and this is a demonstration of no clinically meaningful differences.

We conducted clinical studies in two patient populations. We chose RA and psoriasis to capture two key uses; that's with and without concomitant immunosuppression with methotrexate. Data from these two studies further inform the use across all

the indications.

I will describe the study designs and efficacy results for each study, followed by the safety, and then the immunogenicity results for both studies. So I'll start with rheumatoid arthritis study design and results.

This figure represents the schema for the study in patients with rheumatoid arthritis. The study was a randomized, double-blind, head-to-head comparison of ABP 501 to adalimumab, with both groups receiving 40 milligrams subcutaneously every two weeks.

The primary endpoint was measured at week 24, though efficacy assessments were made throughout the course of treatment. The primary endpoint for the rheumatoid arthritis study is the ratio of ACR20 responses at week 24. We utilize the ratio as the primary endpoint, but we also evaluated the difference in ACR20s. I will show you both analyses.

In order to derive the equivalence margin, we followed the FDA guidance for non-inferiority

studies to establish the lower margin. As a standard in this methodology, we conducted a meta-analysis of similar adalimumab studies.

Following that guidance, we calculated lower margin to preserve at least 50 percent of the treatment effect, which establish the lower margin to be 0.738. We then set the non-superiority margin symmetrically, and, hence, the upper margin is 1 over 0.738, which equates to 1.355.

Specifically, to conclude equivalence in efficacy, the entire confidence interval for the primary measure must be fully contained within the equivalence margin of 0.738 and 1.355.

After we completed the study and locked the database, the FDA recommended we also test the difference of ACR20 scores and apply equivalence margin of plus or minus 12 percent.

This means the observed difference between the two groups would be less than 5 percent in order to confirm equivalence when the entire confidence interval is plus or minus 12 percent.

I'd briefly like to touch on the disposition

of the patients in the RA study. We randomized 526 subjects with 264 to ABP 501 and 262 to adalimumab. The study was well-executed, with 92 to 95 percent in each group completing the study. The reasons for discontinuation were similar between the two groups.

The randomization did balance the two treatment arms in terms of baseline disease characteristics. For example, the baseline DAS28 CRP was an average of 5.66 in the ABP 501 group and 5.68 in the adalimumab group. And this is observed consistently down the table, where there are no meaningful differences for the other disease characteristics.

The baseline demographics that were included in the briefing document also show the two groups were comparable. So let's now turn to the primary outcome.

This slide shows the primary endpoint results, the ratio of ACR20 at week 24. There were 74.6 percent of patients with an ACR20 response in the ABP 501 group, and 72.4 percent of patients in

the adalimumab group.

The ratio of these results using the statistical model, including covariates, is calculated as 1.04, with a confidence interval of 0.95 to 1.13.

As you can see in the diagram, these results include a tight confidence interval that's well within the prespecified margin of 0.738 and 1.355, thus demonstrating clinical equivalence in efficacy between ABP 501 and adalimumab.

When evaluating the difference of ACR20 responses using a statistical model including the covariates, the difference is 2.6 percent, with a confidence interval of minus 3.73 to 8.94 percent, which is within the additional equivalence assessment recommended by the FDA for this study of plus or minus 12 percent. Hence, in both methods of testing, we clearly met the criteria for equivalent efficacy of ABP 501 compared to adalimumab.

We also conducted sensitivity analyses, here showing the use of the non-responder imputation for

missing data, to assess potential differences or influences compared to the primarily analysis, which were based on the full analysis set and the last observation carried forward for managing missing data. And here you can see the sensitivity analysis supports the previous efficacy analyses as the ratio as 1.0, with a tight confidence interval of 0.92 to 1.09.

In addition to evaluating the ACR20 at week 24, we also looked at percent of subjects achieving ACR20, ACR50, and ACR70 over the entire course of the study. And you can see the response curves for ABP 501 and adalimumab track well to each other throughout the time course.

Another measure of efficacy that we studied in addition to all the ACR constructs is the DAS28 CRP. This is a continuous measure that's a composite of disease activity that's also used to monitor the treatment in rheumatoid arthritis.

You can see in these response curves, during the entire study, that the reduction in disease activity of ABP 501 mirrors that of adalimumab.

I'll now review the psoriasis study design and efficacy results. Here you can see the study design with patients being randomized to receive either ABP 501 or adalimumab in a double-blind fashion, starting with a loading dose of 80 milligrams subcutaneously, and then going on to the 40-milligram dose every two weeks, according to the approved use of adalimumab.

The primary endpoint of PASI percent change was evaluated at week 16. Then subjects who had at least a PASI 50 response -- that is, at least a 50 percent improvement in their psoriasis -- were re-randomized.

Subjects either stayed on their prior therapies, as depicted on the right side in the yellow and blue boxes, or switched from adalimumab to ABP 501, as shown in the bottom orange box. Patients remained on treatment after the second randomization for another 8 months, completing the one-year study.

I'd like to briefly explain the primary endpoint, being the PASI percent improvement from

baseline at week 16. This is the most sensitive endpoint for this population since it's a continuous variable and, hence, can best detect any differences in clinical efficacy.

We know the binary outcomes, such as PASI 75 or PASI 90, are more commonly used for studies of new treatments and that's because of the need to quantify a specific clinical benefit. But as a biosimilar, it's more appropriate to compare the continuous measure of PASI to be more sensitive in detecting a difference if a difference exists. That said, we also include analyses of PASI 50, 75, 90, and 100.

In establishing the equivalence margin, we again followed the FDA guidance for non-inferiority studies in order to establish the lower margin, and again set the non-superiority margin symmetrically. We conducted the meta-analysis of published studies for adalimumab in plaque psoriasis and calculated the effect size. And following the approach in the guidance that preserves at least 50 percent of the treatment effect, the lower margin was determined

to be minus 29.

We then applied additional rigor and narrowed the margin to minus 15 to confidently rule out a clinically meaningful difference, and then we again set the non-superiority margins symmetrically.

To help interpret this margin, similar to what I showed for the RA study, the equivalence margin is such that the entire confidence interval for the difference in percent PASI improvement is within the margin. Therefore, with a margin of plus or minus 15, the actual observed difference in the study estimates would haves been less than 8 in order to confirm equivalence.

Here's the disposition of patients in the psoriasis study. We randomized 350 patients to either ABP 501 or adalimumab, with 93.7 percent and 92.6 percent completing the study through the primary endpoint of week 16.

At week 16, approximately 6 percent did not have at least a 50 percent improvement in their PASI score and therefore did not continue in the

study. The remaining subjects still on study were re-randomized, as already described, to complete the one-year treatment. And like the RA study, the reasons for discontinuation were comparable in all three arms.

The baseline demographics of the psoriasis study showed that randomization was effective in balancing the treatment arms, including baseline disease-related factors such as the mean baseline PASI score listed on the bottom, with 19.68 for ABP 501 and 20.48 for adalimumab.

We'll now move on to the efficacy results. For the primary endpoint, the difference in PASI percent improvement from baseline to week 16, we observed a PASI improvement of 80.9 percent in the ABP 501 group and 83.1 percent in the adalimumab group. The difference is 2.18 with a tight confidence interval of minus 7.39 to 3.02. This is clearly well within the equivalence margin of plus or minus 15, and hence we again conclude clinical equivalence.

We also compared the PASI percent

improvement through the time course up to the primary endpoint, depicted in this graph. This shows the comparison of the two groups at weeks 4, 8, 12, and the endpoint, week 16. You can see that the response with ABP 501 was comparable to adalimumab at each time point during the study.

We now also consider what happened for the full year of study, that is, including the re-randomization for subjects who stayed on ABP 501 or adalimumab for the full year or switched from adalimumab to ABP 501, here depicted in orange. And you can see there was no difference in efficacy for the subjects in all three groups.

As I mentioned earlier, the continuous measure of PASI percent improvement is the primary endpoint. However, we know the score is often dichotomized at various cutoffs, and this figure shows the PASI 50, 75, 90, and 100 responses. While these were not designed in the study to be powered for statistical comparisons, post hoc analyses show no significant differences between ABP 501 and adalimumab for any of these treatment

comparisons.

We also looked at the dichotomous PASI responses at the end of the study. You can see the three groups, being those on ABP 501 for the full study in yellow, those receiving adalimumab for the full study in blue, and those who switched from adalimumab to ABP 501, shown in orange. And once again, there are no significant differences observed in these groups.

I'll now show the safety reporting from the two studies, starting with the RA study. To summarize the adverse events reported in the RA study, on the left are the total adverse events for the two treatment arms, with ABP 501 in yellow and adalimumab in blue.

This shows the percent of subjects reporting at least one adverse event and also those with a serious adverse event, noted as an SAE. There were no deaths on study.

On the right side are key events of interest for adalimumab, specifically, the percent of subjects with an opportunistic infection, an

adverse event of hypersensitivity, and malignancy. The percentage of subjects is similar between the two treatment groups for all comparisons, and we will go into more detail for each of these in a moment.

The serious adverse events in this trial were infrequent and were balanced between ABP 501 and adalimumab. The overall accounting of any serious adverse event, shown in the first row, shows that 3.8 percent of subjects in the ABP 501 group and 5 percent in the adalimumab group had serious adverse events.

With so few events overall, the actual events in each classification were very small numbers and did not show a pattern or trend for either product.

Now, summarizing the safety reporting in the psoriasis study, here through the primary analysis at week 16. These data also show a comparable percentage of subjects reporting adverse events and serious adverse events. And again, there were no deaths on study. On the right are the data showing

similar rates of opportunistic infection, hypersensitivity, and malignancy.

Now, the same comparison of safety events, but during the study period after the second randomization. This is week 16 through the end of the study at week 52. The data are again comparable, with the majority of adverse events being typical mild events that occur during a one-year study such as nasopharyngitis, rhinitis, and upper respiratory infections. Again, there were very few reports of opportunistic infections, hypersensitivity, and malignancy.

Looking at the serious adverse events throughout the study, events were again infrequent and were comparable in all treatment arms. The two columns on the left represent the SAEs reported in the two treatment groups through week 16. The three columns on the right account for the reports from week 16 through the end of the study. Since the denominators are not the same after the re-randomization, we have to look at the percentages instead of the frequency counts.

Focusing now on key events of interest, and here specifically infections, the data are presented side by side for the two studies, with RA on the left and psoriasis on the right. Again, the psoriasis study is broken down by treatment phase, two groups through week 16 and then the three groups for weeks 16 to 52.

Infections overall are shown in the first row. In the RA study, 23 percent had an infection while receiving ABP 501 and 26 percent while receiving adalimumab.

In the psoriasis study, the only numerical difference is in weeks 16 to 52, with the adalimumab arm lower than the ABP 501 arm. And this observation is again predominantly the typical nasopharyngitis, rhinitis, and common mild infections seen in the one-year study.

Serious infections occurred in 1 to 2 percent of subjects in any arm of either study. And opportunistic infections were also balanced, with one subject in any arm of each study.

Hypersensitivity is a composite assessment

that includes a large number of different adverse events potentially informing hypersensitivity. The data show an overall hypersensitivity reporting of approximately 3 to 5 percent in either arm of either study, shown in the first row, and all were low grade reactions other than one serious event in either study.

As expected, very few cases of malignancy were developed during the studies. All malignancies were skin cancers, with two cases in the RA study and three in the psoriasis study, and they were distributed across the various treatment arms.

Now, I will discuss the immunogenicity results of the two clinical studies and again start with the RA study. However, first I'll start with a brief description of antidrug antibodies.

Binding antidrug antibodies, or ADAs, are from the body recognizing the drug to be a foreign protein. These antibodies bind anywhere on the drug, and some of these binding antibodies can increase the clearance of the drug, which decreases

the PK exposure, though the drug can still be functionally active.

All subjects with binding antidrug antibodies were then tested for their ability to be neutralizing to the drug; basically, the ability to block the drug from binding to its target.

In the case of adalimumab, neutralizing antibodies block adalimumab from binding and inhibiting TNF, thereby inhibiting the functional activity of the drug. It's also important to note that a patient's antibody response may form binding antibodies at one time point, and then can progress to become neutralizing.

The RA study confirms similar rates of binding and neutralizing antibodies between ABP 501 and adalimumab throughout the six months of exposure. Here the yellow and blue bars represent the percentage of subjects with binding ADAs for ABP 501 and adalimumab. You can see that the development of binding ADAs increases for both products from baseline through week 26, and importantly, the rate is comparable for the two

products.

In the shaded portion of each bar, you can see the percentage for the subset of subjects whose antibodies were neutralizing. These are also comparable for the two products.

To further orient you to the figure, since we will use this representation for the next few slides, the numbers across the bottom are the numbers of subjects in each of the groups who developed binding antibodies or the subset that develop neutralizing antibodies, while the height of the bars represents the percentages of the subjects.

We conducted the same assessments during the psoriasis study, and the results are consistent with both the healthy volunteer study and the RA study.

As you can see in this figure, there are similar percentages of binding antidrug antibodies for ABP 501 compared to adalimumab at weeks 4 and 16. You can also see the subset of antibodies that are neutralizing is similar, as represented by the

lighter-shaded bars with only a 6-subject difference as shown on the bottom numbers of 15 versus 21.

At week 16, binding antibodies were about 10 percent higher in the adalimumab group, 52.1 percent versus 61.9 percent. When this adalimumab group was re-randomized at week 16, a disproportionately higher percentage of those with binding antibodies were allocated to the switch to ABP 501. And this is a key understanding to the remainder of the study.

With the uneven allocation, it's not surprising that from weeks 16 to 52, a slightly higher number of subjects developed neutralizing antibodies in the switch arm, as shown in the orange-shaded box.

It's important to note that this difference in neutralizing antibodies is only 3 subjects, and that all of these subjects who developed neutralizing antibodies already had binding antibodies to adalimumab prior to the switch. Overall, binding and neutralizing antibodies are

similar across the groups.

Finally, to provide an overall assessment, we also compared the two groups receiving either ABP 501 or adalimumab for the entire study. Again, you can see ABP 501, shown in yellow, is comparable in immunogenicity compared to adalimumab. So we conclude the immunogenicity of ABP 501 is similar to that of the reference product.

In summary, the clinical program met the efficacy equivalence criteria in both populations, RA and psoriasis. The study showed similar type, frequency, and severity of adverse events, with no new safety risks identified. And lastly, the study showed similar rates of binding and neutralizing antidrug antibodies for both ABP 501 and adalimumab.

The totality of evidence supports the licensure of ABP 501 as a biosimilar. The analytical characterization showed a highly similar product with the same amino acid sequence and potency and similar effector functions, similar toxicology profile, similar pharmacokinetics, and

finally, two separate clinical studies both showing similar efficacy, safety, and immunogenicity. So the data show that ABP 501 is highly similar to adalimumab, with no clinically meaningful differences.

I'd now like to discuss how this totality of evidence informs the use of ABP 501 in populations not directly studied, and this is the extrapolation of indications.

As you saw, the FDA guidance describes the framework for extrapolation, and this is a key part of the biosimilar pathway since it is not expected that a biosimilar development program will include clinical data in every indication.

Extrapolation from the studied populations of RA and psoriasis to all the non-studied populations takes into account the totality of evidence and is based on scientific justification, including potential mechanisms of action unique to the additional indications, considerations if the pharmacokinetics would differ between the products when used in different indications, potential

differences in immunogenicity, and any other consideration of efficacy or safety that would meaningfully differ between the two products when used in the additional indications.

Extrapolation starts with the thorough understanding of the relevant mechanisms of action for adalimumab and for ABP 501. TNF inhibition is the primary mechanism of action for all indications being sought.

Therefore, the foundation for extrapolation to the arthritides, dermatologic, and IBD populations is to demonstrate similarity in soluble TNF binding and inhibition. We have shown this with multiple assays, as discussed earlier, and in the briefing book.

Mechanisms also reported for inflammatory bowel disease include membrane-bound TNF binding and associated functions, including effector functions such as ADCC and CDC, and modulation of the immune cell functions shown in the MLR assay.

Importantly, all of these functions were demonstrated to be similar between ABP 501 and

adalimumab. Therefore, ABP 501 is expected to have the same activity as adalimumab in all extrapolated indications.

With regards to pharmacokinetics, the question for extrapolation is where there's a reason to believe that PK of ABP 501 would be different than adalimumab when used in another population, not whether the half-life or clearance is the same across the indications.

That said, we show here the ranges of steady-state drug concentrations reported in the prescribing information and published literature for the indications being sought.

Generally, the PK of adalimumab has a consistent steady state trough level across the populations. And given we have shown similar PK between ABP 501 and adalimumab in a sensitive PK study and also in both RA and psoriasis populations, we expect to also have the similar PK in all indications of use.

Considerations of immunogenicity are also important for extrapolation. As you saw, we

studied two key populations to inform all other uses, including patients both with and without additional immune suppression with methotrexate.

This is important since it informs use in all populations -- those with arthritides, dermatologic conditions, and also inflammatory bowel disease, where many of the patients received some concomitant steroid treatment or other immune suppression.

The data show a similar percentage of ABP 501 and adalimumab subjects developed binding or neutralizing antibodies, both in RA study with methotrexate and in the psoriasis study without methotrexate, or any other systematic immune suppression.

Additionally, in the evaluation of immunogenicity, we also considered the impact of the antidrug antibodies on circulating drug levels. We know this information is important for the treatment decisions in some patients.

In both patient studies, we evaluated trough levels and antibodies intermittently. And here you

see those at week 12 in the RA study on the left and week 16 in the psoriasis study on the right.

In both studies, the impact of the antibodies on drug levels was similar, comparing ABP 501 to adalimumab. Specifically, for antidrug antibody-positive subjects, you can see a similar decrease in circulating drug levels in both ABP 501 and adalimumab. And this is consistent across both studies.

In conclusion, following the FDA guidance, we provided scientific justification for extrapolating similarity to all indications. This includes mechanisms of action, including those mediated by both soluble and membrane-bound TNF, pharmacokinetics in three different populations, and no reason to expect a difference between products when used in other populations, immunogenicity with and without additional immune suppression, and safety and efficacy in two very different disease conditions.

All aspects showed ABP 501 is highly similar to adalimumab and leads to the conclusion that

ABP 501 is expected to have no clinically meaningful differences when used in all indications being sought. Thank you.

I'd now like to introduce Dr. Steven Galson, who'll provide Amgen's overall conclusion for ABP 501 as a biosimilar.

Applicant Presentation – Steven Galson

DR. GALSON: Thank you. Good morning. I'm Steven Galson, and I'm responsible for global regulatory and safety at Amgen.

Amgen has over 35 years of experience in the development, manufacture, and commercialization of novel biological medicines. The knowledge gained through this long experience has shaped the development of ABP 501, Amgen's first proposed biosimilar product.

The comprehensive data package that was summarized here this morning was generated through a deliberate, stepwise approach that followed FDA guidance. This comprehensive data package has established that ABP 501 is analytically highly similar to the reference product.

Similarity in PK, efficacy, and safety have been demonstrated in healthy volunteers and in two different patient populations. The totality of data provided from these studies supports the approval of ABP 501 as a biosimilar for all proposed indications.

The execution of our comprehensive development program demonstrates Amgen's commitment to patients. This commitment will continue through the life of this product, with a strong focus on transparency, safety, and availability.

All biologics should be subject to the same traceability requirements so that safety data can be accurately attributed. Amgen supports the agency's draft guidance on distinguishable naming and appropriate labeling for biosimilars. Both of these are essential for effective post-marketing surveillance and risk communication. To this end, Amgen intends to utilize the same pharmacovigilance system for our biosimilar products as for our innovative products. And finally, Amgen remains committed to the high-quality and reliable products

supply that patients and physicians have come to expect. ABP 501 presents a high-quality biosimilar option for patients.

I wanted to thank the committee and FDA staff for their commitment to public service, and this concludes Amgen's remarks. Thank you.

Clarifying Questions to Applicant

DR. SOLOMON: Thanks to the applicant.

We now have some time for some clarifying questions to the applicant. Dr. Brittain?

DR. BRITTAIN: Yes. I have two questions --

DR. SOLOMON: Could you just announce your name?

DR. BRITTAIN: Oh. Erica Brittain. I have two questions about the clinical efficacy studies. I think it's really important that you did the clinical studies. I just wanted to understand the context in which they were done because in the FDA presentation, they mentioned something about they would only be needed if there were -- I think the term was residual uncertainty.

But it sounded like perhaps you had planned to do it all along, and it wasn't because of any shortcoming. And I just wanted to confirm that that was true.

DR. MARKUS: Yes, thank you. That is true. We did not necessarily do two studies. We, in fact, did not do two studies because of some other assessment of uncertainty.

We could have done one study to satisfy regulatory purposes, I'm sure. But we did two studies to provide added confidence for the physicians and patients.

DR. BRITTAIN: Okay. And the second question, I just wanted to clarify that all the confidence intervals that you presented for the clinical studies were 90 percent, not the usual 95 percent that we're used to seeing in like a non-inferiority study.

DR. MARKUS: Right. In the RA study, they were 90 percent confidence intervals. In the psoriasis, we used 95 percent confidence interval.

DR. BRITTAIN: Okay.

DR. SOLOMON: Dr. Bilker?

DR. BILKER: Yes. I have a question about study 263, the psoriasis study. On average, all three arms looked very similar in terms of the changes of the PASI score over time.

But I have a question about patient-level -- specifically, patient-level data. In the Humira ABP 501 arm, if you look at subjects, in what percentage of the subjects did the PASI score significantly worsen after the switch? And were such patients switched back to Humira? And if switched back to Humira, in what percentage of them did the PASI score then improve?

DR. MARKUS: The psoriasis study had a singular switch for patients who were on adalimumab. The patients who were on adalimumab were then randomized to either stay on adalimumab or switch to ABP 501. There was not multiple switches in the study.

DR. BILKER: Right. But if they switched, in what percentage of those switches did the PASI score worsen?

DR. MARKUS: So for those who switched after week 16?

DR. BILKER: Right.

DR. MARKUS: Dr. Kaur, do you want to respond?

DR. KAUR: Primal Kaur, clinical development, Amgen. Overall, the efficacy was similar in the subjects who continued on adalimumab or the subjects who transitioned to ABP 501 at week 16. Slide up.

I could share with you the different PASI binary cutoffs. From week 16 onwards to week 50, we can see the subjects. These are PASI 50. And the same continued for PASI 75, PASI 90, and 100. Next slide up, please.

This will provide you the overview of all the binary PASI cutoffs at week 50. And the orange arm, to orient, is the arm that continued with the switch.

When we reviewed these in totalities of different binary cutoffs for PASI, all the subjects in the switch arm maintained the same efficacy.

And that's also true for the PASI percent improvement, which was the primary endpoint for the study. Slide up, please.

This slide summarizes the PASI percent improvement for all the subjects throughout the study, including the ABP continuous arm, including the adalimumab arm, and including the subjects who switched. And as you can see, the efficacy was maintained in the switch group as well.

DR. BILKER: So there were no specific patients in which it worsened?

DR. MARKUS: Sorry. Could you repeat that?

DR. BILKER: You're giving me the numbers on average, but were there no patients in which it worsened?

DR. MARKUS: I'm sure some patients -- I don't have a subset after the switch.

DR. KAUR: Yes. Over 90 percent maintained a PASI 50. So if we look at the subjects when we started the switch, everybody had 50 percent response, so we were 100 percent then. And as the study continued -- slide up again please -- if you

look from 16, week 16 onwards with 100 percent PASI 50 response, over 90 percent of all the groups maintained the efficacy. So it was similar to all the groups. Thank you.

DR. SOLOMON: Diane Aronson?

MS. ARONSON: Dr. Markus, hi. I have a question about the RA study. In relationship to the 70 percent and the 30 percent, 70 percent had not been on biologics before; 30 percent had been.

I wonder about what happened with the 70 versus the 30 after randomization. And do you have any information about adverse events for the 30 percent that had been on biologic, isolated out from the whole study?

DR. MARKUS: Sure. Dr. Kaur?

DR. KAUR: The biologic subjects who had prior biologic use versus the non-prior biologic use, both of them maintained the efficacy. In terms of the efficacy, I can share with you -- slide up, please.

On the left-hand side of the slide with the two groups, yellow for ABP 501 and blue for

adalimumab, maintained similar efficacy. And on the right side is the subjects who did not have prior biologic use. So if we look within the groups, they maintained efficacy whether they were on biologic or not biologic.

In terms of the safety question that you raised, we have done safety by subgroup analyses for prior biologic use, and we did not see any differences between those groups.

DR. MARKUS: Thank you.

DR. SOLOMON: Dr. Jennifer Horonjeff?

DR. HORONJEFF: Hi, there. Jennifer Horonjeff. I have a question both for the RA and the other studies, psoriatic study in terms of -- can you speak to a little bit about your sample in your inclusion and exclusion criteria? I'm interested in what other comorbidities could have been involved in the sample and how homogeneous it might have been.

DR. MARKUS: So you want to know the -- what the eligibility criteria were --

DR. HORONJEFF: Yes.

DR. MARKUS: -- basically for the two studies? Dr. Kaur?

DR. KAUR: In terms of the rheumatoid arthritis study, I wanted to clarify that you are looking more specifically to more the comorbidities or the severity of the disease.

The inclusion of the criteria involved moderate to severe in the rheumatoid arthritis as well as the plaque psoriasis. And we have the criterias for tender joints, 6 and above; swollen joints, 6 and above. And they would have had been on methotrexate but didn't have a good response, so inadequate response to methotrexate.

We also had criteria of markers of inflammation. So that is a high level in terms of the severity of the disease, in terms of the comorbidities. The subjects, in terms of the malignancies, these are standard criteria as used in the clinical trials.

Any malignancy besides skin cancers or anything that has been treated and remission in the past five years, they were not allowed. Subjects

with comorbid conditions such as hypertension, diabetes which were stable, as deemed by the investigators, were allowed.

We had specific exclusion criteria for the safety concerns in comorbidities, which are a warning and precautions for the adalimumab label such as congestive heart failure, Class 3/Class 4, was not allowed.

Any subjects who had active neurological symptoms, which are suggested of demyelinating diseases, which is a warning and precautions for adalimumab, were also not allowed. Prior adalimumab use was also not allowed.

I hope that answers your question. If you have any specific questions, I'll be happy to answer that.

DR. HORONJEFF: How about any exclusion with any other autoimmune conditions?

DR. KAUR: Yes. So exclusion, in the rheumatoid arthritis studies, I think, if the subject develops a Sjogren's syndrome, which is the dryness of eyes or mouth, secondary to rheumatoid

arthritis, that was the only thing that was included. However, if there were other concomitant autoimmune diseases, which were -- some subjects can have overlap syndromes, those were excluded. And in the psoriasis, most of the comorbid condition criteria were similar as that of the rheumatoid arthritis studies.

DR. SOLOMON: Dr. Mager?

DR. MAGER: Don Mager, University of Buffalo. Hi. Given the primary mechanism of action of the compound, I was wondering if you measured either free or total TNF alpha in any of the clinical studies, and if not, why such information would be excluded.

DR. MARKUS: We didn't measure free or TNF alpha specifically in the studies.

DR. MAGER: Just to follow up, the case was made that in the analytical comparison, that that was a major component of it. But I'm just wondering why you wouldn't follow then TNF alpha and the clinical trials.

DR. MARKUS: That's because in these trials,

we don't typically measure the TNF alpha that way. We try to follow the similar studies that have been done before and had similar measures.

DR. SOLOMON: Dr. Siegel?

DR. SIEGEL: I may have found them in the briefing book. But I noticed you measured -- I had a question about the preclinical data set, particularly Fc receptor binding.

The figure shows binding to the high-affinity variant 158V of Fc receptor 3a, which is only one of the two variants. And my question was, is that down on patient cells that are homozygous, or do you have information on other alleles? I see a note but no figure about the other allele.

DR. MARKUS: Dr. Born?

DR. BORN: Theresa Born, Amgen, biosimilars. Our Fc gamma receptor binding assays were all done with recombinant proteins. They're done in a lysotype format. You did see the data to Fc gamma receptor 3A 158V. We also measured the 158F variant and showed it to be similar.

DR. SIEGEL: So then you didn't do an assay where binding to genotyped patient cells was done?

DR. BORN: We did not do Fc gamma receptor binding to cells, no. It was recombinant assay, being more sensitive to detect differences.

DR. SOLOMON: Dr. Adler?

DR. ADLER: This is Jeremy Adler. I have a couple of questions, one about that same assay or the same slide, CA24. This is on the Fc receptor analysis.

You stated that this was a statistical process control analysis. And according to the statistical process control analytic rules, if the data are offset from the midline, that represents a special cause.

You didn't include the midline here, the median here, so it's hard to assess. It looks like the Fc receptor binding is significantly lower in the ABP 501 group compared to the two different adalimumab groups, according to statistical process control analysis rules.

DR. MARKUS: I'll have Mr. Hotchin explain

how those margins are set.

MR. HOTCHIN: So I think, yes, we picked plus or minus 3 SDs based on that being a generally accepted approach for things like statistical process control. But we weren't applying statistical process control to these data. We just applied those justifications, those limits.

I mean, obviously, yes, you can see maybe a slight additional spread there in the Fc gamma RIIIa binding. But when you consider that that is the first step of the ADCC pathway, when you look at the ADCC data, we really didn't see a similar thing. We saw that the ADCC data were very closely matched between the products.

DR. ADLER: In the CDC data also, those are significantly higher, according to this figure.

MR. HOTCHIN: I think when you look at the CDC data, you can see there that yes, perhaps there's a slight shift upwards. But the results are all within the range of the U.S. reference product, and so we wouldn't really conclude those things to be different. They are within the

experience that's seen with the reference product, so within the rules of the plus or minus 3 SD standard to two assessments plus actually within the range of the reference product. We wouldn't view those as different.

DR. ADLER: This is not a figure of standard deviations and those aren't the analyses you're using. You're talking about using statistical process control analyses, and according to that type of analysis, these are significantly different. These are control limits and not standard deviations.

MR. HOTCHIN: Again, to reiterate, I was mentioning statistical process control just as a justification or to give a sense of why plus or minus 3 standard deviations might be viewed as a reasonable range to apply when looking at data.

The tier 2 criteria are of FDA construct, and they have suggested that this is an appropriate approach. The test actually is whether 90 percent of these lots fall within the range denoted by the gray lines.

So apologies if I've caused confusion by mentioning statistical process control, but that's the test. Right? Is it 90 percent of these lots within the three standard deviation range? And they are, and in fact, they're actually within the range of the reference product.

DR. SOLOMON: Dr. Reimhold?

DR. REIMHOLD: Andreas Reimhold. I had a question about the neutralizing and binding antibody formation, that when they're raised against, for example, adalimumab, would those cross-react with ABP 501 or vice versa? Has that been tested?

DR. MARKUS: Yes, they do cross-react.

DR. REIMHOLD: Okay. You also mentioned that the cell line used to make ABP 501 is different than the one originally used for adalimumab. Is there a scientific reason behind that, that it's a place to add more variability?

DR. MARKUS: Sure. Maybe I'll take a step back for that to help explain. All biosimilars will have to start with a new cell line. They all

start with a new cell construct, so we won't have access to the original cell line.

Every biosimilar, just like any other biologic, starts with the creation of a cell line with the transfection, and that establishes the -- each manufacturer has their own cell bank. So we, like any other biologic manufacturer, will have our own cell line for each product.

DR. SOLOMON: Dr. Oliver?

DR. OLIVER: Alyce Oliver. Can you please specify what the vascular and cardiac side effects were?

DR. MARKUS: I didn't quite catch that?

DR. OLIVER: What the vascular and cardiac side effects were for 501?

DR. MARKUS: Sure. The vascular and cardiac of -- yes? Dr. Kaur?

DR. KAUR: I wanted to clarify if you pertain to the side effects in terms of the SAEs. And were you specifically looking for the rheumatoid arthritis versus psoriasis, or both?

DR. OLIVER: Both

DR. KAUR: Okay. Perfect. So in terms of the cardiac events, they were very rare in both the clinical trials. And I can summarize the two big ones, which is congestive heart failure.

There was one case of congestive heart failure in the ABP group in the rheumatoid arthritis study, and two cases of congestive heart failure in the adalimumab group. And we did not see any cases of congestive heart failure in the psoriasis studies. There were no fatalities because of these events.

The other event we looked into was myocardial infarction. There was one case of myocardial infarction in the adalimumab group in the RA study. And in the psoriasis study, there was one case of myocardial infarction in the ABP group. Those were the only two through the entire development program, and no fatalities were seen.

DR. SOLOMON: Dr. Margolis?

DR. MARGOLIS: Sure. I have two questions. The first one is a continuation of the question before. In your analytic studies, you separated

the UK and U.S. versions of Humira; in the efficacy studies, you didn't. Therefore, you're viewing them as being interchangeable or biosimilar, is the first question.

The second question is that in the extrapolation studies, you didn't talk about hidradenitis. I believe there's an approval for a label use for Humira for that. Are you viewing them as being a separate disease, or is it not one that you're considering?

DR. MARKUS: I'm sorry. I didn't quite catch the second question.

DR. MARGOLIS: Are you not extrapolating to hidradenitis?

DR. MARKUS: Right. So I can answer both of those for you. With regard to the analytics that you saw and you were commenting about the US- or EU-sourced adalimumab, the U.S. product being the reference product and EU as an added comparator, we did those analytical analyses three ways in order to show the similarity, basically, of our product to either of those products.

Then the PK study also had the three groups in order to establish the bridge. With that bridge, that, I think, shows that the European-sourced product is also relevant for consideration in the U.S.

The clinical studies did not mix the two, if you will, within a study. The RA study was conducted against the -- with US-sourced product. They were both global studies, but the US-sourced product was used as the comparator in the RA study, and the EU-sourced product was used as comparator in the psoriasis study.

With regard to the specific indications, we are seeking extrapolation to the indications that are available as of now, and that's the ones we've listed. Other indications are protected still through regulatory exclusivities, and we certainly respect those regulatory exclusivities.

DR. SOLOMON: Dr. Jonas?

DR. JONAS: Beth Jonas. My question is regarding the clinical studies, slide number CD-38, on adverse events. It appears that patients in the

RA study had a lower rate of infections in the first line compared to patients with psoriasis. Particularly, I'm interested in patients in weeks 16 to 52 who have been exposed to ABP 501, seem to have a higher rate of infections compared to patients who had continued on adalimumab.

I want to know more about, number one, the nature of these infections, and were there other risk factors? Or have you looked more closely into other factors that may have predisposed these patients to infections? It just seemed like a safety signal of concern. DR. MARKUS: Sure. Dr. Kaur?

DR. KAUR: So the infections are a known side effect profile for adalimumab program. And the types and the frequencies of infections that we saw in the ABP 501 development program, both in the RA and psoriasis study, are very similar to what is mentioned in the USPI for adalimumab.

So I think your specific concern is pertaining to weeks 16 through 52 in terms of the overall, any infection rates, and the differences

between the ABP and the adalimumab group.

As we looked more carefully into these subjects, most of these infections are actually minor, which are called grade 1 and grade 2, between the groups. And they are mostly viral such as nasopharyngitis, rhinitis, upper respiratory tract infections.

The frequency of moderate to severe infections, such as serious infections, were very similar between both the groups. And as we looked into the discontinuations because of any of these, they were very, very rare events in these groups.

So it's essentially viral, which are run-of-the-mill infections, which caused this numerical imbalance. Overall, the rates are similar. Thanks.

DR. SOLOMON: Dr. Curtis?

DR. CURTIS: Thank you. Hi. Sean Curtis. Clarifying question on slide CD-14. This is your subject disposition slide in the RA study.

With regard to reasons for discontinuation, I don't see any patients listed having discontinued

for lack of efficacy. That's a little unusual. Is that perhaps captured under consent withdrawn, or were there really no patients who discontinued for lack of efficacy?

DR. MARKUS: Dr. Kaur?

DR. KAUR: So in the rheumatoid arthritis study, overall, the discontinuations were very low and the rates were fairly similar. We did look into consent withdrawn, looking for any ongoing adverse events or lack of efficacy. There were only a handful, one or two subjects in either group, which were lack of efficacy.

DR. CURTIS: Okay. Thank you.

DR. SOLOMON: Dr. Nathanson?

DR. NATHANSON: Jeff Nathanson. As you stated, the additional mechanisms of action, other than the binding of soluble TNF, form a basis for the extrapolation to the indication for the treatment of IBD.

My question is whether the functional testing of these other mechanisms of action met the same tier criteria, tier 1, tier 2, as the

functional testing of the primary mechanism of action, binding to soluble TNF?

DR. MARKUS: Mr. Hotchin?

MR. HOTCHIN: The tier 1 criteria were applied to those primary mechanisms of action. The majority there, those were then either tested in tier 2 or tier 3. That was considered based on a number of factors, but it was those tier 1 attributes that covered the main mechanisms of action; tier 2, then for a number of others.

Slide up. You can just see here a breakdown -- it's a little difficult to read -- but in terms of the different testing that was done. But I would emphasize all of these assays were qualified as appropriate for use.

They were shown to be sensitive and capable of detecting differences. We did, as we mentioned in the main presentation, a very comprehensive analysis across multiple assays, and all of these demonstrated similarity, whether that was in a quantitative sense or a more qualitative sense in tier 3.

DR. SOLOMON: Dr. Hancock?

DR. HANCOCK: I have two questions. One is slide CA-19 about the host cell protein assay, the ELISA. Since there are two different cell lines used for the two products, what is the certainty that ELISA is able to detect specific antigens unique to one cell line or the other?

DR. MARKUS: Dr. Karow?

DR. KAROW: Margaret Karow, biosimilars, Amgen. This is an ELISA that was developed using CHO extract because both cell lines are CHO and they derive back probably to pretty much the same parental CHO.

The ELISA does detect host cell proteins for both adalimumab and for ABP 501. And so whether it's the exact same proteins -- of course, you can't say because it's an ELISA -- we did do a 2D gel analysis to look at the individual proteins, and they're very, very similar.

DR. HANCOCK: Okay. So that answers my question. And so you used a generic ELISA but backed it up with a 2D gel, which is not that

sensitive, but it is something.

If I could ask a second question. On the primary structure, the reduced peptide map was shown with evidence of comparability. But I assume you used mass spectrometry as well. This is not mentioned.

But my concern here is that proteolysis was not mentioned, which could generate clip form. So did you use these various techniques to ensure that there was not any clipping in your product relative to the innovator product?

DR. MARKUS: Dr. Karow again?

DR. KAROW: You're right. The peptide map is a cleavage, so it's a Lys-C or trypsin map. We also did an asparagine N to get further details. But the clipping is best seen with the chromatography methods, and so we can see no molecular weight forms in the various chromatography methods that will give you clipping. And they're very, very low levels for both products.

DR. HANCOCK: So you didn't see differences

between the innovator and this product? That was what I was wanting to check. In terms of clipping, the two products were very similar?

DR. KAROW: Yes.

DR. HANCOCK: Okay.

DR. SOLOMON: Dr. Horonjeff?

DR. HORONJEFF: Jennifer Horonjeff. I'm interested in the rheumatoid arthritis study that you talked about the 72-week extension and that that, I believe you said, had just finished, and that one of the primary endpoints as being safety. I'm interested in the safety profile you're looking at and when those results would be available.

DR. MARKUS: Yes. I appreciate that. It was open label studies, so we do know that there were no unexpected events or safety events during that study. We're now going to be looking at that data to summarize it to look at the rates of events as they would occur, given that it's at that point, open label in a single arm.

We look forward to -- we'll certainly be sharing with the agency as soon as the data are

analyzed. We hope to present it at medical meetings, as well as publish the data.

DR. HORONJEFF: Do you have a time frame of when that would become available, looking at that data?

DR. MARKUS: No. Generally, it only takes a few months, but as far as when the medical meeting accepts it or when a journal accepts it, I can't really speculate.

DR. SOLOMON: Dr. Geller?

DR. GELLER: Nancy Geller. I'm interested in the similarity studies. A good way to show equivalence is to make your sample size really small. The sample size for most of these in at least one group is 10. I'd like somebody to comment on how you decided on the sample size for the similarity studies.

DR. MARKUS: Sure. Mr. Hotchin?

MR. HOTCHIN: The sample size, in a sense, is driven by the practical consideration of how many lots would be manufactured during our manufacturing program, and also the number of lots

that could be reasonably selected and tested from the reference product over that time as well.

Within that construct to the tier 1 equivalence testing, my understanding -- and the FDA may comment on this in their presentation -- is that they define those criteria as 1.5 times the standard deviation to account for a typical sample size of the two, like we've shown, and to represent a stringent test under those kinds of sample sizes.

So while you make a good point, I think that criteria of 1.5 times the standard deviation of the reference product was actually designed with these kind of sample sizes in mind to still represent a tight test that requires the means to match quite closely.

DR. SOLOMON: Dr. Feagins? Yes?

DR. STREETT: Sarah Streett. Just to follow up on the question of extrapolation, our patients with IBD we know have significant genetic variability, and phenotypic variability as well, and a significant inflammatory burden that often requires higher dosing. And we've talked about

potentially more complicated other mechanisms of action. I'm wondering if you considered studying that group.

DR. MARKUS: So whether we've considered studying that group? Yes. But we certainly, when we designed the program, took all the potential indications in mind as to which would be informative for similarity specifically since that was the intent of the program.

The IBD population, I agree, is a heterogeneous group. But I think we hence had an extensive set of assays, and very sensitive assays, to inform whether or not the two products would have the same function and activity regardless of the population or the heterogeneity of the patient. So that's really the foundation for the support in IBD, specifically, is going to be the structural over, in this case, functional similarity.

The kinetics again were similar in all the studies we conducted, so there would be no reason to think that kinetics in the two products would differ even though the patients have a high degree

of variability.

Then we had the consistent safety and efficacy in the two populations. I don't know if Dr. Reinisch also could maybe comment about the data we have and how you might think about it in an IBD population.

DR. REINISCH: Walter Reinisch, McMaster University and Medical University of Vienna. Thank you for this question.

I fully agree with you that IBD is a very heterogeneous disease, but from the totality of the evidence which was presented today, I'm very comfortable and don't see any limitation why there shouldn't be a biosimilarity between adalimumab and ABP 501 in patients with IBD as well.

DR. SOLOMON: Dr. Scher?

DR. SCHER: Yes. Jose Scher here. So I'm going back to the primary structure similarity, and the one thing that stands out is the so-called minor quantitative differences in the glycan map. Glycosylation is known to affect PK and also immunogenicity of immunoglobulins down the road.

My question is, can you expand on what you consider minor quantitative differences in terms of percentage of different glycans?

DR. MARKUS: Yes. I think Mr. Hotchin can respond to that. However, I'll remind you that we looked at those with a very sensitive set of assays, but then we did also demonstrate PK similarity and the equivalent safety and immunogenicity. The differences, we might be able to see with very sensitive techniques we showed do not show a difference in kinetics or the clinical aspects.

But maybe Mr. Hotchin can then explain some of the sensitivities of what we might see when we declare something has minor difference in the sensitivity assays.

MR. HOTCHIN: So I think, just as Dr. Markus was mentioning, the glycan mapping methods are very sensitive and are actually able to quantify differences down to the sub-1 percent levels.

As an example, perhaps in the sialylation, we saw some differences in sialylation. We were,

in a transparent manner, showing that. But what we were talking about with differences in total sialylation between 0.2, 0.3 percent and 0.7, 0.8 percent. So although we could discern a difference because of the sensitivity of the method, that is a very small difference in absolute terms.

From a PK perspective, obviously, certain glycans are being associated with differences in PK. Probably the most relevant for a molecule such as adalimumab is the high mannose. We did see some small differences there in the order of, again, a couple of percent, I think it was. But, again, from the PK data that we actually then generated, it's clear that that small difference didn't actually impact the PK. And so there are small differences.

These are things that we can see with very sensitive methods. But from the lack of impact on the function, the lack of impact on the PK, and the lack of impact on anything we've observed in the clinical studies, these really do appear to be

small, minor differences.

DR. SOLOMON: We've got two more questions. Dr. Siegel and then Dr. Reimhold, then we're going to break.

DR. SIEGEL: So patients treated with anti-TNF agents can develop antinuclear antibodies and occasionally a lupus-like syndrome. I'm wondering if, in any of the clinical studies, you looked for those antibodies or have any information about the comparative rate of incidence?

DR. MARKUS: Sure. Dr. Kaur?

DR. KAUR: In the ABP clinical development program, we did not specifically measure the antinuclear antibodies. However, we did try to capture the events of interest of lupus-like syndrome, and there was none either in the psoriasis or in the rheumatoid arthritis study. Thanks.

DR. SIEGEL: Thanks.

DR. SOLOMON: Dr. Reimhold?

DR. REIMHOLD: Andreas Reimhold. Could I ask for more clarification on the EU Humira versus

the U.S. Humira. Is this a matter of semantics now? I would expect it's the same product. Is it just made in a different manufacturing facility and that's why you're treating it a bit differently? Or are there other differences you could share?

DR. MARKUS: Sure. We consider and believe that adalimumab, which is made by another manufacturer, is a global product and consistent globally.

But I think a lot of this is then the legal and regulatory framework that requires us to compare directly to products for which the, in this case, agency, the FDA, has control over or familiar with. So we have to specify where the comparator comes from, and so we did one study with the US-sourced comparator and one from the EU-sourced comparator.

I think we showed analytically and kinetically that those two sources still are at least highly similar to each other, but I can't really specify where either are specifically manufactured. That's a different manufacturer's

product.

DR. REIMHOLD: So you don't know of any differences you can tell us about between those two --

DR. MARKUS: I do not know of any differences between the two, no.

DR. SOLOMON: Good. Well, I want to thank the applicant and the panel for a very robust conversation. And we'll now take a 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience, and we will resume at 10:30.

(Whereupon, at 10:18 a.m., a recess was taken.)

DR. SOLOMON: While people are taking their seats, I'm going to introduce the next speaker, which is the FDA presentation. I'm not entirely certain who's giving that. Dr. Joel Welch will be presenting.

FDA Presentation - Joel Welch

DR. WELCH: Good morning. I'm Joel Welch

from the Office of Biotechnology Products, Division of Review and Research II. I will discuss a review of the analytical similarity studies Amgen conducted to support ABP 501, the proposed biosimilar to US-licensed Humira.

My talk will cover the adalimumab structure and mechanism of action, the manufacturing of ABP 501, the design and the results of studies conducted to support a demonstration of high similarity, and the results and conclusion of our analytical similarity assessment between ABP 501 and US-licensed Humira.

Humira is the originator product manufactured by AbbVie. It is a fully human IgG1 kappa monoclonal antibody that binds and neutralizes human tumor necrosis factor alpha. It has a molecular weight of approximately 148 kilodaltons. The antibody is produced by a recombinant mammalian cell line, and possesses the heterogeneity typical of mammalian cell culture-derived monoclonal antibodies.

TNF alpha is considered to be a master

cytokine critical for function of the immune system, as well as for inflammatory responses. It exists in both a soluble and membrane-bound form, also called the transmembrane form, that can be produced by a range immune-related or other cell types.

The consequences of effector functions of TNF alpha are also varied and include tissue destruction, activation of proinflammatory cytokines, and cell death. Thus, this regulation of this master proinflammatory cytokine can have multiple clinical consequences in diseases like RA or IBD.

The primary mode of action of adalimumab is binding and neutralization of soluble and membrane-bound TNF alpha, thereby blocking the inflammatory pathways triggered by the cytokine. The binding occurs via the variable region, CDR surface, of adalimumab.

While TNF binding and sequestration is the main adalimumab mechanism of action, other mechanisms have been proposed as well. These

include reverse signaling of membrane TNF alpha-positive cells, antibody-dependent cell-mediated cytotoxicity of membrane TNF alpha-positive cells, and/or complement-dependent cytotoxicity of membrane TNF alpha-positive cells. It is possible that the relative role and importance of adalimumab activity for each of these mechanisms may differ from indication to indication.

The potential adalimumab mechanisms have been summarized in recent review articles, and models for adalimumab activity for some of these mechanisms have been developed. In this slide we have categorized them as likely or plausible based on the totality of the evidence in the literature.

The ABP 501 drug substance is a formulated antibody solution that is manufactured using standard bioprocessing techniques. It is produced by engineered mammalian cells and bioreactors and is purified by chromatography, filtration, and other common bioprocessing steps. Viral safety procedures required for biotechnology products have

been established.

Multiple batches of the drug substance have been produced, with some slight process optimization over time. The product has been shown to be consistent after each of these minor changes. The applicant has identified a set of critical quality attributes for ABP 501 that are typical of monoclonal antibodies products.

The drug product is a sterile, soluble dosage form in prefilled syringes or autoinjectors. It has a subset of the same strengths but has a different formulation as compared to US-licensed Humira. The expiry dating for ABP 501 is supported by stability studies.

An analytical similarity program was designed utilizing the proposed biosimilar, ABP 501, US-licensed Humira, and EU-approved Humira. The program had two goals: first, a comparison of the proposed biosimilar to US-licensed Humira was needed to support a demonstration that it was highly similar to US-licensed Humira; secondly, pairwise comparison of

ABP 501, US-licensed Humira, and EU-approved Humira was needed to justify the relevance of data generated using EU-approved Humira as the comparator in clinical studies.

The applicant was able to source a large number of batches of both US-licensed Humira and EU-approved Humira for the purposes of the analytical similarity assessment, though not each lot was used for assessment of all attributes.

For attributes that assess CQAs that are known to affect the primary mechanism of action, at least 10 lots of each product were used in the similarity assessment.

The applicant designed and qualified or validated a panel of assays to compare the three products. Many are orthogonal methods that measured the same critical quality attributes but from different perspectives and using a different methodology.

Based on the comprehensive review of potential adalimumab mechanisms of action, a panel of in vitro biological assays were developed and

implemented as well.

Amino acid sequence identity is one of the components that support a demonstration of analytical similarity. This was evaluated by multiple orthogonal methods. The result of each method supported a demonstration that ABP 501 and US-licensed Humira share an identical primary sequence.

Because TNF alpha binding is highly critical to all mechanisms of action of adalimumab, two measurements of this activity, a soluble TNF alpha-binding ELISA and a TNF alpha neutralization bioassay, were chosen for the most rigorous statistical test, equivalency testing, and support of a demonstration of high similarity.

Other attributes were analyzed using either a quality range analysis or a visual analysis based on the properties of the method being used. For the quality range analysis, the data from the applicant's product lots were compared to a quality range data set generated by the applicant.

For those assays that are more qualitative

than quantitative, they were evaluated by a visual assessment. Examples of these would include traces from secondary structure tests, like FTIR, or circular dichroism.

I will now invite, Dr. Meiyu Shen to discuss results of equivalence testing.

FDA Presentation – Meiyu Shen

DR. SHEN: Good morning. My name is Meiyu Shen, the CMC statistical reviewer from Office of Biostatistics. I am presenting statistically equivalence analysis of two highly critical quality attributes for biological activity.

For this submission, the review team focused on two assays that assessed the primary mechanism of action for independent equivalence testing. One is apoptosis inhibition bioassay, and the other is sTNF alpha binding.

In the equivalence test, the null hypothesis is defined as the mean difference of one quality attribute between the test and the comparator, is either greater than 1.5 sigma C or smaller than negative 1.5 sigma C.

We concluded that this quality attribute passes equivalence test if 90 percent confidence interval for the mean difference between the test and comparator falls within the equivalence margin defined by the range plus/minus 1.5 sigma C. Here, sigma C is estimated from the comparator product measured by the applicant. When there is unequal sample size, the confidence interval for the mean difference is calculated -- is used settled with approximation method.

These slides presented the data graph for apoptosis inhibition bioassay. The Y-axis represents apoptosis inhibition bioassay. The data spread of ABP 501 is narrower than those of US-licensed Humira and the EU-approved Humira, as shown in the graph. However, the means of three product are similar.

Apoptosis inhibition bioassay data are subjected to rigorous equivalence testing. The table here presents equivalence test result for apoptosis inhibition bioassay. The first column is the pair for the comparison. Second column is the

number of lots for the pair. Third column is the mean difference between the test and a comparator.

Fourth is 90 percent confidence interval for the mean difference between the test and the comparator. Next is equivalence margin. The last column is the conclusion of equivalence test.

As shown in the table and also graphs, the 90 percent confidence interval for each of three pairs falls completely with the corresponding equivalence margin. Hence, all three pairwise comparisons pass equivalence testing.

Now, let us look at the data graph for the sTNF alpha binding. This graph shows that the spread and the mean of three products are similar to each other. sTNF alpha binding is also subject to equivalence testing.

The table here presents equivalence test results for the sTNF alpha binding. This table is very similar to the table we just discussed for apoptosis inhibition bioassay.

As indicated in the table and the graphs, the 90 percent confidence interval for each of

three pairs falls within the corresponding equivalence margin. Therefore, all three pairwise comparison pass equivalent testing.

Based on our independent analysis of applicant data, we concluded that all three-way comparisons for both apoptosis inhibition bioassay and sTNF alpha binding pass equivalence testing.

Hence, statistically, equivalence testing results of apoptosis inhibition bioassay and the sTNF alpha binding support that ABP 501 is highly similar to US-licensed Humira, and also support the analytical bridge between all three products.

Next, Dr. Welch will continue his presentation on product quality review.

FDA Presentation - Joel Welch

DR. WELCH: I will now present additional assessments of the product quality of the applicant's proposed biosimilar to US-licensed Humira.

This slide presents a summary of the methodology of quality range analysis. The quality range equals a sample mean plus or minus X times

the sample standard deviation of reference product data. The reference product data were generated by Amgen.

If a high proportion -- for example, 90 percent -- of observed values of a quality attribute for the test fall within the quality range, the comparison of test and reference product regarding that quality attribute support a finding of high similarity.

Here, a summary of the attribute assessed by a quality range is presented. Purity by CE-SDS demonstrated slight differences in both the level of non-glycosylated heavy chain and fragmentation. The impact of differences in non-glycosylated heavy chain is assessed in an analogous fashion to the evaluation of the glycan profile that will be discussed in just a moment.

The differences in fragmentation are unique to two early batches of drug product and not present in later batches. Additionally, given the extremely high purity of each product, 98 to 99 percent, the differences were considered to be

negligible.

Two additional analyses, charge variant profile measured by cation exchange chromatography and end-link glycan analysis by hydrophilic interaction liquid chromatography, demonstrated results for attributes that failed just outside the quality range of US-licensed Humira.

In all cases, the differences were studied, and orthogonal techniques that assess biological activity known to be influenced by such differences were used.

As an example, I will present the case that the differences in the glycan map result in no clinically significant consequences. A comparison of the glycan maps for the three lots of EU-approved Humira in blue, ABP 501 in red, and US-licensed Humira in black, is presented.

The overlays show that each has a similar profile with the same glycans present and consistent but slightly different ratios. Glycans known to affect clinical performance based on literature reports include those that lack core

fucose, denoted as afucosylated forms, which can affect binding to Fc gamma RIIIa on NK cells and ultimately ADCC activity; high mannose forms, which can also affect the PK profile and ADCC activity; sialylation, which can affect the PK profile; and galactosylation, which may influence CDC activity.

I will now summarize the differences in the glycan profile and then the functional and biological assays that evaluate the impact of these differences.

Here, levels of one individual group of glycans, the percent total afucosylation, are presented. The levels of percent total afucosylation were calculated as the sum of all glycan structures lacking core fucose, which is include complex, hybrid, and terminal mannose glycans.

As observed, slightly lower levels of afucosylation are present for ABP 501, though results fall within the quality range proposed by the applicant.

Though not present within this slide, the

applicant also compared levels of afucosylation without the contribution of high mannose forms; a similar trend in magnitude toward higher levels was observed for ABP 501.

Here is a summary for the comparison of the levels of high mannose between US-licensed Humira, ABP 501, and EU-approved Humira. The percent high mannose was calculated as the sum of all high mannose glycans M5 to M8.

High mannose glycans have been reported in the literature to affect the PK profile, as well as may influence ADCC activity. As seen in the figure, slightly lower levels are observed for ABP 501 that fall just outside the quality range for US-licensed Humira proposed by the applicant.

Here is a summary of the levels of sialylation, the sum of all complex and hybrid glycan structures which contain at least one terminal sialic acid. Large changes in levels of sialic acid have been proposed in literature to affect the PK profile. Of note, sialylation levels are quite low for all products, with levels of

approximately 1 percent or less observed.

Here are galactosylation levels. The sum of all complex and hybrid glycan structures, which contain at least one terminal galactose, are presented. Changes in galactosylation have been proposed in literature to impact CDC activity. As observed, ABP 501 possess a higher level of galactosylation, with results falling outside the quality range proposed by the applicant.

ADCC is an immune function where effector cells, like natural killer cells, lyse target cells via antibody bound to their surface. The antibody Fc portion recruits the effector cells via Fc gamma receptor, Fc bridging.

Fc gamma RIIIa, also known as CD16, is the main form of Fc gamma receptor on NK cells. ADCC activity has been demonstrated in the literature to vary by the glycan composition on the antibody.

For this assay, CHO M7 cells that stably express a TNF alpha-converting enzyme-resistant form of membrane TNF alpha on their cell surfaces are used as target cells. NK92-M1 cells stably

transfected with human Fc gamma RIIIa are used as effector cells.

Critically, despite slight changes in the glycosylation profile that were just presented between ABP 501, US-licensed Humira, and EU-approved Humira, similar ADCC activity is observed, as depicted by the red bars that represent the quality range provided by the applicant.

These results, coupled with the equipment PK results that will be presented by our clinical pharmacology colleagues, support our conclusion that slight changes in afucosylation and high mannose levels are not considered to have clinically significant consequences.

As noted previously, the antibody Fc portion is responsible for the recruitment of effector cells, and the avidity of the Fc gamma receptor-Fc bridge may be influenced by the glycosylation pattern of adalimumab.

As shown in the figure, US-licensed Humira, ABP 501, and EU-approved Humira demonstrate similar affinity for binding to the high affinity Fc gamma

RIIIa receptor. The bars in red, again, represent the quality range provided by the applicant.

We also note these further demonstrate that slight differences in afucosylation levels between ABP 501 and US-licensed Humira are not considered to have clinically significant consequences.

To assess CDC activity of ABP 501 and US-licensed Humira, CHO M7 cells, again, were transfected to stably express a TACE-resistant form of transmembrane TNF alpha on their cell surface.

Those CHO M7 cells were loaded with calcium, and complement was added after incubation with different dose concentrations of antibody. The intensity of cell lysis was then assessed as a proportion of fluorescent signal.

These results demonstrate similar CDC activity is observed for all products. We also note it supports the conclusion that galactosylation-level differences between ABP 501 and US-licensed Humira are not considered to have clinically significant consequences.

As outlined in the previous slides,

functional assays were used to address any residual uncertainty in differences in critical quality attributes in glycan profile and their ability to influence product performance. The totality of evidence suggests that the slight changes in the glycan profile do not preclude a determination of high similarity.

The applicant also compared the ability of ABP 501 to bind to only the transmembrane form of TNF alpha. Binding to the transmembrane form is necessary to begin the reverse signaling mechanism of action that may be necessary for efficacy in IBD indications. Three lots of each product were evaluated in this assay. As depicted in this slide, similar affinity is observed for each product.

Amgen also developed assays to measure and compare the induction of regulatory macrophages based on the possible role this mechanism may play in irritable bowel diseases.

Though distinct from reverse signaling, this mechanism is considered plausible to explain the

efficacy in these indications. The study used a mixed lymphocyte reaction, which evaluated the induction of regulatory macrophages through an assessment of their ability to inhibit T-cell proliferation, which has been proposed in recent literature.

Primary PBMCs were incubated with the three products and evaluated for activity. Data representing cell proliferation are presented in this slide alongside controls that reflected the inclusion of either a control antibody or no antibody.

As seen, similar activity was observed for ABP 501, US-licensed Humira, and EU-approved Humira. Though not included in this presentation, Amgen also thermally degraded samples of ABP 501 prior to a second evaluation in this MLR study and demonstrated the assay to be sufficiently sensitive to observe diminished activity for degraded samples.

As summarized in the previous slides, the applicant provided data that evaluated the binding

and neutralization of TNF alpha, binding to transmembrane TNF alpha, CDC activity, and ADCC activity.

Additionally, the applicant performed a mixed lymphocyte reaction in the presence of ABP 501 and US-licensed Humira, which evaluated the induction of regulatory macrophages based on the resulting decrease in cell proliferation.

Additional functional data in support of evaluation of reverse signaling as one of the potential mechanisms of action in IBD is pending at the time of this presentation, denoted as the asterisk.

These data were requested, but the request was not made in sufficient time to allow for their inclusion in this presentation. Based on the extensive characterization of ABP 501 and US-licensed Humira, no differences in the functional reverse signaling data are expected.

These data, if determined to be adequate during the course of the 351(k) BLA review, would further support a demonstration that ABP 501 is

highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.

In summary, the extensive comparison of the functional, physicochemical, protein analytical, and higher order structure attributes of ABP 501 and US-licensed Humira support a demonstration that the proposed biosimilar is analytically highly similar to US-licensed Humira.

Amgen provided a sufficiently robust analysis for the purposes of establishing the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical studies that used EU-approved Humira to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira.

As noted in the previous slide, additional data in support of evaluation of reverse signaling as one of the likely mechanisms of action in IBD is pending at the time of this presentation.

These data, if determined to be adequate

during the course of the 351(k) BLA review, would further support a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. Thank you.

FDA Presentation - Jianmeng Chen

DR. CHEN: Thank you, Dr. Welch.

Good morning, everyone. My name is Jianmeng Chen. I'm from Office of Clinical Pharmacology. In my presentation, I will cover the clinical pharm component of this submission.

The objectives of clinical pharmacology program are to evaluate the pharmacokinetic similarity between ABP 501 and the US-licensed Humira, and to assess if the PK element of the scientific bridge between ABP 501, US-licensed Humira, and EU-approved Humira has been demonstrated to allow the use of data generated using EU-approved Humira.

As such, three studies were conducted to assess PK similarity, including study 217, a pivotal three-way PK bridging study in healthy

subjects, and two supportive studies for PK assessment in patients.

The trough concentrations were collected in RA patients in study 262 and psoriasis patients in study 263. In brief, our assessment showed that the PK similarity was demonstrated between ABP 501, EU-approved Humira, and US-licensed Humira.

Study 217 is a three-way PK bridging study. It's a randomized, single-blind, parallel-group, single-dose clinical study. A total of 203 healthy subjects were enrolled and randomized to three parallel arms, with 67 to 69 subjects in each arm.

All subjects received a single dose of 40 milligram of either ABP 501, US-licensed Humira, or EU-approved Humira through a subcutaneous injection by prefilled syringe.

The primary PK endpoints included Cmax, AUC last and AUC infinity. The study design elements and the PK similarity assessments were aligned with the FDA guidance for industry, clinical pharmacology data to support a demonstration of biosimilarity to a reference product which was

published in May 2014.

The PK results of study 217 is presented in this slide. The plot on the left panel demonstrated the PK profiles following administration of ABP 501, US-licensed Humira, and EU-approved Humira. As you can tell, following three different treatments, the PK profiles for all three products were overlapped.

On the right is the PK similarity analysis table. We compared the ABP 501 versus US-licensed Humira, ABP 501 versus EU-approved Humira, and EU-approved Humira versus US-licensed Humira for Cmax, AUC last, and AUC infinity, and presented the geometric mean ratio with 90 percent confidence interval for these comparisons.

Our analysis saw that the PK similarity was established for all the comparisons, and this is consistent with applicant's data analysis.

The trough concentrations of adalimumab were assessed in RA and psoriasis patients in clinical comparative studies. As you can see, the overall trough concentrations from week 12 in RA patients

and week 16 in psoriasis patients were similar between ABP 501 and the Humira treatment groups, and also between studies.

In summary, the PK similarity has been demonstrated between ABP 501 and the US-licensed Humira. PK data also support the scientific bridge between the US-licensed Humira and EU-approved Humira to justify the relevance of comparative data generated using EU-approved Humira.

The overall PK results support the demonstration of no clinically relevant differences between ABP 501 and US-licensed Humira.

Now, Dr. Kim will present FDA's statistical findings for the RA study.

FDA Presentation - Yongman Kim

DR. KIM: Good morning. My name is Yongman Kim. I will be discussing the rheumatoid arthritis comparative efficacy results, which support the evaluation of whether there are clinically meaningful differences between ABP 501 and US-licensed Humira.

Here is outline of the topics I'll cover. I

will discuss the design and the results of the rheumatoid arthritis clinical study that compared the efficacy of ABP 501 and US-licensed Humira.

I will then address a few potential statistical issues that we have explored as part of review, and will end with some conclusions based on the totality of the comparative clinical data in RA.

Study 262 was a 24-week randomized, double-blind, parallel-group, comparative clinical study in 526 patients with active rheumatoid arthritis despite treatment with methotrexate. Patients were randomized in a one-to-one ratio to ABP 501 or US-licensed Humira. There were investigators in Europe, Latin American, and North America, including sites in the United States.

The primary endpoint was the ACR20 response at week 24. ACR20 is a binary endpoint defined by achieving at least 20 percent improvement in both tender and swollen joint counts, in addition to at least 20 percent improvement in three of five measures of disease signs or symptoms.

Secondary endpoints included the ACR50 and 70 percent improvement criteria, the Disease Activity Score based on assessment of 28 joints, and C-reactive protein or DAS28 CRP and the components of the ACR response criteria.

The applicant's planned primarily analysis was specified in 2011 and was based on comparing 90 percent confidence interval for the ratio in week 24 ACR20 response to a similarity margin of 0.738 to 1 over 0.738. FDA recommendations for these studies were under discussion and had not been established at the time. In 2011, FDA agreed to the applicant's proposal.

Further discussion of this protocol occurred in 2013 and 2015. In 2015, FDA's thinking on the similarity studies had evolved, and the recommendations regarding the use of the absolute risk difference scale and 12 percent margin were made. The applicant did not incorporate these recommendations into the protocol since the recommendations were received after the database was locked.

In addition to the primary analysis of ACR20 response at week 24, we also carried out additional analysis of key secondary endpoints in addition to sensitivity analysis to address the potential impact of missing data.

The determination of the similarity margin is critical because the margin determines what magnitude of difference in efficacy needs to be statistically ruled out with high confidence. We believe that a margin of plus or minus 12 percent on the absolute difference scale is reasonable.

We recommend the use of the absolute difference scale because it is the most clinically relevant scale for the benefit-risk evaluation and is typically used and well-understood as a method for phase 3 trials of new drugs and biologics in RA.

Our selection of the 12 percent margin was based on the examination of the published literature on the effect of Humira in addition to balancing the clinical importance of various differences in efficacy against the feasibility of

the different study sizes.

The lower bound of proposed similarity margin of negative 12 percent also corresponds to the retention of roughly 50 percent of conservative estimates of treatment effect size relative to placebo for Humira based on the lower confidence bounds from FDA meta-analysis.

The lack of agreed-upon similarity margin between the FDA and the applicant was not problematic in this case because the primary analysis rules out the 12 percent margin that we consider reasonable.

Here I describe the primary efficacy results from study 262. In the applicant's protocol-specified primary analysis among all randomized patients, 75 percent of patients on ABP 501 were ACR20 responders at week 24 as compared to 72 percent on US-licensed Humira. The estimated ratio between arms was 1.04, with 90 percent confidence interval of 0.95 to 1.13, which met the prespecified similarity margin.

On the other hand, in the FDA-suggested

analysis, 71 percent of patients on ABP 501 were ACR20 responders, as compared to 72 percent on US-licensed Humira.

The estimated difference between arms was negative 0.4 percent with a 90 percent confidence interval of negative 6.8 percent to 6.1 percent. This confidence interval ruled out the plus or minus 12 percent margin that we consider reasonable.

The lower confidence bound of negative 6.8 percent also corresponds to the preservation of approximately 75 percent of the conservative historical estimate of the effect of Humira. The responses were also similar between treatment arms when restricting to the subset of patients who adhered to the protocol.

This table displays mean differences between treatment arms for several important continuous secondary endpoints that capture different disease symptoms and quality of life. Mean improvements from baseline were similar between ABP 501 and US-licensed Humira for all key endpoints.

One important secondary endpoint is the composite disease activity score, DAS28. Each arm showed similar improvements from baseline of around 2 units, and the 95 percent confidence interval ruled out large differences in efficacy, in particular the upper confidence bound of 0.21 is considerably lower than 0.6 which has been specified by EULAR as a threshold for the moderate within-patient response and was prespecified by the applicant as the margin for this key continuous endpoint.

The similar improvements in DAS28 over time on two treatment arms is also evident in this figure, which displays mean scores at baseline and weeks 2, 4, 8, 12, 18, and 24.

The potential effect of missing data was one of the statistical issues we explored during our review. Although there was relatively low patient dropout in study 262, with around 6 percent of patients withdrawing during the 24-week study, but patient dropout can still impact the reliability of the evaluations of ACR20 response regardless of the

adherence, as well as evaluations of important continuous secondary endpoints like DAS28, because the applicant's prespecified analysis rely on strong and unverifiable assumptions about the missing data.

Therefore, we assessed the applicant's tipping point analysis to explore the sensitivity of results to violations in the assumptions about the missing data. The analysis estimated differences in efficacy between treatment arms under varying missing, not at random, assumptions about the unobserved outcomes.

The goal was to identify those assumptions -- in other words, the tipping points under which the confidence interval would no longer rule out unacceptable differences in the efficacy. Then the plausibility of those tipping points could be discussed.

This table displays estimated differences between ABP 501 and US-licensed Humira in the ACR20 response at week 24 regardless of adherence with varying assumptions about the missing data.

Since there are no scenarios under which the 90 percent confidence interval fails to rule out the plus or minus 12 percent margin in the ACR20 response, the tipping point sensitivity analysis largely support the findings of the primary efficacy analysis in study 262.

The last potential issue I will discuss is the importance of the assumptions of assay sensitivity and the constancy. To reliably evaluate whether there are clinically meaningful differences between two products, a comparative study must have assay sensitivity or the ability to detect meaningful differences between the products, if such differences exist.

A reliable evaluation of the degree to which the proposed biosimilar product preserves the effect of the reference product also relies on the constancy assumption, which is the assumption that estimates of the effect of reference product based on trials from the published literature are unbiased for the setting of the comparative study.

As described in the ICH guidelines,

historical evidence of sensitivity to drug effects in trials with a similar design and conduct to the comparative study, in addition to appropriate trial conduct, can help support the validity of these assumptions.

This table shows important characteristics of study 262, as well as four relevant historical Humira trials from the published literature with the concurrent placebo, which used FDA meta-analysis to inform the selection of the similarity margin.

It appears that the inclusion criteria, concomitant DMARDs, and baseline disease characteristics were reasonably similar between the historical trials and the comparative clinical study.

Furthermore, the Humira ACR20 response rate in the comparative clinical study was consistent with the historical trials, and the patient withdrawal was relatively low. And we did not identify any critical conduct issues in the comparative clinical study. Therefore, the

available information largely supports the assumption that the study had assay sensitivity in addition to the constancy assumption.

I'll finish with some concluding remarks. The applicant's large comparative clinical study in RA demonstrated similarity between the treatment arms with respect to the primary and key secondary efficacy endpoints. As part of our review, we identified and explored a few important statistical issues, but do not believe that these issues affect the overall conclusions.

Therefore, the evidence from the clinical study 262 supports a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira. Thank you.

FDA Presentation - Kathleen Fritsch

DR. FRITSCH: Good morning. My name is Kathleen Fritsch, and I'm one of the biostatistical reviewers for this application. I will be presenting the efficacy results for study 263, the comparative clinical study in subjects with moderate to severe plaque psoriasis.

Study 263 had two parts. The first part evaluated the clinical similarity of ABP 501 and EU-approved Humira in 350 subjects with moderate to severe plaque psoriasis. The primary endpoint was the percent improvement in PASI score from baseline to week 16. The secondary endpoints were PASI 75, response on the physicians' global assessment, and change from baseline in body surface area.

Subjects with at least 50 percent improvement in PASI at week 16 continued to the second treatment period, from week 16 to week 52. Subjects originally randomized to ABP 501 continued on ABP 501, while subjects originally randomized to EU-approved Humira were randomized to either continue EU-approved Humira or switch to ABP 501.

The primary endpoint was the percent improvement on PASI from base line to week 16. The primary analysis was prespecified as a 95 percent confidence interval for the difference in means, using estimates from an ANCOVA model adjusted for baseline PASI, geographic region, and prior biologic use for psoriasis.

The applicant also submitted results based on 90 percent confidence intervals. The prespecified margin was plus and minus 15 percent. The primary analysis population was the full analysis population, defined as all subjects randomized and dispensed medication with at least one post-baseline visit. Missing data was handled using last observation carried forward.

Approximately 95 percent of the subjects completed treatment through week 16 on both arms, and the most common reasons for treatment discontinuation were adverse events and consent withdrawn.

This table presents the results for the primary endpoint. The mean percent improvement in PASI at week 16 for subjects treated with ABP 501 was 81 percent, compared with a mean of 83 percent for subjects treated with EU-approved Humira. The treatment difference was minus 2.2, and the 95 percent confidence interval ranged from minus 7.4 to plus 3.0.

FDA has typically recommended 90 percent

confidence intervals for comparative clinical trials such as this one, which controls the type 1 error rate at 5 percent.

The applicant also submitted results using 90 percent confidence intervals. The 90 percent interval ranged from minus 6.6 to plus 2.2. Both intervals fell within the applicant's prespecified margin of plus and minus 15 percent and therefore met the prespecified criteria for similarity.

The results were similar on the per-protocol population and under a variety of sensitivity analyses for the handling of missing data and supported the main conclusion.

The secondary endpoints were PASI 75, which is at least a 75 percent improvement in PASI, clear or almost clear on the physician's global assessment, and change from baseline in body surface area. No margins were prespecified for evaluating these endpoints statistically.

For these three endpoints, the outcome of the ABP 501 arm was slightly lower than on the EU-approved Humira arm. Because the PASI and PGA

scales both measure the same underlying signs of erythema, scaling, and plaque elevation, the fact that all these endpoints trend in the same the direction within a study is not unexpected. In addition, we would expect greater variability for dichotomized end points versus those based on means.

We also see that the magnitude of the difference in PASI response rates depends on exactly which cutoff point is selected, with smaller treatment differences when PASI 50 is considered and essentially no treatment difference for PASI 90.

Therefore, FDA does not believe that the differences observed in the secondary endpoints are clinically meaningful, and the secondary outcomes do not preclude a conclusion of no clinically meaningful differences.

To interpret a study like 263 that does not include a placebo arm, we need to be confident that the study satisfies key assumptions such as assay sensitivity, which is the ability to detect

meaningful differences if they were to exist.

In addition, we want to be assured that the study was not conducted in a manner that could bias the results toward similarity, and that the specified margin was appropriate.

We want to have confidence that the margins are narrow enough that if there are clinically meaningful differences between the products, that we would be able to detect them.

To assess the assay sensitivity assumption, we compared the inclusion criteria and results of study 263 to the published results of placebo-controlled studies of Humira. The inclusion criteria and baseline PASI scores in study 263 were comparable to the two phase 3 Humira studies, denoted as Saurat and Menter.

The percent improvement in PASI result was also similar across the studies. Therefore, the assay sensitivity assumption appears reasonable. FDA did not identify any issues with the study conduct. Thus, the final question is to assess the appropriateness of the applicant's proposed

similarity margin.

The applicant did not provide justification in the protocol or study report for their proposed margin of plus or minus 15 percent. As the protocol was not submitted to FDA prior to the start of the study, the margin was not discussed with FDA.

Ideally, we could just select an appropriate margin that represents broad agreement of what differences are not clinically meaningful. However, in practice, there will usually be tensions between feasible sample size and the preference for narrow margins.

FDA took two approaches to assess the applicant's margin. For the first approach, FDA computed the percent preservation of effect for which the idea is to ensure that the test product would maintain at least some benefit relative to placebo.

However, the goal of the comparative clinical study is to support the demonstration of no clinically meaningful differences. So FDA also

evaluated what margins would lead to an adequately powered study for a given sample size.

To assess the margin, we will need to look at the estimates available from published studies. Unfortunately, because the percent improvement in PASI was a secondary endpoint in the Humira studies, limited published information is available for this endpoint. We have the mean values for the percent improvement, which lead to treatment difference estimates in the range of 56 to 61 percent but no standard deviations.

Using these point estimates, we can calculate that a 15 percent margin corresponds to a retention of approximately 75 percent of the historical treatment effect estimate of about 60 percent. However, to evaluate the study's power for a given margin and sample size, we will need some reasonable estimates of the variability.\

Even though the Humira studies did not publish standard deviations, standard deviation estimates are available from two other studies of TNF alpha inhibitors, one Enbrel and one Remicade

study.

Because these trials enrolled similar populations, the estimated standard deviations from these studies may be reasonable estimates for Humira as well.

The Enbrel and Remicade studies had estimated standard deviations of 21 and 31, respectively. Using estimates within this range may be reasonable for estimating study power.

Using the sample size proposed in the protocol of 340 subjects and the assumption that the two treatments would have the same effect, we get a sense of what margins would lead to a design with adequate power.

From this graph, we see that the study of the proposed design and sample size would be adequately powered for a margin of about plus or minus 11 percent using the larger and therefore more conservative standard deviation estimate of about 30.

We note that study 263 would meet similarity criteria for any bounds of magnitude 7 or larger

for the 90 percent confidence intervals. Thus, even if there's a lack of consensus on the appropriate margin, this study would meet reasonable margins that could have been selected under these assumptions.

In summary, for study 263, the estimated treatment difference for the percent improvement in PASI endpoint was minus 2.2, with 90 percent confidence intervals ranging from minus 6.6 to plus 2.2. The endpoint met its prespecified criteria of a 15 percent margin.

The results were consistent across various sensitivity analyses for missing data. And although the secondary endpoints trended towards slightly lower response for ABP 501 relative to EU-approved Humira, the results are generally consistent with the primary endpoint and the somewhat larger treatment differences for PASI 75, and sPGA success may be due to the increased variability associated with dichotomized endpoints.

The magnitude of a treatment difference is smaller at other common cut points, such as PASI

90. Thus, we note that study 263 supports a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

FDA Presentation - Keith Hull

DR. HULL: Good morning. My name is Keith Hull, and I'll be discussing the safety and immunogenicity results for the clinical program for ABP 501.

The safety data are derived from clinical studies that used US-licensed and EU-approved Humira as a comparator. As previously discussed, the applicant has established a scientific bridge to justify the relevance of the safety data generated by the EU-approved Humira in the ABP 501 program.

The safety population in the clinical program is comprised of over 1,000 individuals, including patients with RA, psoriasis, and healthy subjects.

The overall safety database is adequate to provide a reasonable comparative safety and immunogenicity assessment using the approved dosing

regimens of Humira.

The safety analysis did not identify any new safety signals compared to the known safety profile of Humira. And there were no reported deaths, and the overall incidence of adverse events of immunogenicity were similar between the treatment groups.

This table provides an overview of the safety profile for ABP 501 in the core controlled studies. At the top of the table, going across, are the randomized, controlled, repeat-dose studies in RA, psoriasis, and a single-dose PK study in healthy subjects.

In each study, the overall incidence of adverse events, serious adverse events, adverse events leading to discontinuation, infections, malignancies, liver enzyme elevation, injection site reactions, and anaphylaxis were similar between ABP 501 and the comparator products. There were no deaths reported in the ABP 501 clinical development program.

Assessment of immunogenicity is an important

part of the safety analysis for any therapeutic protein product or biologic drug since hypothetically, antidrug antibodies may result in reduced clinically efficacy, hypersensitivity, or injection-related reactions.

Consequently, immunogenicity assessment of a proposed biosimilar product is an expected component of the 351(k) licensing application. In this case, immunogenicity was prospectively assessed in the ABP 501 development program during the RA and psoriasis controlled studies; the psoriasis extension study, including a single transition from EU-approved Humira to ABP 501; as well as the healthy subject PK study.

This table describes the cumulative incidence of antidrug antibodies and neutralizing antibody formation in the controlled studies in RA and psoriasis patients, as well as healthy subjects.

The rates of immunogenicity, assessed as the proportion of antidrug antibody and neutralizing antibody-positive patients, were similar between

the ABP 501 and comparator Humira treatment arms during the controlled periods of the study.

During the psoriasis extension study, the rates of antidrug antibody and neutralizing antibody positivity were similar between patients who underwent a single transition from EU-approved Humira to ABP 501 compared to those subjects who remained on EU-approved Humira, providing a reassurance that non-treatment-naïve patients could be transitioned safely from ABP 501.

Of note, the lower rates of antidrug antibody formation in RA patients compared to the other groups is most likely due to the administration of concomitant immunosuppression with methotrexate compared to the psoriasis patients who are not on background immunosuppressive therapy.

The impact of binding antidrug antibodies and neutralizing antibody formation was also examined in the ABP 501 controlled and extension studies, and can be summarized as follows.

Similar rates of antidrug antibody and

neutralizing antibody formation were observed between ABP 501 and US-licensed and EU-approved Humira in the RA and psoriasis studies, respectively.

Antidrug antibody and neutralizing antibody formation had similar impact in both ABP 501 and US-licensed and EU-approved Humira groups with respect to exposure and immune-mediated safety outcomes, including hypersensitivity and injection site reactions.

While there is no clear differential impact on clinically efficacy outcomes, small differences were noted between ABP 501 and Humira in the limited number of neutralizing antidrug antibody-positive patients.

In evaluating this observation further, the FDA considered the following. First, the apparent differences in the treatment responses were also seen at week 4, when the majority of subjects were neutralizing antibody-negative, indicating that these differences were not related to neutralizing antibody status.

Additionally, there is no differences in neutralizing antidrug antibody titers between ABP 501 and US-licensed Humira in study 262 or between ABP 501 and EU-approved Humira in study 263.

The sample size of the subgroups is small, resulting in wide confidence intervals. Further, exploratory post hoc statistical models, including the neutralizing antibody by treatment interaction, were analyzed for both studies.

These analyses did not identify a statistically significant differential impact of neutralizing antibodies on efficacy between ABP 501 or the comparator Humira products.

In light of these additional contextual pieces, the agency believes that the apparent numerical difference in the clinical responses in neutralizing antibody-positive patients do not preclude a finding of no clinically meaningful differences between ABP 501, US-licensed Humira, and EU-approved Humira.

Collectively, these data do not indicate

that the antidrug antibody formation differentially impacts safety and efficacy between patients treated with ABP 501 and US-licensed Humira or EU-approved Humira.

There are sufficient data supporting similar rates of immunogenicity between ABP 501, US-licensed Humira, and EU-approved Humira that the immunogenicity data adds to the totality of evidence to support a demonstration of no clinically meaningful difference between ABP 501 and US-licensed Humira.

In summary, safety outcomes, including immunogenicity, were similar between patients treated with ABP 501 or the comparator Humira products. No new safety signals were identified in the ABP 501 clinical program compared to the known safety profile of Humira.

In an aggregate, the safety and immunogenicity results add to the totality of evidence to support the conclusion that there are no clinically meaningful differences between ABP 501 and US-licensed Humira. Thank you.

FDA Presentation – Nikolay Nikolov

DR. NIKOLOV: Good morning again. In the next 10 minutes or so, I will provide an overview of the scientific justification provided by the applicant to support a demonstration that no clinically meaningful differences are expected between ABP 501 and US-licensed Humira across the indication sought for licensure.

I should acknowledge that the review of this application and the considerations for extrapolation were a collaborative effort among multiple disciplines and subject matter experts, including our gastroenterology and dermatology colleagues.

Amgen is seeking a licensure of ABP 501 for multiple indications for which U.S. Humira is licensed. The clinical program, however, provides clinical efficacy and safety data primarily from clinical studies in patients with rheumatoid arthritis and plaque psoriasis.

As a scientific matter, the agency has determined that it may be appropriate for a

biosimilar product to be licensed for one or more additional indications for which the reference product is licensed based on data from a clinical study or studies performed in only one indication, such as rheumatoid arthritis, and in the case of ABP 501 program, plaque psoriasis. This concept has previously been introduced as extrapolation.

To better illustrate this, I will compare and contrast the stand-alone drug development versus the biosimilar development program, which is consistent with what Dr. Christl presented earlier this morning.

The goal for stand-alone development program for innovator biological products is to demonstrate that the product is safe and effective. Drug development starts with the preclinical research, moves to phase 1, phase 2, and culminates in phase 3 pivotal studies in each indication to demonstrate safety and efficacy for each indication. This is the model of drug development that most individuals are familiar with.

In contrast, in the biosimilar development

pathway, the goal is to demonstrate high similarity and no clinically meaningful differences between the proposed biosimilar product and the reference product, with analytical similarity being the foundation of this assessment.

The goal is not to independently establish safety and effectiveness of the propose biosimilar in each indication, which represents a different paradigm in drug development which we would like the committee to consider.

In the demonstration of biosimilarity, the applicant may also include extrapolation of data, with appropriate scientific justification, which should address issues like potential differences in mechanism of action, PK or biodistribution, immunogenicity, and safety for each indication.

The FDA has also determined the differences between indications do not necessarily preclude extrapolation, but any differences need to be adequately addressed.

In this context, to support the extrapolation of data across indications, the

applicant provided a comprehensive data package to address these scientific considerations.

First, the applicant provided data to support the demonstration that ABP 501 is highly similar to US-licensed Humira with respect to primary, secondary, and higher order structures, post-translational profile and in vitro functional characteristics, purity stability and potency, including TNF alpha binding and neutralization.

Further, the clinical data submitted support the conclusion that no clinically meaningful differences exist between ABP 501 and US-licensed Humira based on similar clinical pharmacokinetics, similar safety, efficacy, and immunogenicity in the rheumatoid arthritis and plaque psoriasis using two approved dosing regimens.

Next, consistent with the principles outlined in the FDA guidance documents and previously discussed by the FDA, the applicant provided scientific justification for extrapolation of data to support that there are no clinically meaningful differences for the additional

indications sought.

Since similar PK profile has been demonstrated between ABP 501 and US-licensed Humira, as discussed by Dr. Chen earlier in the FDA presentation, and given the high degree of analytical similarity between the molecules, as discussed by Dr. Welch earlier, a similar PK and biodistribution profile would be expected between ABP 501 and US-licensed Humira in patients with juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, and ulcerative colitis.

In general, immunogenicity to US-licensed Humira was affected primarily by the use of concomitant immunosuppressive therapy across different indications rather than by patient population.

Consistent with these considerations, the applicant provided data demonstrating similar immunogenicity and safety, including immune-mediated adverse events such as hypersensitivity reactions and anaphylaxis, in two

different settings, rheumatoid arthritis and plaque psoriasis, using two approved dosing regimens either with or without concomitant immunosuppression with methotrexate.

Accordingly, similar immunogenicity and safety profiles would be expected between ABP 501 and US-licensed Humira in patients with juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, and ulcerative colitis.

Further, the applicant provided data to support the denomination that ABP 501 and US-licensed Humira have the same mechanisms of action for the specified indications, to the extent that the mechanisms of action are known or can reasonably be determined, as summarized in this table, and also that attributes relevant to these mechanisms of action meet the appropriate similarity acceptance criteria between ABP 501 and US-licensed Humira.

The primary mechanism of action of Humira, as stated before, is direct binding and blocking of

TNF receptor-mediated biological activities. The scientific literature indicates that this mechanism of action is the primary mechanism of action in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis, as well as juvenile idiopathic arthritis.

The data provided by the applicant showed similarity and have binding and potency to neutralize TNF alpha, supporting the demonstration of analytical similarity pertinent to this mechanism of action.

In addition, transmembrane TNF binding and Fc region-mediated mechanisms of action, which are potential mechanisms of action relevant to the IBD indications, were also similar between ABP 501 and US-licensed Humira.

On this slide I will summarize the scientific considerations for extrapolation of data in the indications being sought for licensure. First, the applicant provided data to support the demonstration that ABP 501 is highly similar to US-licensed Humira and has the same mechanisms of

action as US-licensed Humira.

Further, based on the totality of the data, demonstrating analytical high similarity, PK similarity, and no clinically meaningful differences in rheumatoid arthritis and plaque psoriasis between ABP 501 and Humira comparator products, similar PK, safety, and immunogenicity profiles are expected between ABP 501 and US-licensed Humira in patients with juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, and adult ulcerative colitis.

Therefore, based on these considerations, the agency believes that it's reasonable to extrapolate data to support a demonstration that there are no clinically meaningful differences for juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and the IBD indications between ABP 501 and US-licensed Humira.

In summary, the totality of the data submitted by the applicant supports a demonstration that ABP 501 is highly similar to US-licensed

Humira, and there are no clinically meaningful differences between ABP 501 and US-licensed Humira.

Based on the premise that the additional functional data on the reverse signaling to be provided by the applicant would be adequate, the FDA believes that the data submitted in the BLA support licensure of ABP 501 for the indications for which U.S. Humira is licensed and for which Amgen is seeking licensure of ABP 501.

On behalf of the FDA presenters, I wish to acknowledge our colleagues from multiple disciplines and review divisions who put a lot of work and effort into the review of this application in preparation for today's meeting.

We also wish to thank the advisory committee members for your attention and look forward to your discussion and comments.

Clarifying Questions to FDA

DR. SOLOMON: Great. Thank you very much for that presentation.

We now have time for clarifying questions from the advisory committee. Dr. Adler?

DR. ADLER: Thank you. It's Jeremy Adler. I saw no data presented in either portion of the presentation about the patient weights or patient ages aside from them being only adult patients that were tested.

I was wondering if any data were available on the efficacy or safety across the weight ranges of patients -- for example, patients who are underweight, patients who are malnourished, or, of course, pediatric patients. And is it safe to extrapolate the indication to patient populations that have not necessarily been studied? Thank you.

DR. NIKOLOV: So maybe I can take this first. Nikolay Nikolov. So we have reviewed the data for subgroup analysis based on different demographic and disease characteristics. There were no differences between the ABP 501 and comparator products.

DR. ADLER: Were you provided data on the weight of patients, and was there any information on comparative differences in underweight or smaller patients compared to regular-sized adult

patients?

DR. NIKOLOV: So we have reviewed the data. I'm not sure whether we have it prepared for the presentation, though.

DR. SOLOMON: Dr. Brittain?

DR. BRITTAIN: My questions for the two statisticians. I think, in this particular scenario, a really revealing way to present the data is in terms of percentage benefit retained. And I wondered if you had done that, if you'd have a point estimate and confidence interval for the two studies' primary endpoints?

DR. LEVIN: This is Greg Levin. So as Dr. Kim noted, the margin of plus or minus 12 percent, one of the considerations was in terms of ensuring a certain percent preservation of effect.

It turns out that the confidence interval for the difference was considerably smaller than that margin. So if you look at the lower confidence bound of about minus 6 to 7 percent, as Dr. Kim noted, that would correspond to roughly

75 percent preservation of a lower confidence bound from historical studies.

Somewhere in the magnitude of at least three-quarter preservation, you have high confidence, assuming the constancy assumption holds. That's for the RA study.

DR. BRITTAIN: All right. Thanks. One other question. On slide 7, the one that's titled Impact of Neutralizing ADA, I'm not sure I understand the table exactly. I don't know if you can get that up there.

DR. SOLOMON: Do you know which part of the presentation?

DR. BRITTAIN: The presentation is safety and immunogenicity, and it's slide 7. Yes, I guess I wasn't really understanding -- you have N equals zero, N equals zero, N equals 17, zero, 1, 24. So are these means -- who are they for? Which Ns -- what subgroups do these means correspond to?

DR. NIKOLOV: These Ns that you're referring to, these are the number of subjects that were neutralizing antibody-positive at that time point.

DR. BRITTAIN: Right.

DR. NIKOLOV: So in the group of neutralizing antibody-positives at week 16 for study 263 and week 26 for the study 262, these were the cumulative number of patients that were positive for neutralizing antibodies at those time points.

But in that group, at week 4, essentially only one was positive for neutralizing antibodies in the EU Humira arm, and four and five from the other study, within that group, subgroup of neutralizing antibody-positive patients.

DR. BRITTAIN: I'm sorry. I'm still not really getting it. So for example, the 52.02 is the mean of which patients at week 4?

DR. NIKOLOV: If you're asking about the efficacy assessments at week 4?

DR. BRITTAIN: Yes. I see like the 52.02 for --

DR. NIKOLOV: Right. So this represents the efficacy in that subgroup of patients who were neutralizing antibody-positive at the end, but just

looked at earlier time points. And this is --

DR. BRITTAIN: Oh, okay. I get it. I'm sorry.

DR. NIKOLOV: This is to indicate that in this group, there was essentially no antidrug antibody-positive patients that -- and the differences were still observed, indicating that the neutralizing antibodies were not driving the difference.

DR. BRITTAIN: Yes. Okay. And it could be -- since these are not baseline characteristics, it could be comparing that N equals 17 of 48 to the N equals 24 of 62. It's not necessarily clear to me what that means.

DR. NIKOLOV: I understand your point, and I hope we clarified it.

DR. SOLOMON: Dr. Bilker?

DR. BILKER: I just wanted to ask, if this ABP 501 is ultimately approved, is it anticipated that post-marketing studies will be mandated to show that the extrapolation was correct for each of the extrapolated indications?

DR. NIKOLOV: A demonstration of biosimilarity would mean that FDA has determined that the molecules are highly similar and there are no clinically meaningful differences, and that would not be limited only to the indications that were studied.

The no clinically meaningful differences, which includes the extrapolation of the conclusion of no clinically meaningful differences, would apply to the other indications.

We would not expect to see differences even if they were studied. The FDA is not planning to request or to require post-marketing studies to confirm that.

DR. KOZLOWSKI: Steve Kozlowski, FDA. But we expect all biological products to have pharmacovigilance, and so that's a broad expectation for all products that would be approved.

DR. SOLOMON: Dr. Miller?

DR. MILLER: Donald Miller. Following up on the extrapolation, Humira was recently approved for

uveitis. So will extrapolation now occur to uveitis automatically, or will the company have to make some kind of application?

DR. NIKOLOV: So the extrapolation would apply to indications for which the applicant is seeking licensure. And those indications would be labeled if the product is determined to be biosimilar. There are certain indications that are protected under market exclusivity that would not be included, even if there is a sufficient scientific justification.

In the case of uveitis or hidradenitis suppurativa, the applicant is not seeking licensure for those. So they will not be labeled even if they provide a justification for the extrapolation to those indications until the expiration of orphan exclusivity.

DR. MILLER: Then after expiration of the patent, then it would automatically be extrapolated?

DR. CHRISTL: If a sponsor wanted to seek licensure for additional indications for which the

reference product was licensed at an appropriate time due to exclusivity or other issues, they would need to request licensure by the agency. They could submit a post-approval supplement requesting licensure of their product for that indication, and at such time, they would need to provide adequate data and/or information to support that particular indication.

DR. SOLOMON: Dr. Scher?

DR. SCHER: Jose Scher. So I'm going to back to the same table. I'm also having some trouble understanding the table of neutralizing antibodies.

Does this mean that -- let's just take the psoriasis patient -- does this mean that the delta in those patients that had positive neutralizing antibodies went down 48 points on a PASI scale score? Or is it related to the percentage of patients that achieved PASI 75? It's unclear to me. And if I may add the question as to whether or not these are statistically significant differences?

DR. NIKOLOV: I will start this and maybe have my statistical colleagues add to that. During the review, the FDA noticed these differences in neutralizing antibody-positive patients in the percent PASI change from baseline. The patients who were neutralizing antibody-positives on ABP 501, had slightly lower PASI percent change from baseline, which about 48 percent compared to 62 percent in the EU Humira group.

This is at week 16 at the time point of primary endpoint assessment. However, the same group of patients were essentially neutralizing antibody-negative at week 4, and the difference with the delta was still there in the percent change in PASI.

It was still lower in the ABP 501 compared to the EU Humira when they were neutralizing antibody-negative, suggesting that there are some other factors that drove this difference in this small subgroup.

DR. SCHER: So the data on brief is not what you're describing. So if you have an antibody-

negative individual, the response rate is similar to the overall patient population?

DR. NIKOLOV: Correct.

DR. SCHER: So this is a subgroup of patients that do develop neutralizing antibodies and their response is lower?

DR. NIKOLOV: Correct.

DR. SCHER: Statistically significantly lower?

DR. NIKOLOV: I don't think it's statistically significantly lower. These are post hoc subgroup analysis, and I can maybe let my statistical colleagues comment.

DR. FRITSCH: Yes. Kathleen Fritsch. There are very small groups, and as Dr. Brittain pointed, this is not a true subgroup analysis. Developing the antibodies happens during the treatment so it's not -- so you really need to look overall at the whole population.

If these effects are problematic with in terms of the antibodies, the only way you could be able to tell that is if, in the overall population,

you would see a significant difference.

It's helpful to see what those particular subjects look like, how they might compare to subjects who do not develop antibodies. But as both of those effects are post-treatment, it's just an exploratory analysis that doesn't really -- it's not a true subgroup analysis based on baseline factors.

DR. SOLOMON: Diane Aronson?

MS. ARONSON: Diane Aronson. I appreciate the applicant's transparency with the glycan mapping, and I have a question of the FDA about that.

While the difference was small, my information about sialic acid, an overexpression can help late-stage metastatic cancer cells enter into the blood stream.

Would the FDA consider any other hypervigilance about this in the labeling? Or because it's so slight, it's seen with Humira as well?

DR. WELCH: Joel Welch. I'd highlight again

that the sialic levels we're talking about are incredibly small for the products, you know, 0.2 versus 0.7 percent. In terms of labeling associated with that, I'll defer to perhaps someone else from FDA.

DR. KOZLOWSKI: I don't think that would be something that would have clinical concern for us, and therefore, I don't think it should be anything that should be labeled.

I mean, we have lots of antibodies in our bloodstream all the time, and they do have some sialic acid, too. So this is really not a variant or a change that is so different than the spectrum of what you would expect with antibodies.

As Dr. Welch noted, we magnify that graph to show you. If you did a hundred percent scale, you'd never be able to discern the differences between those points.

DR. SOLOMON: Dr. Becker?

DR. BECKER: Hi. I'm Mara Becker. As a pediatrician, one of the biggest challenges we have in using Humira is the discomfort of the

injections. I thought it was interesting that, at least in some of these data, that the injection site reactions were lower in ABP 501.

I remembered in some of my preparatory work that there may have been some differences in the acid/base components of this drug compared to adalimumab. I was wondering if anyone could comment on that or whether there was any information on comfort of the injection when they switched over in the psoriasis study.

DR. NIKOLOV: So I can speak for the FDA and mention that these differences would not be considered clinically meaningful from our perspective. I don't really know. Maybe we can leave it to the sponsor to address whether that might be due to differences in the formulation.

DR. MARKUS: Hi. I can address it. We don't it's clinically meaningful, different, either, but we don't have citrate in our formulation, which is probably associated with some of those observations.

DR. SOLOMON: Dr. Geller?

DR. GELLER: I was wondering about the long-term effects of neutralizing antibodies. Does that mean the drugs stops working? I guess the only question that can be answered is, what happens with Humira long-term when you develop neutralizing antibodies? And what happens after week 26 in those studies?

DR. NIKOLOV: This is Nikolay Nikolov again. The clinical significance of immunogenicity, which is either binding antidrug antibodies or neutralizing antidrug antibodies, it's very difficult to assess given the differences in the immunogenicity assays, the way to test for immunogenicity. So it's very difficult, for example, to compare between different immunogenicity assay, different programs.

I don't think we have a good idea about how long-term neutralizing antibodies would impact efficacy, for example. So the expectation is that the binding, the neutralizing antibody, would block the TNF inhibiting properties of the molecule and would result in reduced efficacy. But that's not

really consistently seen with patients who are neutralizing antibody-positives.

DR. SOLOMON: Dr. Adler?

DR. ADLER: A follow-up. It's Jeremy Adler. As a follow-up to that and related to some of the other questions, the subgroup of patients who were switched from the Humira to ABP was only 77 patients, and 25 percent of them developed neutralizing antibodies.

I understand that this was not statistically significant. But it such a small sample size, it seems to me an overstatement to say that there are no significant differences with such a small sample size.

DR. SOLOMON: I think you're referring to the table on slide 5, Incidence of ADA?

DR. ADLER: Yes, that's correct, Incidence of ADA. It's under plaque psoriasis, study 263, the fourth column from the right.

DR. NIKOLOV: This is Nikolay Nikolov again. Maybe I should step back and try to explain the rationale for the FDA's expectation of asking for

these transition data.

I think our primary concern has been to ensure a safety in case there is transition between the reference product to the proposed biosimilar, whether there might be any major devastating immune-mediated adverse events, such as anaphylaxis or something major with respect to safety.

Immunogenicity is certainly a part of that assessment, but we're looking really for major adverse events or major differences. The sample size, even though small, is somewhat reassuring that there are no major differences between the patients who transitioned and patients who continued.

DR. ADLER: But this is too small a sample size to even comment on major adverse events because if there's an anaphylaxis that occurs in, let's say, 1 percent of patients, you don't have the statistical power to detect the difference with 77 patients in one group. I don't mean you. I mean in general, we don't have the power to detect the difference.

DR. NIKOLOV: I think in our view, a sample size of this range is reasonable, again, to identify any big immune-mediated events.

DR. SOLOMON: Could I just ask a follow-up? You had said if in the event that there's a change between products -- so this gets to this interchangeability question -- I just wanted to ask somewhat of a philosophical question.

Do you anticipate that if this was -- if the applicant had asked for interchangeability, would that have been approved here?

DR. NIKOLOV: No. I think the agency is still developing the interpretation of the -- or the implementation of the interchangeability parts of the regulation. So we haven't come out with a public statement, so I cannot really comment on that. But we clearly don't think that this study of this design would be sufficient to address the interchangeability aspect, again, given the caveat that we haven't come out publicly with a policy on that matter.

DR. CHRISTL: Right. This is Leah Christl.

In the context of demonstrating biosimilarity, we're looking for certain products where they're given to patients that are immunocompetent, could mount an immune response, that we would want to look at the safety of that product for patients who had been previously treated with the reference product, so these non-treatment-naïve patients; whereas part of the prescribing decision, a prescriber may choose to then prescribe the biosimilar product.

So we're looking in a descriptive manner as to whether or not there were any very large or overt safety differences, if that happened in the context of that single transition.

The single transition does not go toward switching or alternating between the products that would be expected in terms of data to support that pharmacy-level substitution. What we're talking about is data looking at a single transition that could support a prescribing decision for these products.

DR. KOZLOWSKI: Steve Kozlowski, FDA. The

comment about the size of this data and major differences, I think you have to think about this data in the context of all the other data you've seen. So there isn't a difference in immunogenicity when you compare the products before this in two indications, one with an immunosuppressant, one without. There's all this data about how similar the structure of the molecules is.

Then you have a study of a smaller number of patients just look, well, is it doubling? Is there something huge happening? And that's not happening. So to think of this study alone as the support for the immunogenicity, I think, is really not considering the huge amount of data that you have from other parts of this and this totality of evidence.

Although the transition may be a risk in itself, it's a risk that has to consider all the other data that the immunogenicity isn't different.

DR. SOLOMON: Dr. Waldman?

DR. WALDMAN: Yes. I want to go back to

extrapolation. The clinical studies that were done demonstrated biosimilarity where the mechanism of action is known to be neutralization of TNF. So I think it's fair to extrapolate to other indications where that's the known mechanism of action, the other arthritides. But in inflammatory bowel disease, the tables that we were provided in the literature suggest that that neutralization of TNF alpha may not be sufficient to be clinically active in that disease.

I guess my question has to do with whether in the absence of a clinical comparison in inflammatory bowel disease populations, we have enough information to jump from the in vitro analyses that we have to essentially clinical efficacy. That's the question.

DR. NIKOLOV: I will start and have my colleagues to add. And I'll get to Dr. Kozlowski's point that we're reviewing the application in its totality. We are heavily relying on the analytical similarity. And most of what's assessed analytically is a lot more sensitive than the

clinical endpoints that are used for assessing no clinically meaningful differences.

That's true for almost all the clinical indications that are at least proposed for licensure. This is the reason we approach the extrapolation based on the knowledge about analytical similarity with the lining up PK similarity, and additional supportive evidence from two indications -- we would generally expect one, but in this case two indications -- that supported the molecule is active, not just in vitro but in vivo.

This is really the primary driver for supporting the extrapolation argument for the indications that we don't have direct clinical data for. I don't know if that addresses or answers your question?

(Dr. Waldman negatively shakes head no.)

DR. NIKOLOV: No. So let me ask: You would want clinical data in those indications? That's my --

DR. WALDMAN: So to be very direct, the in

vitro systems are artificial and rigged, I mean appropriately rigged. We do laboratory work all the time, so we set these systems up. They're very sensitive, but they hyper-amplify signals. So it might, in fact, be difficult to see differences when the differences would cull out better in lower responsive systems. That's one piece of it.

The other piece of it is if you look at the mechanism of action table for the inflammatory bowel disease, what scares me, what concerns me about that table is the mechanism of action of activity in inflammatory bowel disease likely plausible -- what concerns me is what we don't know on that table that might be biologically mediating the effects of these agents in those indications.

So given that there is a little bit of a black box built around those diseases and the activity of these agents in those diseases, I would have felt more comfortable extrapolating to inflammatory bowel disease if a comparison had been done in inflammatory bowel disease. Just one guy's opinion.

DR. SOLOMON: Dr. Margolis?

DR. MARGOLIS: Yes. So I must admit I'm having trouble with the semantics of biosimilar interchangeability, and now the cute word "bridging." So you allow a bridging study to show that the UK and the U.S. Humira were the same; yet analytically, in analytic studies, we show there were slight differences, just like there are with ABP and Humira.

But when asked if these studies were good enough to show that there's interchangeability, which must be true if you're going to allow the UK product and the U.S. product to actually be the same for all these studies, but that's not going to be true with this product.

It seems to me that there's -- you already know what interchangeability is because you said you could do a bridging study, which seemed to be very unrigorous, if that's a true word. But now you're telling us that you don't know what interchangeability is.

So are the UK products and the EU products

similar enough that they should be sold in the U.S.? Is it exactly the same product, and the analytic differences we're to disregard? Or what are you trying to tell us?

DR. KOZLOWSKI: I think the purpose of the bridging is to say that the EU-approved and US-licensed product are close enough that one can use it as a comparator in certain studies.

Even outside of biosimilarity, there are non-inferiority studies done for indications which may not use U.S. product to get a U.S. indication. And the key is showing that that comparator material is relevant for what you want to do. Is it relevant for a non-inferiority trial? Is it relevant for this exercise?

I also think the terminology really is confusing because interchangeability is probably a very tricky word to use to talk about that because interchangeability in the context of this refers to substitutability in a very specific set of additional standards.

I think the EU material is, is there enough

scientific bridging data based on analytics, and in most cases PK, to say that that's a valid comparator to use in a clinical study? And outside of biosimilarity, again as I noted, we've used that standard for other comparative studies.

DR. SOLOMON: Dr. Adler?

DR. ADLER: We've seen PK data today to show the equivalence between these different drugs, but this has all been adult data. And as a pediatrician, this does concern me that we've been shown no PK data in children.

Do we have sufficient evidence to show that those are similar populations between children and adults? I don't see enough data here to make me comfortable that there is sufficient evidence for similarity in children.

Are there data on -- that the PK is even the same in children?

DR. CHEN: This Jianmeng Chen from FDA. The PK similarity is done in healthy subjects in adults, and we don't have any PK data in children. So for ethical reasons, we cannot recruit healthy

children for PK study only.

For extrapolation from adult to children, we do not expect major difference in PK in terms of product difference regarding the highly similarity analytical analysis.

DR. NIKOLOV: Maybe I can add to that. There might be differences in PK between adults and kids, for example. But the question, the scientific question, that we're asking the committee to discuss is whether there are any differences between the molecules that would result in differential PK in the different indications.

In other words, are there differences between the molecules that you would see differences in the PK of the two products in kids than what you see in the healthy subjects which we considered a sensitive patient population to detect PK differences.

DR. ADLER: But we've been presented with no pediatric data at all. So even if the molecules have the same primary, secondary, tertiary structures, the quaternary structure -- we've,

first of all, seen no data on that. And we don't know that it's necessarily the same. This is a huge leap of faith.

DR. NIKOLOV: So we certainly acknowledge that there is no data, direct data, in many of the indications, including the pediatrics. But again, we ask the committee to think about totality of the data. And are there concerns that the PK, for example, would be different in kids?

DR. ADLER: Okay. The totality of the data includes no pediatric data.

DR. SOLOMON: We have two more questions, and then we're going to break for lunch. We have Dr. Geller and then Dr. Hohman.

DR. GELLER: I wonder if the response, the efficacy of Humira in kids, is similar to that in adults. That's asking for comparisons across clinical trials, which are not randomized comparisons. But nonetheless, if the response rate were far lower -- I mean, we're concerned with efficacy as well as safety here.

DR. NIKOLOV: So maybe I can start

addressing this and if someone else wants to add. But again, we have a substantial body of evidence of the molecules being similar, with the addition of the similar PK and similar efficacy in maybe partly or unrelated indications.

So the question is what differences or do we expect differences in the other indications that haven't been studied? We certainly acknowledge the discomforts of no data, or no direct data.

DR. SOLOMON: Dr. Becker, as a pediatric rheumatologist.

DR. BECKER: What I was going to say was certainly from a GIA perspective. The efficacy and safety of Humira is well-known, and we feel comfortable with that based on some clinical data that actually has some time associated with it, which is unlike many of the studies that we rely on.

So when I looked at these data, I did try to think about the construct of biosimilarity and how similar is this agent to the reference product that I do prescribe and do utilize and understand the

safety profile for.

I think those data are out there, at least for GIA, in some long-term efficacy studies and safety studies. I can't speak to IBD, I'm sorry. But certainly, I do utilize all these concepts that they keep relying on, which is the biosimilarity rationale, to help me think through extrapolating it to my patient population, which are smaller and more metabolic and all kinds of different things. So that's how I'm approaching it.

DR. SOLOMON: Dr. Hohman, you have the final question.

DR. HOHMAN: Yes. I'm Bob Hohman. So if you did these biosimilar studies on various lots of Humira, how would the differences -- would there be differences analogous to some of the differences we see between Humira and ABP 501?

DR. WELCH: I'm sorry. You're asking if the Humira itself varies in the trials?

DR. HOHMAN: Yes. Yes.

DR. WELCH: Part of the analytical similarity assessments is obtaining enough batches

of reference product to have a truly representative sample set. And that's the question, not just the number of lots but also sourcing a large range of dates as it being -- there could be some trends over time.

The applicant was able to obtain almost 2000 lots over a course of five to six years. So that's a very meaningful, I think, set of data. And then each one of the lots that was used within the clinical trial also was used in the similarity assessment.

DR. HOHMAN: Yes. But the analytical differences, some of these small analytical differences between Humira and ABP 501, would you find those same things with the different lots of Humira?

DR. WELCH: Well, in the context of the similarity assessment here, we're using Amgen's data. And based from the data, we showed you that there are some differences that they have presented as well.

DR. SOLOMON: Okay. I want to thank

everyone for an informative morning. We're going to break for lunch. We'll reconvene again in this room in one hour, at 1:15.

Please take any personal belongings with you. Committee members, please remember no discussion during lunch. The committee room is behind us, and I believe lunch is going to be brought there.

(Whereupon, at 12:15 p.m., a lunch recess was taken.)

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

(1:14 p.m.)

Open Public Hearing

DR. SOLOMON: Okay. Welcome back. If people can start taking their seats, we're going to reconvene, and it's going to be the public comments session.

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

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

For example, this financial information may include the sponsor's payment of your travel,

lodging, or other expenses in connection with your attendance at the meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your

cooperation with that.

So there's a roster of speakers. And speaker number 1, will speaker number 1 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. GINSBURG: Hello. Seth Ginsburg and the Global Healthy Living Foundation. I have no disclosures to make today regarding my travel. On behalf of the non-profit Global Healthy Living Foundation and its arthritis organization, CreakyJoints, I want to thank the FDA for its commitment to listening to a diverse set of stakeholders today. We are not scientists. We're doctors. We are patients.

Now, as the co-founder of Creaky Joints and the Global Healthy Living Foundation, I know about arthritis. I was diagnosed with spondyloarthritis at the age of 13.

For patients, biosimilars represent hope as well as fear. Hope for expanded treatment options through a broader formulary. Fear of being

switched from a drug that works to one they don't know, and not participating in the promised cost reductions.

Nevertheless, at Creaky Joints, we are optimistic about biosimilars and we look forward to seeing them in our therapeutic space, where through Arthritis Power, our PCORI-sponsored work as a patient-powered research network, we can track patient-reported outcomes.

In order to achieve the promise originally intended by the BPCIA in 2010, we are addressing patient and physician confidence. We believe the FDA and biosimilar manufacturers can support this effort by examining their supply chain and support services, creating unique naming and clear labeling, as well as interchangeability policy decisions that prevent payer-level switching for non-medical reasons. These issues will instill confidence.

For this particular BLA, we believe the applicant has shown exemplary effort to increase patient and physician confidence. First, they have

provided clinical studies that prove safety and efficacy for two indications, rheumatoid arthritis and psoriatic arthritis -- I'm sorry, and plaque psoriasis -- surpassing the FDA requirement of just one.

Second, the applicant created assays with high levels of sensitivity to gauge the biosimilarity of the molecule and the reference product. In the future, we suggest more weight be given by members of this committee to the sensitivity of the assays created by applicants -- well, some of us are scientists.

Although it's a controversial topic among the patient community, we support FDA's position to allow extrapolation. We understand that you can't have biosimilars without having extrapolation. It is needed in order to reduce cost and allow biosimilars to reach many patients, and once this expanded access and savings is achieved, our hope is that more healthcare dollars will be allocated to innovative therapies.

However, we respectfully oppose

extrapolation when the mechanism of action for the extrapolated indication is not clearly understood, or the drug is considered scientifically or therapeutically outdated. Science is only part of biosimilar success. Use and satisfaction is where success ultimately will be measured by us patients.

We sincerely thank the FDA for emphasizing the value of the patient perspective through public meetings, and we continue to mobilize our growing patient community to create a better life for those who will benefit from biosimilars. We have great confidence in the work you're doing here today, which in turn we hope will instill confidence in us patients and our families with biosimilars in the future. Thank you for the opportunity to be here.

DR. SOLOMON: Thank you.

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

MS. FOSTER: Good afternoon. My name is Wendy Foster, and I'm the senior advocate for

U.S. Pain Foundation. Neither I nor U.S. Pain has any conflict or received any compensation for speaking today.

I'm here today to discuss with you the importance of public safety within the chronic pain community, specifically, a practice used by insurers and benefit pharmacy managers, along with others not directly involved with a patient's treatment plan.

With the ever-changing technology, advances within medicine taking place, chronic pain patients appreciate the value of options in treating their invisible illness. As no two individuals are alike, healthcare providers have recognized the treatment for chronic pain is not a one-size-fits-all model.

As we move forward as a nation with pharmacological developments such as biosimilar medications, it is important to recognize how such alternative therapies may prove to be a disadvantage for pain patients.

Such an example into how new age technology

may lead to non-beneficial outcomes to patients includes the practice of non-medical switching. This is when a person, medically stabile on a treatment or medication, is switched to an alternative therapy option for non-medical reasons.

The decision is not one made out of the best interest of the patient, but an attempt to control costs. Such a practice can be detrimental to a person living with a rare, complex, or incurable chronic pain condition.

Patients who have been stable on their previous therapy may suffer negative side effects on their new therapy or become less responsive to treatment, even if returned to their original medication.

There are several ways by which a health plan can switch a stable patient to alternative therapy, regardless of the potential health impact or impacts it may have. Some of those include making formulary changes that limit or restrict access to a particular therapy, increasing out-of-pocket costs or moving a drug into a

disadvantaged tier during the year, and blocking the use of co-pay cards for certain drugs which then increases out-of-pocket costs.

Speaking as a chronic pain patient living with an unknown neuromuscular disease, Parkinson's, spinal stenosis, debilitating migraines, and the effects from a stroke, I can personally say to the committee that managing invisible illnesses, particularly for chronic conditions, is a very difficult and timely process. It may require several changes to medication before finding one that is effective for the patient with the least amount of side effects.

We go through years of painful trial and error, in some cases without emotional support from family members or friends, until we're able to work with a healthcare provider and together find therapy that works best for our individual bodies, conditions, and needs.

We can prevent a chronic pain patient from additional visits to the emergency room, appointments with their physicians, lab testing,

and hospitalization if we put the patients' best interests before insurers.

Non-medical switching is a gamble. You're taking a chance on a person's life when you deny them access to a treatment that is currently working and has been found to be the best option for their disease, disorder, or condition.

I thank you for your time in considering the need for new policies which will ensure public safety for consumers living with chronic pain. Thank you.

DR. SOLOMON: 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.

MR. SPIEGEL: Good afternoon. My name is Andrew Spiegel, and I am representing the Alliance for Safe Biologic Medicines today. I am reading the statement of our chairman, pediatric rheumatologist, Harry Gewanter, who was unable to attend the hearing today due to the sudden

hospitalization of his wife. We have no disclosures, financial disclosures.

"Biosimilars provide opportunities for increased access to more life-altering treatment options, hopefully at reduced costs to both the patient and society. While similar by definition, these are different molecules from the reference products and along with the size and complexity inherent in all biologics, have the potential to produce unexpected effects in patients, including unwanted and harmful immune responses.

"We support the FDA's history of intense and appropriate scrutiny of all medicines, both at the time of application, as well as throughout the medicine's lifespan. It is the only way to produce the high level of confidence necessary for biosimilars to be fully accepted and utilized by patients and their physicians.

"Reducing that level of confidence begins with maintaining and building the FDA's high approval standards. Thorough evaluations start with solid analytical and clinical biosimilarity

data, and proceed to clinical data focused on potential adverse effects and efficacy in the most sensitive situations.

"Since immunogenic effects may vary significantly between indications, the immunogenicity profile of a biosimilar should be studied in the patient popularity [sic] with the highest risk of an immune response.

"We believe the approval of a biosimilar should be decided on a case-by-case basis for each potential indication based on sufficient supporting data, rather than justifying an automatic blanket extrapolation to all indications. Ultimately, the burden of proof must be on the biosimilar manufacturer to demonstrate that the product is highly similar in structure, function, and in patient response to the reference product.

"For example, when Health Canada was considering approval of infliximab biosimilar, Inflectra, comparative data was only available for RA and AS. Approval was granted for a PSO and PSA, based on extrapolation, since these conditions have

similar mechanisms in action to RA and AS. But Health Canada did not approve for IBD indications, ulcerative colitis and Crohn's Disease, however, due to differences between Inflectra and the reference product that could have an impact on clinical safety data and efficacy of these products in the indications.

"Only when newly submitted data was presented and shared-- no new or unexpected safety signals in IBD -- did Health Canada then allow an extrapolation-based approval for the UCD and UC indications. We encourage the FDA to take this cautious, comprehensive, and data-driven approach to approval as well.

"Clear product identification is critical after approval to ensure safety and confidence in biologic medicines. We applaud the FDA's leadership in promoting distinct and distinguishable names for all biologics, innovator and biosimilar alike. We continue to believe that the benefits of distinct naming would be best realized through meaningful and memorable suffixes

such as that used in the FDA's approval of Zarxio.

"Memorable suffixes such as that -- indeed ASBM surveys show U.S. biologic prescribers prefer suffixes based on manufacturer name over random by a 6 to 1 margin. ASBM surveys of 401 pharmacists also showed 77 percent prefer manufacturer name-driven suffixes to random letters."

Thank you for your time, and I will be back in a few minutes to read my own remarks.

DR. SOLOMON: 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.

MR. SALCEDO: Good afternoon. My name is Robert Salcedo and I represent BioSciences Corp. And I have no conflict of interest to reveal. We at BioSciences have a mission to provide affordable biologics to billions.

First of all, congratulations to the Amgen team. Great work on the clarity of presentation, the robustness of your analytical similarity, the

transparency of the data in the science you presented today, the demonstration of the stepwise approach for your process and manufacturing program, and the extensive clinical program that you presented today. Congratulations.

Thanks for the FDA for making this historic day possible, the exhaustive assessment that these complex applications required and all the work that you've done to make something very complex, very simple. Thank you for the information you provided today and for the scientific rigor that you're showing in the evaluation of these biosimilars.

While all the work presented today is admirable, these large clinical trials are very expensive, which may defeat the purpose of the BPCIA. Where this data goes is to increase access and affordability for these very expensive drugs that are very nearly needed for our patients.

While patient safety is paramount, we encourage the agency to continue to push to sponsors to create a more analytical understanding as a way to reduce the costs in the conduct of

these unnecessary and very expensive clinical trials that would make this product very, very expensive.

We at Biosimilar Sciences have the mission to support companies to provide affordable medicines to patients all over the world. BioSciences encourages the agency's support to continue approval of these life-changing medicines, while continuing to evaluate the rigor of the science and continue to use science as the first step in their approval process.

Once again, BioSciences thanks the FDA for the openness of this forum, and for all the data you presented today. Thank you.

DR. SOLOMON: Thank you.

Will speaker number 5 step up to the podium and introduce yourself. Please state your name and any organization you are representing for the record.

MR. SPIEGEL: Good afternoon again. My name is still Andrew Spiegel and I still have no financial disclosures. The remarks that I will

present to you now are through my role as the Executive Director of the Global Colon Cancer Association.

Following the loss of both of my parents to cancer in 1999 within two days of each other, I co-founded the Colon Cancer Alliance to advocate for colon cancer patients around the U.S. In 2011, we broadened our efforts and founded the Global Colon Cancer Association, taking our mission to the global level, and that organization now advocates for more than six million colon cancer patients worldwide.

I also am representing today the Digestive Disease National Coalition, which I chair. The DDNC is a coalition of more than 50 patient groups and physician organizations dedicated to advocating for digestive disease patients.

Biologic medicines have helped more than 300 million people worldwide. These medicines have helped triple the life expectancy of the most advanced colon cancer patients, and we expect biosimilars to bring tremendous benefits to

patients, not only offering new treatment options, but doing so at a reduced cost.

We are excited to see biosimilars entering the U.S. healthcare system, but in order to feel comfortable using biosimilars, the patient community wants to know that they are as safe and effective as their reference products. Lack of clinical data and insufficient transparency regarding that data, can be obstacles to patient and physician confidence, and thus to widespread biosimilar adoption.

Because biosimilars, by definition, are not identical to their reference product, it is important that the FDA insist upon high standards for safety and efficacy when approving biosimilars. The manufacturer must be required to demonstrate the structural, functional, and clinical similarity of their product to the innovators.

Extrapolation is an area of concern for the patient community. At a minimum, approval for each indication should be granted individually rather than in an all-or-nothing approach.

Then I was going to discuss Canada, but since I did for Dr. Gewanter a couple of minutes ago, I'll skip that part. But I will reiterate that the approach taken by Canada was one that we would suggest for the FDA. We don't suggest that safe extrapolation is not possible. We simply think each indication should be approved individually based on solid data.

Once approved, information and transparent labeling that lets us make informed treatment decisions is critical to building confidence and increasing biosimilar use. For example, we need to know whether a biosimilar was evaluated in treating our disease, or whether the approval was based on extrapolation from clinical data in another disease. We want to know whether or not the product is a biosimilar and whether it's interchangeable with its reference product.

Further, comprehensive data collection on a biosimilar is also of utmost concern. Strong post-market surveillance data improves care and limits risks to patients. Real world data helps us

better understand use of these medicines and helps promote more efficient, safer, and personalized use. Strong post-approval pharmacovigilance will improve care and provide further confidence in biosimilar medicines.

Further, clear product identification and naming are critical to ensure safety and confidence in biologic products. We agree with the FDA's approach in promoting distinguishable names for all biologics. We continue to believe that the benefits of distinct naming would be best realized through meaningful, memorable suffixes. For patients to realize the benefits of biosimilars, we need to feel confident that our healthcare and our safety remains the primary concern and we need to be provided full and accurate information about each medicine in order to make informed choices.

Thank you for the opportunity to comment on this issue.

DR. SOLOMON: Thank you.

Will speaker number 6 step up to the podium and introduce yourself? Please state your name and

any organization you are representing for the record.

MS. LEMISKA: My name is Emily Lemiska and I am associate director of state advocacy for the U.S. Pain Foundation, a national non-profit created by people with pain for people with pain. I'll be reading the testimony of Casey Cashman, our executive director, who is unable to be here today. Neither I nor U.S. Pain have any conflicts.

We are both chronic pain patients living with rare, complex, and incurable conditions, and here is Casey's testimony, which has been adjusted slightly to fit the time limits.

"I am here to speak on behalf of not only my organization, but all people living with chronic pain. As the committee continues learning more about biosimilars, an exciting and promising medical advance for the future of many conditions, I'd like to contribute to the conversation another perspective of these therapies, which may not always prove to be in the best interest of patients.

"The U.S. Pain Foundation recognizes that biosimilars are structurally similar to biologics and are used to treat some of the same illnesses. But because of the complexity of duplicating living organisms, biosimilars have the potential to be less effective or cause more side effects.

"U.S. Pain has been active in state advocacy efforts to ensure patient safety and transparency are at the forefront of this discussion. We applaud those states that have passed legislation with provisions noting that biosimilar substitution should occur only when the FDA has designated a biologic product as interchangeable.

"We also appreciate those states that require a patient's treatment team to record how and when the patient was treated with biologics or biosimilars. However, we believe these provisions do not go far enough to protect vulnerable patients whose treatment plans can be easily altered, possibly with damaging consequences.

"We believe any switching of medication should only take place with the full knowledge and

consent of the prescribing physician in consultation with the affected patient. Insurers should not be playing doctor, but unfortunately many patients are being forced off their medications to an alternative therapy option to control costs. This practice, known as non-medical switching, occurs too often.

"Non-medical switching does not just ignore the delicate, time-consuming process physicians and patients undergo to find a successful medical therapy. It also disregards the negative health impact. When patients lose access to the therapy that stabilizes their condition, they may lose the ability to manage their disease, facing re-emerging symptoms and side effects.

"If the patient has an adverse reaction or the therapy is ineffective, it can result in additional, unnecessary doctor's appointments, emergency room visits and even hospitalization, and thus can increase overall costs.

"U.S. Pain and I recognize that highly targeted and even personalized therapies,

particularly biologic drugs, are revolutionizing the treatment of many life-threatening or chronic conditions, but it is clear there needs to be a fine balance between providing new and sometimes less expensive medications for those who are chronically ill and forcing patients from a stable therapy that has been managing their condition.

"Those of us living with chronic pain need and deserve to remain on the treatments that allow us to do basic things like stand before you today to testify. We have heard from many in the pain community who are scared of being switched off their medication or have suffered negative effects from switching.

"We ask that you consider the harmful impact of non-medical switching on patients as it relates to biosimilars and biologics. Please help restrict this harmful practice. Thank you."

DR. SOLOMON: Thank you.

Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the

record.

MR. CARDENAS: Good afternoon. My name is Jasey Cardenas of the United Spinal Association, and I'm speaking on behalf of Larry LaMotte, on behalf of the Patients for Biologic Safety and Access, PBSA. And we have no financial ties to disclose.

PBSA is a coalition of 24 patient advocacy organizations, including United Spinal Association, which is dedicated to protecting patient access to safe and effective biologics. We previously provided a full written statement for the record.

While communities are eager for new and affordable treatments, patients are keenly aware of the possible risks associated with biologics and biosimilars, including immunogenicity and the lack of long-term safety data of new treatments.

PBSA believes that the complexity of each biologic medicine requires that FDA ensures all biologic and biosimilars are thoroughly tested and meet the highest safety standards. Both the products currently under review by the Arthritis

Advisory Committee during these two days of consecutive meetings have far less clinical and post-market data than the first FDA approved biosimilar, Neupogen.

These two products before the advisory committee are much larger and more complex in structure, and yet for most of the indications there are only statistical data and very little clinical evidence. If there are doubts about the data for any indication, committee members should ask to vote on each indication rather than all of nothing vote.

A PBSA principle is that FDA should enforce the provisions of the biosimilar law, that a biosimilar must be highly similar to the reference biologic and that there are no clinically meaningful differences between it and the reference product in terms of safety, purity, potency, and potency of the product.

How can it be confidently determined that there are no clinically meaningful differences in the safety of products without corroborating

medical evidence? We ask the committee to thoroughly analyze and discuss the adequacy of data and medical evidence presented in terms of safety, particularly long-term safety.

When stabilized on biologic, patients are concerned about being switched for non-medical reasons to a non-interchangeable biosimilar. This was a point of substantial debate and discussion at the February 9th advisory committee meeting considering the infliximab biosimilar application.

At that meeting, committee members expressed concern about the potential for patients being non-medically switched to and from biosimilars multiple times, once non-interchangeable switching was allowed.

In a meeting in May with Dr. Woodcock and other FDA officials, PBSA brought up our concern about non-medical switching of biosimilars not deemed interchangeable. The law clearly addresses switching as allowable only if a biosimilar is deemed interchangeable.

Dr. Woodcock expressed at our meeting that

FDA could publish an official statement that switching a stable patient to a non-interchangeable biosimilar holds risks, and only physicians in consultations with patients should make or drive such a decision. We look forward to the agency issuing such a statement.

However, in its comments today on the ABP 501 application, the FDA once again endorses a single transition for non-treatment-naïve patients. We believe this to be unacceptable. Our concerns about non-medical switching have been heightened by the new potential presence in the market of three approved biosimilars for the same indications by several patients of new information.

Recently, pharmacy giant CVS published, "Basics about Biosimilars: The Saving Potential and the Challenges." In it, they spell out an aggressive intention to switch patients to biosimilars. They state because biosimilars are therapeutically equivalent to reference biologics, we expect minimal grandfathering of patients, and since the February meeting, there is additional

evidence of the safety and efficacy of switching the previously approved biosimilar, infliximab.

The analysis of Danish government policy allowing non-medical switching revealed that those who have been under treatment of Remicade and were switched to infliximab for non-medical reasons found that 7 percent of patients stopped treatment due of lack of effect of the biosimilar.

Thank you for the opportunity to provide the views of patients on the biosimilar approval process.

DR. SOLOMON: Thank you.

Will speaker number 8 step up to the podium and introduce yourself? Please state your name and any organization that you are representing for the record.

MR. PITTS: Good afternoon. My name is Peter Pitts. I'm the president of the Center for Medicine in the Public Interest and I have not received any funding to participate in this hearing.

Today's discussion has been wide-ranging.

I'd like to focus specifically on two issues: patient safety and clinical outcomes.

If the FDA chooses to approve this product, it'll be the first time that an adalimumab biosimilar will be available, a true biosimilar, anywhere in the world. Attention must be paid. The sponsor today is not requesting that the FDA designate this biosimilar as interchangeable, nor is the FDA asking you to vote on interchangeability.

I believe that you must keep this fact front and center, as it will have an important impact on the agency's consideration of, among other things, labeling language, and the safe use education by patients and physicians.

Because of the complexity and uncertainty with regard to monoclonal antibodies, we can't always tell which product attributes or parts of structure will be relevant to ultimate clinical outcomes and which won't be.

That's why it's critical to take a conservative approach and ensure that the

biosimilar and reference product are as highly similar as possible, across a wide variety of structural and functional attributes.

As you consider the question in front of you, consider how the FDA can best help to educate both physicians and patients about the merits and differences of biosimilars because in the case of the product under consideration today, and for those in the pipeline, a key issue will be non-medical switching. You've heard it before. You're going to hear it again. It's very important and interchangeability driven by insurance companies and pharmacy benefit managers, PBMs.

What safeguards can the FDA put in place to ensure that limited switching data, such as the data presented today, is properly understood by payers, physicians, and patients? Biosimilarity and measurement of efficacy in a clinical trial is only one dimension. Another is effectiveness relative to real-world patient outcomes data.

Another item to consider in your discussion is how post-marketing surveillance data can be

reported in a way that differentiates between innovator and biosimilar, and captures the clinical experiences of patients switched from one product to the other.

Finally, it's important to remember that while biosimilars present the opportunity for broader access through lower prices, this is neither a scientific question, nor in the scope of FDA's authority.

It should not impact your vote on purely scientific and regulatory questions. When it comes to biologics and biosimilars, we cannot afford to be penny wise and pound foolish. As Dr. William Mayo said, "The best interest of the patient is the only interest to be considered." Thank you.

DR. SOLOMON: Thank you.

Will speaker number 9 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. BECKER: Good afternoon. My name is Cindy Becker. I don't have any financial

disclosures and I'm not associated with any organization. I'm just a mom. I also co-facilitate two support groups for parents of children with inflammatory bowel disease, one here in Montgomery County and one in Northern Virginia.

I am the mother of a 19-year-old young woman who was diagnosed with severe Crohn's disease when she was 16 years old. Some of you might remember me. I spoke with you back in February and told you what having IBD was like from a parent's perspective.

This past couple of weeks, I asked a number of young adults with IBD to tell me what having IBD means to them. Today I'm here to share their stories. As I do that, you're going to notice a few common themes: courage, strength, perseverance, diligence, and a maturity far beyond their years, more so than me. And these are -- I call them young adults. They're kids. They're 18 to 23. Sorry, guys. But these are their stories.

"Having IBD means having to struggle constantly to maintain a daily regular life. It's

imperative to always keep in mind the what-if scenario of how you might feel next week, tomorrow, or even in a couple of hours. Having IBD means being careful, being misunderstood, but most importantly, staying strong."

"Having IBD is a defining characteristic of my life. Initially, it was a huge embarrassment. After going to Camp Oasis and living with it for so long, I've matured and I've come to terms with the struggles of living with a chronic illness. Having IBD has forced me to become a stronger person."

"Having IBD means that I have to pay extra attention to everything I do and when I do it. It has taught me to be particular, punctual, and super responsible. I now know I have to take my medicine regularly."

"Having IBD means being constantly aware of everything that affects my life. I have to be careful about what I eat. I have to make sure I get enough rest. I have to stay away from my friends when they're sick, and I use hand sanitizer religiously. I have to make sure I'm taking my

pills and I have to know what their side effects are. IBD is something that's a part of me and it affects what I do at every turn."

"Having IBD means living a life of never knowing when you might have to put your life on hold. I have a plan A, and plan B, and C, and D, always. Any time I want to set a new goal for myself, I have to be mindful of the reality that a flare might once again sneak up on me, and I know that I might have to put everything on hold, and put my dreams and everything on hold for a while, because sometimes I'll end up in the hospital for a couple of weeks, and I can't even figure out how I got there. And when I do flare, it'll take a long time, sometimes a year, before I can go back into remission."

"Having IBD as a young adult is challenging for me, to say the very least. My life is only beginning. I have the same dreams as every other young adult. It's time for me to be able to live a fulfilling life with better treatment options. My current options are leading me back to the

operating room for the fourth time, and I'm 19. Treatment options could mean that I won't have to continually put my life on hold again and again."

Those were their stories.

My daughter, Susan, has been in remission for almost a year, the first time since her diagnosis in 2012. When I asked her if she would reach out to her friends that she made through Camp Oasis to help me with this, she agreed.

After the stories came in, I found her in her room, crying. As we talked she explained that she's actually forgotten what it was like to be sick. She's forgotten what it was like to be in pain. And she forgot what it was like not to be able to eat solids, because her senior year in high school she was on a liquid diet for over six months.

If we can find the right medicine, be it a biosimilar or something else, and it's safe, that will help these young adults and others with IBD so that they, too, can forget what it's like to be sick, I urge you to do that. Thank you.

DR. SOLOMON: Thank you.

Speaker number 10 I don't believe is here, so we're going on to speaker 11. Will speaker 11 step up to the podium and introduce yourself?

DR. SALFELD: My name is Jochen Salfeld. I'm the vice president of Biologic Discovery at AbbVie. I led the team of scientists that invented Humira in the '90s. Biosimilars may have minor differences in clinically inactive components, but we are concerned that the structural difference between Humira and 501 are not minor and may not be clinically inactive, specifically for inflammatory bowel disease.

First, 501 has significant structural differences from Humira. AbbVie is testing every batch of Humira for many of the structural attributes you're looking at today. We do this because we believe that these attributes can impact the different and sometimes not well-understood mechanism of action of Humira.

Several batches of 501 fall completely outside of our experience with Humira since launch.

One example is galactose, which impacts the functioning of the Fc region, and consequently the molecule's role in inflammation.

In fact, AbbVie has rejected potential manufacturing modifications resulting in smaller structural differences than those that you have seen today because we are concerned about the potential impact on patients.

Second, the structural differences identified today may be clinically relevant, particularly in IBD. The way Humira works in IBD is not well-understood, but there are clearly additional mechanisms leading to effective use of Humira in IBD beyond TNF binding.

For example, for full performance of Humira in IBD, the antibody likely has to bridge multiple immune cells with the antigen binding sites and the FC region simultaneously. Consequently, the entity and its sugar profile is critical in determining the performance in complex diseases like IBD. This profile includes galactose, which I already mentioned, and sialic acid. All batches of 501

fall significantly outside the sialic acid quality ranges for Humira, identified by Amgen. Sialic acid has been demonstrated to play a role in antibody function beyond FC binding. Amgen has not tested that established functioning.

Trying to minimize the structural differences, Amgen has relied upon other functional assays. These assays may not be sensitive enough to identify the impacts of structural differences, and may not fully capture the complex mechanism in IBD.

There are also concerns about the robustness of some of these assays. Most of these assays use non-human engineered cell lines that do not reflect the complexity of human immune cells. Further, some key functional assays do not meaningfully compare 501 to Humira, just as few as three samples, and which are they? Are they those within or outside the quality range of Humira as identified by Amgen?

AbbVie is not just saying clinical investigation for every indication, but there is

uncertainty created by significant structural differences, uncertainty regarding the exact mechanism of action in IBD, and uncertainty regarding the functional assessments relevant to IBD.

Therefore, we respectfully ask, is there sufficient scientific justification in 501? Will it perform like Humira in IBD, where they have no clinical data in IBD? Thank you.

DR. SOLOMON: Thank you.

Will speaker number 12 step up to the podium and introduce yourself? Please state your name and any organization you represent for the record.

DR. STOLOW: Yes. Good afternoon. I want to thank the FDA for the opportunity to speak today. I am Joshua Stolow, M.D. I am representing the Coalition of State Rheumatology Organizations or CSRO.

I am a practicing rheumatologist in San Antonio, Texas, and more importantly, I am the father of a 20-year-old college student who was diagnosed with ulcerative colitis at age 2 and has

truly gotten his life back from treatment with a biologic agent in the last four years for this devastating disease.

The CSRO represents state and regional societies to advocate for excellence in rheumatic disease care, especially in patients with rheumatoid arthritis, psoriatic arthritis, and other autoimmune disorders.

Rheumatologists have extensive experience in the use of biologics. We look forward to having new biosimilars approved by FDA and possibly with cost savings. Our main concern, however, is patient safety. Also important are the issues of naming, post-approval, pharmacovigilance, non-medical switching, and interchangeability. We are pleased that FDA has proposed a distinguished suffix for biologic product naming.

CSRO is concerned about extrapolation. The CSRO has always maintained that the FDA require clinical data for each indication, and that original clinical data generated by the biosimilar manufacturer be noted on the label.

The CSRO has concerns about non-medical switching and the potential interference by third party payers with clinical decision-making between physicians and patients. Pharmacovigilance is critical, and we advocate that biosimilar manufacturers monitor for immunogenicity.

We feel that FDA must exercise care and communications with patients and physicians on the issue of switching and when switching should occur. The Danish Registry study on inflammatory arthritis and psoriasis showed in a post hoc analysis that non-medical switching in the psoriatic cohort may have a deleterious effect and lack of efficacy in approximately 6 percent of patients who also had to discontinue therapy three months after the switch. These patients had disease duration of 6 to 9 years.

The study of 77 patients did not have input from the FDA, and the FDA has noted that small sample size and wide confidence intervals make it difficult to draw statistical inference by observed case analysis.

It seems that based on small studies, that the use of biosimilars as a first choice, as opposed to non-medical switching, would be more appropriate. Emergence of antidrug antibodies, including neutralizing antibodies, can affect PK and maintenance of clinical response. It will require more robust studies to further evaluate immunologic tolerance, especially in non-medical switching from the innovator drug to a biosimilar.

Thank you for your attention to this important matter.

DR. SOLOMON: Thanks.

Will speaker number 13 step up to the podium and introduce yourself? Please state your name and any organization you represent for the record.

DR. FELDMAN: I'm Dr. Madelaine Feldman, and I'm speaking for the Alliance for Patient Access.

I'm a practicing rheumatologist in New Orleans and on the clinical faculty of Tulane University Medical School, and I also have a child that was diagnosed with JRA at the age of 10. I'd like to preface my remarks by saying I am in

complete and total support and welcome the development and use of biosimilars, including adalimumab biosimilar, ABP 501. I have no financial disclosures to report.

As I said, I'm speaking on behalf of the Alliance for Patient Access and my daughter, Sidney. The Alliance is a national network of physicians dedicated to advocating for patient access.

I'd like to highlight the term "access" because none of us are really naïve enough to believe that just approving a biosimilar gives a patient true, hands-on access to the medication, because even if the biosimilar is offered at a 30 percent discount, I don't have any patients that would be able to afford it.

This means access is ultimately controlled by third party payers. This becomes the crux of the switching argument involving interchangeability. We know that a biosimilar cannot be interchanged for the originator without physician's permission unless it's been deemed

interchangeable by the FDA.

These criteria, which have not been established, would require robust, controlled trials determining the safety and efficacy of switching back and forth between originators and biosimilars.

We also know from firsthand experience that the third party payer chooses the biologics that the patients take, based on a rebate system whereby the insurance companies or their PBMs receive money from pharmaceutical companies that essentially keep other competing drugs off of the first tier.

So what happens in real life? I've had patients that were stable for years and forced to switch to a different one because a new rebate has been negotiated with a different pharmaceutical company, or their employer switched companies who now have a better deal with a different pharmaceutical company.

Of course the payers are denying that they are switching the patients. The physician can write any prescription they want. The insurance

company just won't pay for it. Thus, state substitution laws will not protect patients from this type of switching, and the switching goes on back and forth, year after year, making a single switch approval by the FDA moot.

This is non-medical switching. We know, without guidance from the FDA, that non-medical switching of biosimilars is going to happen. And with two more adalimumab biosimilars coming down the pike, imagine the explosion of switching possibilities. So who is there to make sure that our patients are not the guinea pigs for the great American switching experiment? It is the FDA.

I'm asking you today to recommend the FDA not allow this type of non-medical switching between and among originators and biosimilars until the appropriate switching studies have been performed and the biosimilar meets interchangeable criteria. Do not allow third party payers to usurp your power at the expense of the American people. Do not allow them to decide what is interchangeable.

As far as the labeling information, biosimilar sponsors provide significant data to the FDA as part of their application package. It makes sense that the product labels should in turn provide that data, not simply offer the reference product's data. If the reference product's data is used on the label, it should clearly state that those studies were not done by the biosimilar developer.

Finally, indication extrapolation. I urge the FDA to continue to move carefully when considering and approving applications that require indication extrapolation. This particular biosimilar has not been studied in inflammatory bowel disease, nor does it have the real world experience that the last and most recent biosimilar, infliximab, had in Europe and beyond. Because of this, I think there is concern about extrapolating to indications not yet studied.

By considering and implementing these recommendations, the FDA will continue to inspire prescriber confidence, protect patient safety, and

encourage the adoption of biosimilar treatments. Thank you very much.

DR. SOLOMON: Thank you.

Will speaker number 14 step up to the podium and introduce yourself? Please state your name and any organization that you represent for the record.

DR. CRYER: Good afternoon. My name is Dr. Dennis Cryer, and I'm the lead physician, co-convener of the Biologics Prescribers Collaborative, or BPC. I have no financial disclosures to make, no conflicts of interest.

I'm here on behalf of physicians who routinely prescribe biologic medicines and professional organizations with numerous biologics prescribers as members. Our comments today will be general, focusing on four key biosimilar policy issues, rather than on a specific biosimilar product.

First, each biological product should have a meaningful and distinguishable non-proprietary name. FDA's draft guidance proposed that biosimilars be assigned an FDA-designated suffix,

comprised of four randomized letters that would be unique for each product.

However, our experience as biologics prescribers tells us that in addition to being unique, the suffix should also be memorable. BPC strongly encourages FDA to adopt a suffix format that is memorable and reflective of the manufacturer name, as originally illustrated by filgrastim-sndz.

Second, biosimilar product labeling must contain all needed data about the biosimilar product for physicians to make appropriate prescribing decisions for their patients. The label is a critical tool for physicians to make prescribing decisions and manage potential adverse events.

As such, it is of utmost importance that any drug label be complete as well as accurate. Not only should the label have a statement of biosimilarity, it is important, first, to note if the biosimilar has been deemed interchangeable with the reference product, and second, to include a

summary of the full clinical data or a hyperlink to that data.

As FDA finalizes its guidance on biosimilar labeling, we urge the agency to include the product-specific information that physicians overwhelmingly consider to be important.

Third, FDA should proceed with thoughtful caution when considering biosimilar application requests for indication extrapolation. Biologic medicines are often indicated and used to treat multiple and unrelated disease states.

Under the new abbreviated approval process, data are presented for certain indications but not others, and FDA approval of a biosimilar requires only one clinical study to demonstrate safety, purity, and potency of the proposed product.

As such, the collaborative does not support automatic indication extrapolation of every indication the reference product is licensed to treat. However, BPC would support extrapolation for additional indications if sufficient scientific justification for extrapolating clinical data has

been provided.

In particular, data should address possible differences in immunogenicity, expected toxicities among sensitive patient populations, as well as the mechanisms of action in each condition.

Fourth, FDA should provide clear and concise guidance to industry surrounding interchangeability between biosimilars and their reference products. As more biosimilars that could be put forward for interchangeability enter the developmental pipeline, it is critical that sponsors are provided sound guidance to ensure patient safety and physician confidence.

We encourage FDA to provide direction on interchangeability by issuing a draft guidance as soon as possible, and to provide clarification on this issue at the federal level. We encourage FDA to consider the implications of these policies on biosimilar products as these biosimilar products advance to the market. The policies adopted will determine physician confidence that is essential for appropriate use.

Thank you for this opportunity for the Biologics Prescribers Collaborative to speak before the Arthritis Advisory Committee today and to share our perspective on issues critical for the safe use of biosimilars and other biologics.

DR. SOLOMON: Thank you.

Speaker number 15 is not present, so we move to speaker 16.

MS. ARNTSEN: Number 15 is here.

DR. SOLOMON: Oh, sorry. Speaker 15, step up to the podium and introduce yourself. And please state your name and any organization that you represent for the record.

MS. ARNTSEN: Kathleen Arntsen, Lupus and Allied Diseases Association, PBSA, and ASBM. Good afternoon. I'm here as a leader advocate and patient who lives with multiple autoimmune diseases, takes over 40 drugs a day, and has unique sensitivities to both active and inactive ingredients in drugs.

No one-size-fits-all products exist for complex patients like me. Our immune system

response to treatments is unique, contrary, and at times adverse. Given that the FDA has not yet finalized guidance on issues that impact patient safety such as indication extrapolation, switching, interchangeability, naming and labeling, please keep in mind complex autoimmune patients like me who do not fit the norm and are labeled outliers by their treating physicians.

We are so hypersensitive that even the slightest change in manufacturing, dose, or method of delivery can provoke immunogenicity and disease complications. Sufficient proof of clinical efficacy, safety, purity, potency, and tolerability must be provided for each distinct patient population to grant indication extrapolation, not just projected clinical safety and efficacy data.

To be designated as interchangeable, biosimilars must unequivocally produce the same clinical result in any given patient as the biologic reference product. Therefore, we support a policy requiring rigorous criteria that includes nonclinical and clinical data.

We also support unique non-proprietary names in order to assure patient safety; provide vital transparency, and aid in accurate product identification during the prescribing, dispensing, and pharmacovigilance processes; promote compliance; and ensure timeliness in addressing adverse events.

We ask you to evaluate the biosimilar through real-world post-marketing surveillance to maintain efficacy and patient safety. Pharmacovigilance is essential as these treatments may product immunogenic reactions in patients who may also be hypersensitive to changes in production methods or impurities.

Substitution of biosimilars for branded biologics should only occur when the FDA has designated a biologic product as interchangeable and patient protections are upheld, including communication between pharmacists and prescribers, to guarantee complete transparency. And a prescriber should have the authority to prevent substitution when warranted.

As an individual who was harmed by the egregious payer utilization management practice step therapy, and am now blind in my right eye and in danger of losing it, I am extremely concerned that patients who are stable on a biologic will be switched for non-medical reasons to a biosimilar that has not been determined to be interchangeable by the FDA.

We realize that the FDA does not have any jurisdiction over insurers or PBMs, but we must anticipate that payers will promote the use of biosimilars. And therefore, we urge you to provide robust safeguards to protect patients such as applying strong scientific safety standards and publishing an official statement that switching a stable patient to a non-interchangeable biosimilar is perilous.

CVS has actually put forth a publication indicating they will apply step therapy protocol to ensure patients are pushed to the preferred drug, and they expect nominal use of grandfathering, which means that patients currently successful in

managing their diseases will be forced to switch therapies to appease cost control measures.

We cannot emphasize this strongly enough or loudly enough -- payers will switch stable patients for non-medical reasons from biologics to non-interchangeable biosimilars. So we charge you with establishing patient safeguards stating that non-medical switching of stable patients is extremely precarious. It should only be determined by the treating provider and patient.

Biological medicines are prescribed to individuals with serious, life-threatening diseases, and therefore the potential for immune reactions and serious adverse effects is heightened exponentially in this population.

This was illustrated in a Danish biosimilar study where the author stated that more research was needed before switching could be recommended due to the lack of effect and adverse events.

I thank you for the opportunity to share my unique perspective and for continually recognizing the importance of the patient voice during the drug

review process.

DR. SOLOMON: Thank you.

Will speaker number 16 step to the podium and introduce yourself? Please state your name and any organization that you represent.

MS. SIMMON: Thank you. I'm Christine Simmon. I'm the executive director of the Biosimilars Council and senior vice president of the Generic Pharmaceutical Association. I have no financial disclosures to make.

On behalf of our members, I would like to commend the agency on its continued progress in its implementation of the BPCIA. We greatly appreciate the work the agency has done towards the creation of a regulatory framework that maximizes patient access to these medicines. The Biosimilars Council was pleased recently to ratify the BsUFA II goals letter to facilitate product reviews. It's a great accomplishment.

The Biosimilars Council is a division of GPHA, which works to ensure a positive environment for biosimilar products and works to educate policy

makers, providers and patients about biosimilars. Member organizations include manufacturers and stakeholders working to develop biosimilars with the intent to compete in the U.S. market. The council recognizes that development, production, and approval of biosimilar products must be grounded in sound science.

As part of the BPCIA, FDA was granted important discretion to determine scientific requirements on a case-by-case basis to ensure safety and efficacy. In so doing, the agency relies upon the same scientists that assess applications for new biological products and who are experienced with the product or product class.

The foundation of biosimilar development is based on extensive analytical characterization of the application, as well as any necessary additional clinical trials. As such, the council is confident in the agency and the process, and we will continue to work to educate providers and patients so they can be, too.

So that is why the council has opposed

regulatory guidance requiring a statement of biosimilarity on the product label. In most cases, the scientific information necessary to approve a biosimilar will primarily focus on establishing biosimilarity between the two products.

This means that safety and efficacy information will come from studies of the reference product rather than the biosimilar. Including a biosimilar product's biosimilarity data in addition to that of the reference product would only provide unnecessary information and create confusion for prescribers and patients.

This differentiation between biosimilars and their reference products risks undermining the important provider education that is already being done by you, the agency, today.

Informing providers that "Biosimilars have no clinically meaningful differences in terms of safety, purity, and potency from the reference product," but then requiring a differentiator in the labeling, sends mixed signals to providers responsible for establishing patient familiarity

and comfort with these products. So while we are largely supportive of the draft guidance on labeling, the council recommends that this proposed requirement be removed.

Regarding extrapolation, extrapolation of data is already an established scientific and regulatory principle that has been utilized for many years by the innovator industry.

For example, in the case of major changes in the manufacturing process of innovator biologics, FDA has used comparability or extrapolation of information for nearly 20 years. In such cases, clinical data are typically provided to confirm safety and efficacy of one indication, and taking into account the totality of information gained from the comparability exercise.

Based on the acceptable outcome of the comparability and clinical evaluations, the data may be then extrapolated to other indications. Extrapolation is really critical to the success of biosimilars for U.S. patients.

In conclusion, the council applauds the

agency for its efforts to support the biosimilar pathway in the United States, and thanks it for the opportunity for public comment at today's meetings. Our members look forward to bringing lifesaving biosimilar medicines to the patients here in America that have been waiting for a while and who really rely on these medicines. Thank you.

DR. SOLOMON: Thank you.

Will speaker number 17 step to the podium and introduce yourself? Please state your name and any organization that you represent.

MR. PHILLIPS: Good afternoon. My name is Thair Phillips. I'm president of RetireSafe, a nationwide non-profit advocacy organization for older Americans. I'm here today representing our 300,000 supporters, including our 50,000 email activists. I have nothing to disclosure for my presence here today.

As I've stated at previous advisory committee meetings, RetireSafe looks forward to the promise of increased access offered by biosimilars, but we are still concerned with safety. My

statement today will deal with safety issues that continue to exist.

It is beyond amazing that after meetings and hearings and biosimilar approvals, we are still without critical final guidance. It is difficult to imagine what scenario or motive would explain this lack of movement.

Two years ago I reported on a survey we took concerning the safety and effectiveness of biosimilars. We felt it was necessary to update that survey since it's been so long. Once again, both the answers and comments from this most recent survey voice an overwhelming desire for common-sense safeguards when it comes to the naming, labeling, switching, approved indications, and the open communications required for biosimilars.

While questions about safety always bring a positive result in percentages, the percentages were again unusually high, with most answers in the high 80s and one in the high 90s. I don't have time today, but I'll talk more about that survey at tomorrow's ADCOM meeting.

These survey respondents are concerned Americans who continue to feel left out of the process. As you may have already heard many of the stakeholders here today feel left out or ignored. It is imperative that today I discuss cost.

In the Biologicals Price Competition and Innovation Act, Congress specifically limited FDA's scrutiny to "ensuring no clinically meaningful differences in safety and effectiveness," and "determining biosimilarity."

By congressional legislation and FDA's own direction, costs should not enter into the conversation. Yet the following quotes are taken from the February ADCOM meeting concerning the biosimilar approval:

"So the real purpose of this and the reason behind this pathway is to provide access and to reduce cost."

The second statement: "For all of these reasons and because we have the responsibility to take a risk to provide new products that are biosimilars, to reduce the cost of bringing drug to

market, and to reduce the cost to patients, we really need to go ahead and take this risk."

Again, cost is not one of the areas for review, and accepting more risk to reduce cost is not a goal. Determining safety, effectiveness, and biosimilarity are the only goals. Cost should never enter into the conversation.

Finally, this week I feel we have a unique opportunity to gain some unfiltered insight. Within a two-day span, Amgen will be both a biosimilar applicant and a manufacturer whose innovator drug has a proposed biosimilar. Amgen may have the best perspective and be the best source of unencumbered facts about many of the safety issues we have discussed in the last two years. Let me touch on two of these safety issues.

To the best of my knowledge, Amgen believes that a biosimilar should have a distinct suffix that identifies the manufacturer, and Amgen does not support non-medical switching. While RetireSafe and others may not agree with Amgen on every issue, I think many of us testifying today

agree on these two issues and possibly others. I think the advisory committee and the FDA should pay special attention to Amgen's stance on these two safety issues.

I'll end as I have ended past testimonies. Americans trust the FDA. I personally heard Dr. Woodcock say in a House hearing that safety would not be sacrificed when it comes to biosimilars. I take her at her word.

As a voice for the people you protect, we ask that the questions and issues cited above be given appropriate consideration. To do otherwise would undermine the trust Americans have in the FDA. Thank you.

DR. SOLOMON: Thank you.

Will speaker number 18 step to the podium and introduce yourself? Please state your name and any organization that you represent.

DR. BEHEN: My name is Dr. Susan Behen, and I'm a volunteer advocate with the Arthritis Foundation. And I have no disclosures to report.

Arthritis can be very complex to treat and

diagnosis can be difficult. I finally received my diagnosis of psoriatic arthritis after two years of symptoms. I trained in general surgery at the Johns Hopkins Hospital in Baltimore, and then did a specialty fellowship in colon surgery. The physicians here on the panel all remember the time, the dedication it required during college and medical school, the determination to get through residency.

After six years of surgical training I finally began my career, got married, and started a family. The fall of 2008 is memorable for many, due to the impact of the global financial crisis. But for me it was also the beginning of the end of my career that I loved.

I was 48, had a busy practice. I was the primary breadwinner for my family, and I had finally paid off all those student loans. I was experiencing joint pain, swelling in some of my fingers, the hands, my wrists, and my feet. I thought maybe I was working too hard. We thought it was overuse, but the symptoms progressed despite

rest.

I saw a hand surgeon, some physical therapists. I did exercises. I had splints for possible carpal tunnel, injections for tendonitis. Finally, I saw my rheumatologist, who put these symptoms all together with my psoriasis, an autoimmune disease, and I was diagnosed with psoriatic arthritis.

I began my treatment for psoriatic arthritis with a TNF alpha blocker right away. I discussed all these issues with my doctor -- the risks, the benefits, and my personal situation as a surgeon. The response was very dramatic, and I am so grateful for the relief of the pain and the inflammation.

I'm truly in awe of the researchers who were able to develop these remarkable treatments. I had no idea I'd be sitting next to one. The damage to my joints and tendons, however, has caused weakness such that I'm unable to continue to do the demanding physical work of surgery. I left behind patients that I had followed for many years after

treating their breast cancer or colon cancer.

To give you an idea of how complex arthritis can be to treat, one estimate of rheumatoid arthritis patients who took one of the three first-generation biologics for at least six months showed that between 40 to 50 percent of them failed to show at least 50 percent improvement.

Of patients who failed on a biologic, the rheumatologists switched their patients to another biologic 90 percent of the time. So biosimilars could represent a great opportunity to both increase access and lower costs, which is important to all of the stakeholders, but patient safety must be the highest priority.

Unique names will help ensure robust post-market surveillance and will contribute to a higher level of patient and provider transparency, which we believe are key components of the overall patient safety.

So should this drug get approved, the FDA should make post-market surveillance a high priority, ensuring effective, robust ways to report

adverse events and to track patient responses to the drug.

Thank you very much for the opportunity to speak on behalf of the Arthritis Foundation and to share my personal story with the committee today.

DR. SOLOMON: Thank you.

Will speaker number 19 step to the podium and introduce yourself? Please state your name and any organization that you represent.

MS. BUCHANAN: Hi. My name is Sara Buchanan. I'm the director of advocacy for the Crohn's and Colitis Foundation of America. I've nothing to disclosure.

CCFA advocates on behalf of the 1.6 million Americans suffering from Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel, diseases or IBD.

The emerging biosimilars market poses an exciting opportunity to expand the marketplace for groundbreaking biologic therapies that have significantly helped our patients. CCFA supports a robust market for treatments, and prioritizes

affordable patient access to safe and effective medications.

We submitted a written statement, and I wanted to highlight a few points today. The first is that CCFA joins with other organizations here to express concern regarding the switching of patients from an originator biologic to a biosimilar that has not received interchangeable status.

We've heard from several in the IBD community that are afraid patients would be coerced to undergo a switch to a non-interchangeable biosimilar through medical management techniques.

Given the different approval requirements for biosimilars and interchangeable biosimilars, it is imperative that any decisions to put a patient on a non-interchangeable biosimilar are kept solely between the physician and the patient and that these decisions are not subject to pressure from third parties.

CCFA urges FDA to proactively protect the patient and physician decision-making relationship, particularly in the case of biosimilars that did

not seek interchangeability. And we agree with our colleagues asking for a clarifying official statement from FDA.

The second is regarding indication extrapolation. CCFA has refrained from advocating for extra IBD-specific evidence when approval for another condition has been deemed sufficient for extrapolation by FDA.

We are willing to accept FDA approval of therapies indicated for Crohn's disease and ulcerative colitis by extrapolation based on the other studies in other conditions, especially rheumatoid arthritis. We do urge extra caution when approving extrapolation to indications for pediatric patients.

Lastly, regarding education, CCFA has recently launched a biosimilar education campaign for patients, starting with a webinar that is available online. We urge FDA to continue to educate both patients and physicians on biosimilars. The lack of understanding about biosimilars in both these groups could lead to slow

uptake of biosimilars, misuse, and in the worst circumstances, malpractice.

Thank you for the opportunity to speak and for your considered review of this application.

DR. SOLOMON: Thank you.

Will speaker number 20 step to the podium and introduce yourself? Please state your name and any organization that you represent.

MR. CARDENAS: Good afternoon again. My name is Jasey Cardenas of the United Spinal Association, speaking on behalf of Alex Bennewith, also of the United Spinal Association. And we have no financial ties to disclosure.

United Spinal Association is the largest disability-led non-profit organization, founded by paralyzed veterans in 1946. It has since provided service programs and advocacy to improve the quality of life of those across the lifespan living with spinal cord injuries and disorders such as multiple sclerosis, ALS, post-polio syndrome, and spina bifida.

One of the proposed indications for ABP 501

is listed as number 4, reducing signs and symptoms in adult patients with active ankylosing spondylitis, AS. As you know, AS is a chronic, inflammatory rheumatic disease that primarily affects the vertebral column and sacroiliac joints.

Over time, the disease process promotes extensive remodeling of the spinal access via ligamentous ossification, vertebral joint fusion, osteoporosis, and kyphosis. These pathological changes result in a weakened vertebral column, with increased susceptibility to fractures and spinal cord injury.

Spinal cord injury is often exacerbated by the highly unstable nature of vertebral column fractures in AS. A high incidence of missed fractures in the ankylosed spine, as well as increased incidents of spinal epidural hematoma, also worsens the severity of SCI.

Spinal cord injury in AS is a complex problem associated with high morbidity and mortality rates, which can be attributed to the severity of the injury, associated medical

comorbidities, and the advanced age of most patients with AS who sustain an SCI.

There are some studies which exist, different responses in different disease states. In a couple of American College of Rheumatology abstracts for AS and RA studies respectively, the infliximab biosimilar data show a difference between adverse events in RA and AS patients depending on whether or not they switched from a biosimilar to an innovator.

The European League Against Rheumatism investigators in Denmark reported on an observational nationwide study of 647 patients with rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis treated with Remicade for periods ranging from 3.5 to over 9 years who were non-medically switched.

Forty-five patients stopped treatment due to lack of effect. Some patients experience these events just three months after the switch. The authors concluded that the lack of effect post-switching, "warrants further investigation

before such a non-medical switch can be recommended."

Preliminary observational data presented at European Crohn's and Colitis organizations in 2016 of patients with inflammatory bowel disease that were switched to biosimilar infliximab show no clear signals of difference in safety. However, after the switch, a five-fold increase in loss of response and trend towards more frequent primary failure and loss of response in ulcerative colitis compared with Crohn's disease patients was found.

Data on switching from the reference product to a biosimilar for ABP 501 is available from the study published by the Journal of the American Academy of Dermatology, with 77 patients switched from the reference product to the biosimilar. Patients in the switched group achieved both lower mean response and a lower rate of response at week 50 compared to those who did not switch.

In addition, a higher proportion of switched patients developed neutralizing antidrug antibodies when compared to those who did not switch. These

data are too small to make any conclusive findings. In addition, the FDA is not authorized to consider pricing or competitive economics in its review of proposed biosimilar drugs.

In crafting the Biologics Price Competition and Innovation Act, Congress explicitly limited FDA's scrutiny to assuring no clinically meaningful differences in safety and effectiveness in determining biosimilarity.

Despite this, both biosimilar advisory committee meetings held to date have had repeated references and discussions regarding costs. Consequently, we believe that FDA must insure future biosimilar advisory committee discussions are focused on matters of safety, efficacy, and determining biosimilarity.

Committee members should be advised in advance that advice and judgements should be based on only those matters. We should never have a situation where advisory committee members are voting on approval of new products based on cost. Rather, they should be based on safety and

efficacy.

United Spinal Association is a founding member of the Patients for Biological Safety and Access, PBSA, which is dedicated to protecting patients' access to safe and effective biologics. On behalf of my members and the broader disability community, thank you for the opportunity to speak today.

DR. SOLOMON: Thank you.

Will speaker number 21 step to the podium and introduce yourself? Please state your name and any organization that you represent.

MS. McCLASLIN: Good afternoon. My name is Tiffany McClaslin, and I am senior policy analyst at the National Business Group on Health. Our members would like to thank the committee for holding this important meeting on biologic license application 761024 for ABP 501.

The National Business Group on Health represents approximately 425 large employers, including 72 of the Fortune 100, who voluntarily provide health plan coverage and other health

programs to over 55 million American employees, retirees, and their families.

The Business Group and our members appreciate the opportunity to state for the public record that we strongly support a regulatory environment, which favors a robust uptake of quality, safe, and efficacious biosimilars.

While we appreciate that the complexity of competition among large molecules differs from that of small molecules, we support the notion that, in general, competition fosters innovations that have the potential to redefine markets.

We know that the availability of generic drugs has reduced drug prices and increased patient access to medications, and we believe competition among biosimilars may be able to do the same. As biosimilars are competing for market share with each other, it could be expected to lead to lower prices, as well as potentially greater access to these products.

To this end we support the direction that FDA has laid out with regard to biosimilar

development, requiring that a biosimilar demonstrate biosimilarity to the reference product, and we believe that the FDA has put in place the appropriate patient safeguards to permit data extrapolation to inform biosimilar usage.

Again, we thank the committee for holding this important meeting today, as well as all of those at FDA, CDER, OND, and other sister agencies. We recognize the significant challenges associated with your work, and we appreciate your continued commitment to a clear pathway by which manufacturers may bring biosimilars to market.

Additionally, we'd like to thank the sponsor for its commitment to innovating in the biosimilar space, which we hope will lead to lower prices and increased access to both life improving and lifesaving medicines for patients, payers, public programs, and other consumers. Thanks again.

DR. SOLOMON: Well thank you. The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its

attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Dr. Nikolov will now provide us with a charge to the committee.

Charge to the Committee - Nikolay Nikolov

DR. NIKOLOV: Good afternoon again. As we prepare to the committee a discussion and voting this afternoon, I would want to provide a brief reminder of the issues, the regulatory framework, and the underlying decision-making for 351(k) marketing applications for proposed biosimilar products, and the questions to be discussed and voted upon.

As discussed, Section 351(k) of the Public Health Service Act defines the terms biosimilar or biosimilarity to mean that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in

terms of safety, purity, and potency of the product.

A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines in its discretion that certain studies are unnecessary in a 351(k) application.

The issues that we would like the committee to discuss are whether the totality of the scientific evidence supports that the applicant provided adequate data to support the demonstration that ABP 501 is highly similar to US-licensed Humira, with respect to primary, secondary, and higher order structures, both translational profile and in vitro functional characteristics, purity, stability, and potency, including TNF binding and neutralization; and also whether the clinical data submitted support the conclusion that no clinically meaningful differences exist between ABP 501 and

US-licensed Humira; and also whether the applicant provided sufficient scientific justification for the extrapolation of data to support that there are no clinically meaningful differences in the indications sought for licensure.

We note that a lot of open public hearing stakeholders shared concerns with issues like naming, labeling, interchangeability, non-medical switching, and cost. We acknowledge the importance of these issues.

The agency has dedicated significant resources on addressing these critical issues of the implementation of the biosimilars legislation. We also acknowledge that these are highly intertwined issues, but I would like to ask the committee to focus the discussion on the data presented.

Specifically, on whether the data supports a demonstration that ABP 501 is highly similar to the reference product, US-licensed Humira, notwithstanding minor differences in clinically inactive components.

The second discussion question is that we would like the committee to discuss the adequacy of the data to support a conclusion that there are no clinically meaningful differences between ABP 501 and US-licensed Humira, in the studied conditions of use, specifically rheumatoid arthritis and plaque psoriasis.

The last discussion question is whether the applicant has provided sufficient scientific justification to support that there are no clinically meaningful differences for the additional indication sought for licensure.

The FDA is also requesting the committee's discussion on concerns with extrapolation to specific indications and what additional data would be needed to support that extrapolation.

At the end, question 4 is a voting question on the committee's recommendation whether based on the totality of the evidence, ABP 501 should be licensed as a biosimilar product to US-licensed Humira, for each of the following indications for which U.S. Humira is currently licensed, and for

which Amgen is seeking licensure.

These include rheumatoid arthritis, juvenile idiopathic arthritis in patients four years and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, adult ulcerative colitis, and plaque psoriasis.

The voting will be followed by discussion on the reasons for your vote. I just want to clarify that the voting question would be a yes and no question, which includes yes or no for the indications all together.

With this, I would like to thank you, and I will turn the meeting back to you, Dr. Solomon.

Questions to the Committee and Discussion

DR. SOLOMON: Great. Well, thank you.

So to take each discussion point one at a time, what I think will be most effective, and the first discussion point is about highly similar between the ABP-501 and US-licensed Humira. This really gets down to the analytics, the PK, the PD, et cetera. And so there are a lot of broad issues that we could focus on, but I think we really have

to keep it focused on these specific questions at hand to be most effective.

So why don't I open it up, and we'll take a list as people want to make some comments, but we'll have some back and forth as well. So Diane?

MS. ARONSON: Diane Aronson. I'm not sure where to ask this question, but I think it's here, because it mentions notwithstanding minor differences in clinically inactive components. Just from the FDA, some approval history about Humira. From the get-go, was IBD and Crohn's disease included?

DR. SOLOMON: Just for the record, while there's an answer being formulated, I'm just going to read the question.

Please discuss whether the evidence from analytic studies supports a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. Does FDA want to --

MS. ARONSON: And I have a specific question about whether the formula has changed since its

initial approval and with one question about one of the ingredients.

DR. KOZLOWSKI: So manufacturing changes may not be public information. What we can say is many biologic products have undergone many manufacturing changes, and many of those changes have been based entirely on analytics. So it's not a study in one or two out of multiple indications. It's entirely based on analytics.

And where the Europeans actually share this data more openly, and you can look -- some of these products have had 37 manufacturing changes, most of which have been justified by analytical comparability.

MS. ARONSON: When I look up the formula for Humira, I come up with polysorbate 80. Polysorbate 80 I look up. And it says it may be harmful for people with Crohn's disease, may induce low grade infection, and it promoted robust colitis in mice predisposed to this disorder.

So I'm just wondering whether the lots used in -- was it 2006 to 2008 -- back then, may have

had this, and then there was a formula change that there may not be apples to apples. I don't know if this can be answered, but I didn't want to leave here with this question.

DR. KOZLOWSKI: So I think polysorbate 80 is an active ingredient in both the reference product and the biosimilar candidate product.

DR. SOLOMON: To focus on some of the chemical and pharmacologic issues, I don’t know if any of the committee members with specific expertise in those areas want to revisit any of the discussion we had this morning regarding some of the assays. Obviously, there were differences noted in the assays. Dr. Siegel?

DR. SIEGEL: Thanks. I just wanted to come back to the issue of Fc receptors that I raised a little bit. I think that's not irrelevant, because in my mind it's pretty simple.

Every monoclonal antibody that has Fc receptor activity is effective in inflammatory bowel disease against TNF, and every reagent that does not have Fc receptor binding activity,

etanercept and certolizumab, is not effective. So I think that's reasonably clear.

So in terms of this package, in the in vitro binding assays, there was equivalency. I raised the point that this package, unlike the package we discussed back in February, didn't have binding of the monoclonal antibody to NK cells, which could be argued to be more physiological.

So that's something that was done in another package, wasn't done here. I think there, there was a difference in the in vitro binding to recombinant Fc receptor in vitro assays. So there that difference was then reflected in some significant -- or some differences in NK binding. So I think I accept the ability of the in vitro assays to predict the NK cell binding assays.

Here there wasn't really any difference that the FDA presented or I could see in terms of binding. So I think -- I just wanted to give my opinion about that issue because I think it is important.

DR. SOLOMON: The implications of your

comment are exactly what, just in thinking about all the indications?

DR. SIEGEL: Because there were a lot of discussions on how you can extrapolate or if extrapolation is possible to IBD. And I think, in my mind, the key issue of whether a reagent could be used in IBD is its Fc receptor binding. And at least in my mind, that was, in the in vitro assays, equivalent.

DR. SOLOMON: Thank you.

DR. BERGFELD: Wilma Bergfeld. I'd like to address the discussion question number 1 and say yes. I think that the evidence that's been presented, both analytical studies for the demonstration that the ABP 501 is similar to the reference drug -- and I think it's been aptly demonstrated to us by both the company as well as the FDA.

DR. SOLOMON: Okay. We can go home.

(Laughter.)

DR. SOLOMON: Other comments? Any concerns based on other assays that were presented?

DR. SCHER: Jose Scher again. So maybe this is a question for Richard. You seem to have more expertise in immunoglobulin biological activity. So I'm going back to the glycosylation issue, the post-translation modification of these molecules.

The company or the sponsor demonstrated that there is no PK differences. But when it comes to immunogenicity, and I raised the question before, could that be related to those clinical differences that we see in the clinical data?

DR. SIEGEL: So I think differences in immunogenicity could certainly result from differences in glycosylation. And I thought it was important that immunogenicity was specifically tested in comparison to the reference product.

I'm not an expert on glycosylation per se, but I don't think it's possible to empirically predict what glycosylation changes would result in immunogenicity. So that's why I think that has to be tested, which, in my opinion, it was.

DR. SOLOMON: Any other concerns about the immunogenicity issue?

(No response.)

DR. SOLOMON: Okay. We can move on, if there's really no discussion. There is considerable expertise at the table around pharmacologic issues and chemical issues, so I don't want to leave any of that hanging.

DR. KOZLOWSKI: I just think before moving on from the highly similar, the panel should really think about do any of these things impact your thoughts on extrapolation? Are any of these things you really have additional questions on? And I think it's important to make sure that's closed before moving on.

DR. SOLOMON: Yes. Agree.

DR. WALDMAN: Scott Waldman. This is for Richard Siegel. The question, can we extrapolate from Fc receptor binding activity in vitro to the ability to extrapolate to a mechanism of action that wasn't tested? For me, that's what it's going to come down to.

DR. SIEGEL: I think that is something that you have to look at data where Fc receptor binding

has been checked in both types of assays. We don't have that in this package. We've seen that in other circumstances, that the Fc receptor binding in a recombinant protein correlates.

I'd like to hear the -- I think it would be great to have the FDA opinion on whether they believe those assays are correlated, because --

DR. SIEGEL: Right. Correlative means that the in vitro would predict the -- the next step would be NK binding. The third step would be clinical efficacy, and that's where there is a good correlation between reagents that do engage Fc receptors in efficacy. But it would be great to hear FDA opinion, potentially, on that, on the correlation.

DR. WELCH: I think we would highlight that. Again, it goes back to the totality of the evidence and the exhaustive nature of not just these in vitro assays, but the structural characterization as well. In terms of, for example, the ADCC assay, it was not just validated and qualified and verified on inspection. Some

rather exhaustive characterization of that assay itself was performed.

For example, the applicant compared NK cells to the PBM cells, showed that they had equivalent response. Correlated the response of ADCC versus afucosylation changes, high mannose changes, showed that those were highly correlated. Additionally, a control antibody was used for a molecule that wasn't a TNF alpha, but had a very high ADCC activity, and the dynamic response of the assay changed as a consequence, which you would expect.

So the assays themselves were shown to not just be precise and reproducible, but also highly sensitive to the critical quality attributes we think would affect the product performance.

DR. SOLOMON: Dr. Robinson?

DR. ROBINSON: June Robinson. I would like to suggest that the question of extrapolation really belongs to be deferred until we get to question number 3.

When we opened this session, there was the charge to the committee that we were basically

treading new ground and what we were doing was looking at the mechanism for endorsing a biosimilar.

In this question number 1, we are talking about analytic studies, and it is our job to say to the FDA and to the applicant that the way in which those analytic studies have been done is appropriate, and move forward to the next question.

DR. SOLOMON: That's a good point.

(Laughter.)

DR. SOLOMON: It is the basis for making inferences about extrapolation, so I think when we get to question 3, we'll rely on our conversation here. I think that's why we want to make sure we've had a robust conversation.

Okay. Well, we don't need to belabor this one if there's no further conversation. I think that there's been several points made. Dr. Siegel discussed binding assays, and also Dr. Scher asked about glycosylation and whether it had a relationship to immunogenicity. And I think that those issues were well discussed. We can --

DR. KOZLOWSKI: I hate to belabor, but one thing I'd really say is there were some differences in glycosylation. And again, I think if the committee thinks some of those differences could play a role in different indications, it would be good to discuss that now, unless it can come up later in the discussion.

DR. SOLOMON: Well, we could definitely bring it up later if there's no comments now, but I think that's a good point.

Okay. So we're going to move on to question number 2.

Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the studied conditions of use, rheumatoid arthritis and plaque psoriasis.

Dr. Brittain?

DR. BRITTAIN: I think that the clinical studies for the two indications that were studied demonstrate a fairly high degree of similarity. I was pleased to see no matter how you slice the

outcomes -- the primary outcome, the versions of the primary outcome, the secondary outcomes, time and time again, we do see exactly the same result in the two groups, or very similar results.

The low missing data rate was also very helpful so that when they did sensitivity analyses, in the most extreme sensitivity analyses, it was also the same. So that's all very positive with respect to this application, I feel, for the two studied indications.

I did want to make a comment, just a more general comment, really, for the FDA in general, that I'm not really sure I'm comfortable with preserving 50 percent of the benefit as being equivalent to saying something is highly similar. It's similar. It's better than nothing; a lot better than nothing. But I'm a little uncomfortable with that. I just wanted to make that statement.

If I had mentioned this before, I also think that it would be maybe more transparent to also present the results in terms of preservation of

benefit, both for the point estimate and the confidence interval. I know if I were a patient, that's what I would want to know.

I think the transparency of whatever the results are for the physicians and patients is going to be really important. Again, this isn't a criticism of the current product because the results are so far away from the margin that was set. But had the results been very close to the margin, I might have been quite uncomfortable.

DR. SOLOMON: That's very helpful.

Dr. Oliver?

DR. OLIVER: Alyce Oliver. I agree with what Dr. Brittain said. I think that there's been enough evidence to show that there's no clinically meaningful difference between the two studies between RA and psoriasis. However, I still have a problem, even though it's non-statistically significant, that there are the presence of the neutralizing antibodies when there's a switchover.

I do think it's a very relevant discussion that there will be non-medical switching, and that

that needs to have a larger group of people looked at going from brand name drug to the biosimilar to see if those neutralizing antibodies actually have a consequence.

DR. SOLOMON: Thanks. The question is narrow, and the data are pretty clear. We could stray pretty far easily -- interchangeability, switching, immunogenicity, et cetera, et cetera. And I think that it's at least worth us having the conversation. I'm not sure if that's how we'll vote, based on those issues, but --

DR. GELLER: I thought the two clinical trials were good. I like the FDA's analysis a little bit better than the company's, but only a little. I think they showed quite the same thing. I don't think anybody's answered the question of long-term effects, and this gets back to what Dr. Solomon just said.

DR. SOLOMON: So long-term effects, meaning that if they're switching over time or if there's immunogenicity, does that change --

DR. GELLER: Or they're switching back and

forth, which is possible.

DR. SOLOMON: Yes. Right. If you read this question, it's not really clear whether there's switching -- there's no switching discussed, but we all know that that's what the backdrop is. The clinical context is switching. So it's a little hard not to think about that when reading this question.

DR. REIMHOLD: Andreas Reimhold. We're talking about switching and non-pharmaceutical -- or the switching by drug plans. I think it does have to come up, and maybe we can add additional questions or additional recommendations outside of the framework of these questions, since these are important topics to us as a group and it needs to find a place somewhere.

DR. NIKOLOV: This is Nikolay Nikolov from FDA. Maybe I should clarify since Dr. Solomon brought up the question that this discussion point might not be as clear.

I think we base our determination of no clinically meaningful differences on the direct

comparison, and not necessarily the transition data for the determination of biosimilarity or no clinically meaningful differences.

Just want to clarify that this is really focused on the direct head-to-head comparison during the double-blind, randomized, controlled periods. And again, this is again in the context of the highly analytical similar products.

DR. SOLOMON: Thank you. Trying to keep us on task.

DR. NIKOLOV: Well, we have specific questions that we have to address for our review and decision-making, so we'll certainly try to convey this to the committee. And we understand that there are a lot of burning, high-profile questions and issues that were brought by the open public hearing speakers, and they're certainly on our radar again.

I just want to reiterate that the agency is currently thinking about this and working on this. But we have specific data and specific questions for the committee to discuss to help us with our

decision at the end.

DR. SOLOMON: Jennifer?

DR. HORONJEFF: Jennifer Horonjeff. I don't know exactly if this is going to be the place to bring this up, but since we're talking about looking at the studies with both psoriasis and RA, what I would have liked to have seen, too, is the inclusion of more patient-centered outcomes that can be relatable to the consumer who's going to be using them.

It looks like these ACR20 and the PASI, but at the same time, how is that meaningful to the patient. And I remember the last package we were asked to review in February, they did have more data that was more meaningful to the patient to be able to see. So since these two groups were the groups that were studied, I think it would have been a nice thing to be able to include other areas that could be looked at.

In terms of the RA study, with the longer-term, 72-week study that you guys have finished up -- I guess my question is, when we're presenting

these types -- we've convened here all together and you say that we have that data. It's months away from analysis.

Why don't we have that during our discussion today? Why the urgency? Because I think that would help really build some confidence either between us here at the table and to those listening in the audience and beyond, to make sure that we feel more confident about these medications.

DR. SOLOMON: Thank you.

DR. NIKOLOV: Maybe I can respond to that. But we would be really excited if there was good patient-reported outcome that could be studied in our indications. Unfortunately, we don't have many of these. But for example, for ACR or for the HAQ composite endpoints, there are patient-reported outcomes as individual components, like the physical function, which again shows consistent results with the primary endpoint.

DR. SOLOMON: Jose?

DR. SCHER: Jose Scher. I just wanted to ask a question. So is there a mandate for the

companies to perform short trials versus long trials? When you look at the February package, they had a 54-week data set both on efficacy, immunogenicity, and other outcomes. Is there a reason for not having a standardized way of performing these studies?

DR. NIKOLOV: I don't think there is a standardized preset time point or duration for safety or efficacy. Usually in the comparative clinical studies, these are equivalence studies that are based on specific endpoint, and that endpoint is chosen based on the data available in the published literature, and that determines when the endpoint would be assessed. For some studies, for some products, it might be week 14, week 30, or week 24, depending on the indication and on the product.

With respect to the safety, I think chronic administration beyond three months
or -- administration beyond three months we consider as chronic administration. And depending on the amount of the safety database -- again

that's determined on a case-by-case basis. In this case, we determined that that's reasonable to assess, descriptively, comparative safety and effectiveness and comparative safety and immunogenicity between the products. But the answer is, I don't think there is a preset duration.

DR. SOLOMON: But the point of having a longer-term study might be helpful as far as understanding the relevance of immunogenicity. If it develops by week 24, we want to see if there's waning of clinical benefit by week 52. This seems like a very reasonable expectation.

DR. NIKOLOV: Right. That's true. And if there were differences in the immunogenicity, we would certainly be more concerned, and we may need to see additional data.

In the case of ABP 501 program, both the incidence and the titers of binding antidrug antibodies and neutralizing antibodies were very similar, comparable, between the two products. So we didn't really have a concern or reason to expect

longer-term safety or efficacy data.

MS. ARONSON: Just some points of clarification on where I'm hearing this. As far as the two clinical trials, no inferiority of significance was identified, and maybe some slight improvement, as Dr. Becker pointed out, with site reaction due to the formulation. Am I correct in those two sides?

DR. SOLOMON: Injection site reactions, I don't think Dr. Becker was making it --

DR. BECKER: I did. I asked that question. The numbers were less, but they were very, very small numbers in both groups. So I don't know if I'd have a robust response to that. But they were less in the 501.

DR. SOLOMON: Great. Thank you.

Are there any concerns about the -- there were some issues raised about the body mass index and trying to understand whether -- I know that extrapolation is question 3, but we're talking about clinical data in question 2. And the data that are presented in the trials in RA and

psoriasis are what we have, plus the analytics data to extrapolate.

The issues around not understanding BMI and pediatrics, I think, do play into transitioning from question 2 to question 3. Understood that question 3 is really about the analytics and the chemistry. But having the subset of data and having a broader representation of patients -- because we're all really trying to feel confident with the extrapolation -- and I think that that's a common theme around the table.

Dr. Geller, and then we'll work our way down.

DR. GELLER: Just sitting here and considering the clinical trials, I wonder why the company chose these two diseases for its clinical trials rather than the others on the list. And in particular, I wonder if these are less severe diseases.

DR. SOLOMON: We can let the company speak to that. Yes?

DR. MARKUS: Thank you. It's Richard

Markus. We probably could have done one trial. And like I said, we chose to do two for added comfort, even though there's clearly still discomfort in general. I might add that the psoriasis study is a one-year study if you're talking about duration of exposure and duration of data. So we do have safety and immunogenicity data for a year.

So we did the two studies for added comfort, and we chose the two to bracket -- I think they're both diseases that are well measured, have good response rates. You can identify in psoriasis, say, the response is quite robust, and you're actually looking at the skin and measuring response.

So we chose them to go -- have a population that has no immune suppression and a population that's consistent with additional immune suppression, for the added information of safety and immunogenicity. That's how we selected the two.

DR. NIKOLOV: This is Nikolay Nikolov.

Maybe I can just add to that. I just want to clarify for the committee that there is no expectation, from the FDA at least, that there will be studies in multiple indications. We have not specifically recommended one indication or one population versus another.

In general, the clinical endpoints that are used for these clinical studies are far less sensitive than anything else before we get to the clinical studies. There are crude measures that can compare activity of a product versus placebo, and it has been shown historically to work well.

But when we talk about comparing differences between two molecules or two products that are potentially very similar, it's almost impossible to design a study to detect these differences. So we really want to emphasize this. And this is one of the reasons we don't think that the clinical efficacy is the key of determining biosimilarity.

Again, the biosimilarity is determined based on the analytical similarity, which is really a cornerstone in the assessment of biosimilars. And

then the supportive data are the clinical exposure, clinical PK, and potentially clinical efficacy; and in some cases might be a pharmacodynamic endpoint, not a clinical endpoint for efficacy for other programs.

So I just wanted to share our thinking about the development of biosimilars. We certainly acknowledge the community's nervousness and need for additional reassurance or confidence that these products would work in different indications.

Unfortunately, we are seeing biosimilar sponsors proposing to do multiple studies in multiple indications, which to us is not the right way to approach biosimilars.

DR. SOLOMON: Dr. Adler?

DR. ADLER: I wanted to respond to the body mass index or weight, and then just one other comment. It's Jeremy Adler.

With all clinical studies that we read in the literature, we always have to think about how generalizable they are to our practice. And without knowing the patient population in terms of

their weight, their body mass index, or even their age, although we know they're all adults, it's hard to know how this would apply to the broader practice for any one of our sets of patients, just in response to that one question, although pediatrics may be a separate issue for other reasons.

But the other just comment I wanted to make was, by the FDA not requiring a certain sample size or a certain duration of study, having small studies or short duration studies, bias is towards the null result. The smaller the study, the more likely to find non-significant results. So by not requiring any certain sample size, it's easy to come up with a sample size that you suspect will have no differences, even if differences may actually be present.

I just wanted to put that out there.

DR. SOLOMON: Dr. Streett?

DR. STREETT: Just to follow up also on the question of BMI and moving toward more personalized therapy, I wondered if levels were proposed by the

company to be available. Increasing data in IBD shows that they are very impactful and monitoring care and adjusting therapy. Are levels going to be -- I'm talking about drug levels and testing for antidrug antibodies.

DR. MARKUS: You're asking if we have the --

DR. STREETT: [Inaudible - off mic.]

DR. MARKUS: -- whether or not we'll make a test available? Sorry. So you're asking if we're going to make our PK-type data, the -- which test are you asking about? Whether we're going to make an immunogenicity assay?

Well, that's different. So drug levels are a different assay immunogenicity assay. That's what I'm trying to seek clarification. But we are exploring, with a commercial and non-Amgen lab, the ability to have another lab make the immunogenicity tests available, but that's not been concluded yet.

DR. SOLOMON: Wolpaw, and then Margolis.

DR. WOLPAW: Dr. Nikolov, I think you brought up a really important point, and I'd ask for a bit more clarification. And that is, you

said that the FDA will not be asking the manufacturers of biosimilars to show clinical evidence for every indication, right? Which makes sense to me.

So I would say that it's almost philosophical. So for me, since it's a biosimilar and not a bioidentical, why does the FDA feel justified in making that leap from the PK data and so on to the clinical extrapolation? I think that for me is the fundamental question going on here today.

DR. NIKOLOV: I think this is really the crux of the issue and the discussion today. We understand that a lot of the committee members are more familiar with the clinical data, but we didn't have a whole lot of discussion on the analytical similarity. Everyone agrees that the molecules were highly similar.

This is really the point that we want to convey, that we have reviewed the data and we have confidence in the data that the two molecules are so similar that we can rely on the safety and

effectiveness of the reference product, based on these data, with the aligning clinical pharmacology and additional clinical safety, efficacy, and immunogenicity in those indications studied.

So this is really important for us to convey to the committee. Whether the committee agrees or not, that's certainly up for you to discuss and decide. But this is really the premise of our approach to the biosimilars.

Again, these are not new molecules that we don't know anything about. We know a lot, and this proposed biosimilar for discussion, we think it's highly similar, or similar enough, to give us confidence that the mechanisms of action would be the same for all the indications that they are seeking licensure for.

This is supported by the clinical pharmacology or exposure data, and again, the clinical data in the additional clinical studies. It's not the clinical data that drives our decision.

DR. SOLOMON: You want a follow-up question?

DR. WOLPAW: I think that is the crux of the problem, is that you have people who are clinicians, and you are asking us to make a judgment that is out of our comfort zone. So thank you. That was quite helpful.

DR. NIKOLOV: Yes. Maybe just to add to that. We really, really made every effort to compile an advisory committee that would have the right expertise. I can confess that this was extremely difficult, but we did what we could.

As you can see, this is somewhat a very diverse committee, again, acknowledging that a lot of the clinicians are not familiar with these concepts. And we're trying to both educate, present the data, and ask you to discuss -- again, we certainly understand that there is a lot to ask from you for today and tomorrow, too.

DR. SOLOMON: Do you want to make another comment?

DR. KOZLOWSKI: So just to follow up on what Dr. Nikolov said. So it is a hard challenge for you to think about the analytical data when you

come from clinical backgrounds. But the reality is, again, manufacturing changes and other things. You've been, in some sense, unknowingly depending on analytical tools and comparability for decades.

So it really is an education issue. And I think that's why I invited you to rechallenge us, because there subtle differences in glycosylation. And based on a lot of experience, we're comfortable -- granted, uncertainty was raised, raised in the public discussion sections about this. But based on a lot of knowledge and experience we feel this is the information that we would use in making judgments and that we have used. Nothing is absolutely guaranteed, but neither is a clinical trial.

I think the role of the clinical trial is really once there's this baseline idea of analytical similarity, it's confirmatory. And the right clinical trial to do is the one that would be most sensitive to a difference, not necessarily an indication based on some other reason.

So that's really again the perspective we

have. And if it's difficult to understand, we want you to challenge us and ask more specific questions.

DR. SOLOMON: Dr. Margolis? Please just state your name again. Everybody just try to state your name for the record.

DR. MARGOLIS: Okay. I'm sorry. David Margolis, University of Pennsylvania.

Just to be clear about the clinical trials because I think there's some confusion here is that most clinical trials of biologics for psoriasis, for plaque-like psoriasis, have been 16-week studies with primary outcomes. To view these studies as being shorter may be unfair.

Having said that, they'll go on to have safety studies that go out to a year and even longer, and may switch from one product to another. There certainly are studies that have compared against active comparators of biologics that have already been approved versus ones that are about to be approved. So I don't want people to think that 16 weeks is somehow a shorter study, because that's

often what's done for approval for psoriatic drugs.

The other question was in terms of BMI, and it would be interesting to hear what's true for rheumatoid arthritis. In terms of BMI, psoriasis patients tend to be, let's say, robust in terms of their BMIs. So I don't think you're going to find a whole lot of truly skinny psoriasis patients that are going to be on the lower level of BMI.

That's been a reproducible finding. It's not necessarily something that they sought out, to find more robust patients in their studies. You're going to see that in almost every psoriasis study that's done, whether it's a topical or a systemic agent.

DR. SOLOMON: Dr. Hancock?

DR. HANCOCK: William Hancock. So I just wanted to make the point that today's analytical tools are extremely powerful. And the group that did the study, I think had a very wide range of analytical techniques. So I think that's an important point. The problem, of course, with these powerful tools you can now start to measure

very low levels of certain variants.

So then you're left with a conundrum. You see it. What does it mean clinically? But we now have the ability to do very detailed structural characterization of these complex molecules.

DR. SOLOMON: Why don't we go to Dr. Streett, and we'll work our way back.

DR. STREETT: Thank you. I think that just getting back to the discomfort with extrapolation, I know it's been mentioned that we do that, maybe without even being aware in different situations, but this is a new level of extrapolation across indications.

I think -- well I'll speak for myself -- if there was a mechanism in place where we were going to follow these patients clinically, real world, to see how they do, then I think that would make me feel more comfortable with that clinical impact of these potentially subtle differences in mechanism of action in IBD and things that we can't measure in an assay.

DR. SOLOMON: So just to push on that point

a little bit, it was raised earlier about a post-marketing surveillance program. Was that planned? And I think the comment was made, we'll do our typical phase 4 suggestions, but we don't have any specific requirements that we're seeing about a follow-up safety or efficacy, effectiveness.

DR. NIKOLOV: Maybe I can address this one. So if we have concerns about safety and efficacy, even in the indications that were not directly studied, I don't think we will feel comfortable with approving a product as a biosimilar all together. So asking for post-marketing studies is really contrary to the principles we use for assessment and approval of these products.

DR. SOLOMON: Let me just work our way back. I think it was Dr. Adler, and then we'll come back.

DR. ADLER: Jeremy Adler, yes. I want to echo that sentiment. But to that point, if we have any discomfort with potential safety signals, then maybe we shouldn't approve these. But we see there is more infectious adverse events in the ABP 501

group compared to the adalimumab group.

Now, that was one of many different outcomes looked at. And again this is a small study, so it's underpowered to detect adverse events. But the fact that we see it, any potential signaled adverse event, raises that question. If we can't do a post-marketing surveillance study or if we can't require post-marketing surveillance study, then perhaps this should be more concerning to us here.

DR. NIKOLOV: One clarification. Are you referring to the increased number in incidents after the transition?

DR. ADLER: Maybe I am. There was increased number after the transition.

DR. NIKOLOV: In both RA and psoriasis studies during the period of controlled comparisons, actually the incidence and the rates were slightly higher in the comparator products or at least similar in the psoriasis study.

I guess you're referring to the extension, which is the single transition from EU adalimumab

to -- or EU Humira to ABP 501?

DR. ADLER: Yes, correct. So it was the transition study. Maybe I should not talk about the transition study since we're not --

DR. NIKOLOV: Right. So again, I just want to remind the committee why we generally ask for or expect to have transition data, and this comes back to the safety of immune-mediated events that can result from the minor differences that we cannot maybe pick up analytically, but they can result in somewhat different immune response. These are usually injection site reactions, hypersensitivity, anaphylaxis. And these are the primary focus of the descriptive safety comparison with the transition.

There is no really reason to expect that transitioning from the reference product to the biosimilar would result in more immunosuppression or different infections. So these numbers are likely to represent a chance finding between the two groups, and are unlikely to reflect clinically meaningful differences.

DR. ADLER: Chance findings can happen in any study, of course, but I'm not sure that we can -- well, the transition study aside, since that's a separate issue, back to the issue of these being small studies, they're underpowered to detect safety signals. All of these studies are. So it would seem that a post-marketing surveillance study would be appropriate.

DR. SOLOMON: Dr. Geller, and then we'll come over here.

DR. GELLER: So we're talking about extrapolation, whether we're actually addressing it -- or calling it question 2 or question 3.

So I understand the letter of the law says extrapolation is permissible provided the trial was okay and the underlying basic science was okay. But what if the extrapolation -- we say, yes, extrapolate, and what if it's wrong? Will we ever know?

DR. KOZLOWSKI: So again, I think if you just look at the clinical studies, you worry about this. We feel the totality of the evidence, all of

the things together, makes this something we feel is appropriate to approve for these indications. And that's a decision of the agency.

But I think the question about are we wrong, we can be wrong about approving a new drug. Safety things can come up. We can have a drug that's been successful on the market for years, and there's a manufacturing change or a problem with the factory that we don't pick up on inspection or something, and then we need to be able to have surveillance on that.

So I think what's critical to say about this is not so much whether we're going to have specific product studies for each of these, but whether our post-market surveillance is good on all of these products. And I think that's certainly an agency goal. And our draft naming guidance, one of the driving forces of our logic and goals in how we approach this, was to have product-specific pharmacovigilance.

I think, again, we don't feel that if we approve a biosimilar for certain indications, that

we have uncertainties such that we would design a specific study for that. But the idea that we would want to be able to have post-market pharmacovigilance on all products is very, very -- is a key agency initiative, and I think addresses the fact about sometimes we're wrong about something. But again, it's not just about biosimilars. It's about originator products. It's about products with manufacturing changes. So the surveillance is critical across the board.

DR. SOLOMON: Dr. Hohman?

DR. HOHMAN: It's Bob Hohman. Like it or not, according to the FDA, the criteria for this, we're supposed to evaluate it based on the analytical similarities -- or not between the two products.

So now we're spending a lot of time talking about clinical studies, which is just confirmatory. In a way it's not fair. It's not fair to put that much attention on the clinical studies when it was secondary to the primary study, which was the analytical identity -- the similarity between these

products, because we're not going to get the answer. The answers that we want, we're not going to get from these studies on the clinical side.

DR. SOLOMON: Dr. Adler? Oh. I'm sorry. Dr. Bergfeld and then Dr. Adler.

DR. BERGFELD: I want to say that I feel very comfortable. What you just said about the FDA's surveillance after the drug has been approved, or a drug has been approved, it sounds to me like you're redoing some of the post-marketing studies.

Instead of calling them studies, you're going to have to call them surveillance. Whatever you do, if you're redoing a lot of the activities of the FDA and streamlining it more, it would seem the post-marketing portion would also be streamlined.

If that be so, then the clinicians sitting around this table would feel a level of comfort that there was someone that would receive some data and we would report some adverse events.

DR. KOZLOWSKI: So again, there are other

people who more expert in exactly what we're doing in terms of surveillance. But we're both interested in passive surveillance, the MedWatch, but also active surveillance, the Sentinel program.

There certainly is an interest, the agency as a whole, in doing high-quality pharmacovigilance that is sensitive to things that happen on the marketplace. So that is certainly an interest to the agency, and again, above and beyond just biosimilars.

DR. BERGFELD: Could I ask another question? What is your experience with following Humira over the years it's been out?

DR. KOZLOWSKI: We have post-market safety update reports that -- we have the things that are required. I mean --

DR. BERGFELD: Are there any signals coming?

DR. NIKOLOV: So there have been several class labeling changes for safety concerns that came over the years. And again, they come through I think primarily passive surveillance over the years.

But we do pick up signals. We investigate these signals, and if they are significant enough we update the labels, whether it's for a specific product or class labeling changes, as is the case with the TNF inhibitors. There have been multiple of these over the years.

DR. CHRISTL: If I can jump in really quickly. Leah Christl from FDA. Just to very specifically address your comment, the biosimilar products will not have a post-market surveillance program simply because they're biosimilars, but they will be subject to the same post-market surveillance and pharmacovigilance requirement as any approved product.

So they will have the same expectations in that post-approval phase in terms of collecting adverse event data, making reports to FDA, so on an so forth, as any other biological product. There's no abbreviation of that aspect of it. It's an abbreviated licensure pathway or approval pathway, but they'll be subject to the same requirements as any other biological product post-approval.

DR. SOLOMON: Dr. Adler, and then Dr. Wolpaw.

DR. ADLER: To come back to the basic science and molecule and pharmacokinetic side of things -- and this is Jeremy Adler, by the way -- so we've seen a lot of data to show that this molecule is highly similar to the original Humira molecule, but we've seen that for primary, secondary, tertiary structure.

We haven't seen data, and I understand it's difficult to measure the quaternary structure and all of the other pieces except for what we're calling the minimally biologically active or non-biologically active.

But the point I wanted to get to is, since we can't adequately measure how different the quaternary structure is, that's where it seems to me that these little tiny studies on switching, both within the ABP 501 study, as well as what we've heard from the -- and we've seen from the infliximab biosimilars switching; even though we're not talking about switching in this meeting, that,

to me, signifies there may be some immunologic significance to the larger structure of the molecule.

Again, I'm a clinician; I'm not a basic scientist, but if there is a signal seen in switching from the original product to the biosimilar, either here or infliximab or somewhere else, with increased adverse events or increased neutralizing antibody formation, that suggests there's some sort of difference that we're not otherwise measuring here.

DR. WELCH: I guess I would note that antibodies, just as a class, are highly stable structures for which there is a great deal of understanding for their stability profiles -- how they degrade, how they behave -- as well as in terms of their quaternary structure, and the exhaustive nature of the -- the structural characterization would find that one of those tests would likely be able to show the difference if there were truly one there.

DR. ADLER: Those are the antibodies that we

know to measure. But the immune system creates lots of antibodies that we don't measure.

DR. KOZLOWSKI: But again, antibody domain structures are very well understood. The way they fold is the disulfide bonds influence that, and they were looked at as part of this analysis. If there was really some misassociation of domains, it would show up in some of the other spectroscopy in terms of changing other parts of the structure.

So we think it would be very unlikely that there is changes in the way the subunits or domains of the antibody interact with each other.

DR. SOLOMON: Dr. Wolpaw? And then maybe we're going to have a 15-minute break after this one, and then we're going to move on to question number 3.

DR. WOLPAW: So given that you're asking us to decide if we can use analytic studies to extrapolate to diseases, I wonder if there's any follow-up to the infliximab biosimilar decision that was made, if we could use that in some way to better understand our ability to take analytic

studies to clinical extrapolation.

DR. NIKOLOV: I'm not sure whether we can comment on an application that's not for discussion today. I think for the Celltrion's application, we took a similar approach, even though there were some differences in the ADCC mechanism of action. And that was up in the public domain, and Europe voted for approval of all indications. Health Canada did not.

We took the approach that these differences -- even with these differences that ended up within the quality range of the reference product, we considered these molecules highly similar and determined that this is a biosimilar with extrapolation to all the indications, which is an approach that we take for this product as well.

DR. SOLOMON: Okay. I'm going to try to summarize, and then we're going to for a break.

Dr. Brittain and others talked about how, that the clinical data were highly similar and there was little missing data, which was important.

Dr. Oliver and Dr. Geller asked or pointed

out the importance of long-term effectiveness data.

Dr. Reimhold asked a question of whether we should be splitting off some other questions to perhaps vote on, or at least have some other discussion questions.

Dr. Horonjeff pointed out the importance of patient-reported outcomes. It was mentioned that many of the rheumatologic outcomes really do have an important patient component.

Dr. Scher talked about the standard length of assessment and possible immunogenicity that we could pick up with longer trials. However, it was pointed out that many psoriasis trials are 16 weeks, so this is really robust data for psoriasis.

I think the FDA team attempted -- I'm not sure they succeeded -- to educate the rest of us about the importance of the analytic data and the framework that you've been thinking about a lot longer and more deeply than some of us who are assembled. So we appreciate the input.

Dr. Wolpaw asked the question of why can we

extrapolate, which I think is an important issue. There was a comment made by one of our chemists that, really, we have excellent analytic ability, and we were shown some excellent assays with important similarities noted in the data.

There was a discussion about phase 4, the importance of post-marketing surveillance and the FDA points it out that this is a standard part of the procedure. But there was no specific concerns that would dictate specific phase 4 questions around biosimilars.

There were some questions about the quaternary structure, and I think the FDA answered those issues. And I think I hopefully summarized most of the conversation, but I'm sure I missed some points.

So we will break for 15 minutes. Why don't we come back at ten till, and we'll take up the next question.

(Whereupon, at 3:36 p.m., a recess was taken.)

DR. SOLOMON: Okay. We are going to

reassemble. So we've gone through questions 1 and 2, and now we're moving on to question 3, which is up for you to read. And I'm just going to read it for the record.

Please discuss whether the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira for the following additional indications for which US-licensed Humira is licensed:

Juvenile Idiopathic Arthritis in patients 4 years of age and older: psoriatic arthritis; ankylosing spondylitis; adult Crohn's disease; adult ulcerative colitis. If not, please state the specific concerns and what additional information would be needed to support such a demonstration. Please discuss by indication, if relevant.

So I think there's been some concerns obviously around the inflammatory bowel diseases, the fact that the mechanisms are not as well understood, and there's also been some concern about pediatric populations that have been voiced.

Do people want to pick up on those issues?

Dr. Waldman?

DR. WALDMAN: I'll nucleate the discussion.

DR. SOLOMON: Okay.

DR. WALDMAN: So a straw man for the group to consider. Because I have less clarity now than I did before we started answering all these questions.

So the straw man. The paradigm, the framework for biosimilarity is to reduce residual uncertainty, in part based on the mechanism of action, and this question is specifically asking us about clinically meaningful differences.

My observations, listening to the discussion, listening to the presentations and reading the materials, is that we have a clear mechanism of action for TNF binding. Maybe not so clear a mechanism for action in ulcerative colitis and Crohn's disease.

The TNF alpha mechanism of action applies to, as far as I know, all the arthritidies and psoriatic arthritis. And so the compounds are

pretty similar in analysis. They perform similarly in mechanism of action for TNF alpha binding, and they perform similarly clinically in the two studies that were done. By the way, a very robust package; it's a wonderful package.

And so from my perspective it's clear that from -- this is me speaking -- it's clear that you can extrapolate by mechanism of action from reduced residual uncertainty to the arthritides and to the dermatologic applications.

What's not clear to me is the unknown mechanism of action for inflammatory bowel disease, and the fact that we don't have -- maybe not the right terminology -- the bridge to clinical activity in that indication.

And so for me, the residual uncertainties were not reduced based on mechanism of action in a clinically meaningful way. I'm just putting the pieces together using the regulatory terminology. So I open that up for discussion.

DR. SOLOMON: Don?

DR. MILLER: Don Miller. I'll take the

opposite point of view. Just because we don't know for sure how it works in inflammatory bowel disease doesn't mean that we can't extrapolate. The company did look at a lot of potential mechanisms of action. In fact, on company slide CA21, they look at two dozen or so potential mechanisms where the two products seem to be identical. So to me, I feel pretty comfortable with the GI indications.

DR. SOLOMON: Diane?

MS. ARONSON: Dr. Miller just expressed where I was sitting, so thank you.

DR. SOLOMON: Dr. Adler?

DR. ADLER: Jeremy Adler. Thank you. So I share your concerns, Dr. Waldman, and one of the questions I have in follow-up to the last set of discussion before the break is, so it's been demonstrated pretty clearly that this molecule is highly similar to the original molecule. It sounds like the science is pretty clear on that.

The question that I have, given how strong the technology is, to identify even at the quaternary structure level that this molecule is

similar to the originator molecule, how much experience do we, the medical world, have with identifying something that's highly similar structurally and then seeing how it plays out clinically?

Do we actually know, in fact, that clinically it winds up being the same? Do we have a track record of this? Are there examples of where there are unanticipated clinical outcomes? And again, this is the clinician speaking. I don't have an understanding of the basic science.

But assuming these molecules are nearly -- we can't say nearly identical -- highly similar, how confident are we that that actually does confer identical or nearly identical clinical activity? Do we have evidence of that?

DR. SOLOMON: Do any of the pharmacologists want to take that on, or anybody from the FDA?

DR. KOZLOWSKI: So again, as I mentioned before, there's experience with manufacturing changes, and there are actually are third parties that have compared products that they've purchased

and predicted manufacturing changes occurred based on subtle differences in structure.

So these products have been used, sometimes with clinical data for the manufacturing changes, sometimes not. And I also think every time you use a different lot, you're using a slightly different product. Because if you look at some of these graphs with distributions of lots, some of it's assay variability, but some of these assays, like glycosylation, may be incredibly tight.

So really, one lot of patients get, it's over here. The next lot, it may over there. So when it comes to how close is close enough, I think within the clinical world -- again without necessarily knowing it -- there have been subtle differences in the products your patients have been getting.

DR. ADLER: But those are across the same drug with different variations in manufacturing.

DR. KOZLOWSKI: Right. But again, this is a bigger change, different cell line. But the concept is, right, it's a molecule. Right? And

the question is how structurally different is the molecule?

So there are slight structural differences lot to lot. There are some structural differences between these molecules that may be larger. But there's also clinical data that is confirming that, which may not be true of many of these manufacturing changes, and it's certainly not true about lot to lot variation.

DR. ADLER: So just to be clear, should I understand that the knowledge of the molecular structure has been linked to clinical outcomes with other drugs to show that that actually can predict that it's a similar outcome in other situations?

DR. KOZLOWSKI: So there have been manufacturing changes that have had large clinical studies. Some of them have had subtle differences. Some of them have succeeded. There have been probably some manufacturing changes that have not passed the clinical study. But again, the vast majority of these changes have not had any effect. Some of them have had PK comparisons. Some of them

have simply -- again, the experience in the marketplace has not shown any changes.

So it's a lot of different kinds of changes and different kinds of data. But the idea that these differences -- any one of them is suddenly, potentially a risk for a huge clinical difference, I think that's unlikely based on this large history of manufacturing changes. It depends on the change. It depends on the functional data.

That's why the sponsor, the assays they did and as reviewed by the FDA, very much looked for whenever there's a difference, is there a functional assay that might show whether or not that difference is likely to matter.

So as an absolute case, do we always know any subtle difference for sure, 100 percent, about what it's going to mean? Probably not. But we use this judgment all the time, and we've used it for decades, since biologics have started.

If it wasn't for manufacturing changes, biologics would have never been able to meet the marketplace. So this is a bigger change because

it's a different cell line and a different manufacturing, but that concept that we make a multidisciplinary judgment about the impact of a change -- and I think the history of these products has been very successful. So obviously, we have not been making lots of bad judgments in terms of these comparability exercises.

DR. SOLOMON: Dr. Geller, did you have a question? No. Dr. Curtis.

DR. CURTIS: Yes. Sean Curtis. As a comment, I share certainly some of the uncertainty that Dr. Waldman articulated. It's just when I think about this, I'm not convinced a clinical trial, which is sort of the inference of the comment, will sort of decrease the uncertainty.

I think that's really my own personal opinion, that given the crudeness of the clinical endpoints, particularly in IBD, that the difficulty in running those trials, the variability one gets in those responses, and frankly the size of a trial one would have to do to try to decrease that residual uncertainty, I'm just not personally

convinced that that would add much to the data set.

So that's where I try to balance in my mind, this uncertainty with, well, what more could we do to decrease the uncertainty? And I'm just not convinced a trial is the answer.

DR. SOLOMON: Is there anything you can imagine that would decrease the uncertainty?

DR. CURTIS: So I actually, personally, think that the current package is adequate. I think we can never know with certainty, but we make many decisions without absolute certainty. There are drugs approved for which we don't frankly know the definitive proof of action. I think the fact that we know the originator works in IBD -- we've talked ad nauseam about the robustness of the analytics -- I personally feel like it's an adequate package.

DR. SOLOMON: Dr. Becker?

DR. BECKER: So I may be showing my ignorance here, but I think your point, Scott, is a really good one, as far as -- sorry, it's Mara Becker -- as far as these potential mechanisms of

action, but I think at the end of the day, they're still just likely implausible. And I'm not sure -- maybe it has been done, but I'm not sure -- that the reference product, that Humira, has actually been proven without a doubt to have these mechanisms of action, either. And when I look at the data that was brought up by Don Miller and the concept of where the CDC graphs fall, and the Fc binding falls, and the ADCC falls, they are quite similar.

So I'm not sure if we're getting hung up on the mechanism of action that A, is still just likely or plausible, and B, may not have been proven beyond the shadow of a doubt with the reference product to begin with. I could be ignorant, for sure, but I think that's where -- I don't want to get caught up on tangents that may never be solved, not even with the reference product that we're comparing it to.

DR. SOLOMON: Dr. Streett? Did you --

DR. STREETT: Oh, no. I just was going to make a -- I don't know if anyone is aware of this

biosimilar, erythropoietin product, that caused an autoantibody production in an aplastic red cell anemia. Just as an example of --

DR. KOZLOWSKI: Steve Kozlowski. So there's a historical event, which was a manufacturing change, probably formulation and container closure, which led to pure red cell aplasia, which was a long time ago. And again, we've come a long way since there. That's a product which has a very high immunogenicity risk profile. We would treat the burden of data, I think, based on the product immunogenicity risk. This is not the same as here.

There was also a biosimilar study done for Europe where there was two cases of neutralizing antibody to an erythropoietin product. There was a root cause analysis of that, but interestingly enough, it was picked up in development.

That product was never marketed. With the route of administration, it was a risk for pure red cell aplasia. So you could say, that shows there are risks, but it could also say that at least within the package that the European regulators

expected, that was sufficient to have picked up that problem.

DR. SOLOMON: Dr. Solga?

DR. SOLGA: Dr. Steve Solga, responding to Dr. Waldman again also. I share your concern, but I reached the opposite conclusion; just I like to stay in the shallow water along with maybe Dr. Becker and say, look, we don't know. And reading directly from the law, the law says we don't have to.

The law says that the applicant submitted under the subsection, shall include information demonstrating that the biologic product and reference product utilize the same mechanism or mechanisms of action, blah, blah, blah, blah, blah, but only to the extent that the mechanism or mechanisms of action are known for the reference product. And I think that there's a lot that's not known about biologics in general in GI, and that shouldn't be ABP 501's burden and to figure out today.

DR. SOLOMON: It was just a straw man that

Dr. Waldman --

(Laughter.)

DR. SOLOMON: Yes. That's good. No, it's great discussion.

Dr. Mager?

DR. MAGER: I just wanted to mention, I also agree with the FDA's interpretation and I think that the analytical data are compelling; that these are very highly similar and can be extrapolated.

I also wanted to mention, because the pediatrics component came up earlier -- and I think that I'm also very comfortable seeing this extrapolated to pediatrics as well -- I think unlike small molecule, the physiological mechanisms that sort of govern and regulate the disposition of antibodies are fairly well understood, and I don't see any reason here why you wouldn't expect comparable pharmacokinetics in that patient population as well.

When you consider things like binding to the target, influencing the disposition, you don't have any of that here. Even though it's not a

prerequisite, the PK looks pretty comparable across the diseases as well. So I think many of the mechanisms governing the pharmacokinetics of these compounds are well understood and will likely translate fine in the pediatric population as well, even without the data present.

DR. SOLOMON: Dr. Brittain?

DR. BRITTAIN: So I did just want to respond to Dr. Curtis' comment, if I understood it correctly, that he didn't think he would learn anything more from a clinical trial, if that's what you said. I understand that the whole paradigm here is that you're not going to do a trial in every indication, and I accept that. But at the same time, I feel I would clearly learn more from having the clinical data, if one could have it, a blunt instrument as a clinical trial is, nonetheless.

DR. SOLOMON: Okay. The pediatric issue I think we've have some conversation on, but not a huge amount. And I guess the question that I have as an adult clinical rheumatologist and researcher

is, are there other examples where drugs haven't translated to pediatric populations in their clinical pharm in ways that can help us think about this extrapolation?

I understand that in the adults, the data are very, very similar. And I don't know of a reason why it should be different in pediatrics, but I'm perhaps not smart enough or aware of the literature to know if there is a reason that we haven't uncovered yet. Any pediatric clin pharm expertise sitting here that can help us?

DR. BECKER: So I guess that's me. So I think for this drug particularly, certainly there could be examples where kids -- we would, of course, love to have the saying children are not just little adults.

In this drug particularly, there are only two dosing strategies that are stratified by weight, and at least in the cursory look at PK for the reference drug, it's not really dissimilar between kids and adults that significantly.

So we are not talking about micromanaging

dosing per kilo. It's literally 20 milligrams for kids less than 30 kilograms, and 40 milligrams for kids greater than 30 kilograms. So it's a little bit, maybe, easier to extrapolate. And certainly from a monoclonal antibody perspective and a disease process perspective, we're still targeting TNF too. So that mechanism of action holds true for kids as well as adults. So I was comfortable with it.

DR. MARATHE: This is Anshu Marathe from FDA. So to answer your question on pediatric extrapolation from the agency's perspective, extrapolation in pediatrics is not something new. We've got a guidance out here, which was published, which very clearly lays out the principles, even for new molecules, when and where can an extrapolation be possible. And one of the few prerequisites is that the disease progression should be same.

So here we're talking -- here it's a different scenario where we consider that the molecules are similar analytically and that allows

us not to just extrapolate across indications, but also to pediatrics. And also in pediatrics, we're even more comfortable because we've done this in new molecular paradigm as well.

As Dr. Mager just highlighted, in terms of biologics, any kind of extrapolation from a PK perspective is much easier in biologics compared to small molecules, which makes us even more comfortable in the biologic space.

There have been examples of extrapolation, and here, in terms of biosimilar, we're talking of a slightly different paradigm as well. We are thinking that the molecules are the same based on analytical similarity. So we're not only just comfortable extrapolating across indications, but as well as in pediatrics.

DR. SOLOMON: Thank you. Are there other comments on this question? Dr. Adler?

DR. ADLER: It's Jeremy Adler. Thanks. So I actually agree with the previous comments on pediatric patients, and we extrapolate all the time in pediatrics and have a long history of this. The

only concern that I have is that we have seen no data on dosages for smaller individuals, whether it's adults or pediatrics. We've only seen data on one set of dosing, and that's all. Otherwise, I don't have any specific pediatric concerns. It's more body size.

DR. SOLOMON: Do those data exist? I'm asking the applicant, the agency.

DR. MARKUS: Richard Markus. The psoriasis study had the 80 milligram loading dose followed by the 40 milligram. Otherwise, everything was 40 milligrams.

DR. SOLOMON: Okay. Dr. Reimhold?

DR. REIMHOLD: Andreas Reimhold. I was just summarizing in my mind earlier that in terms of clinical trials in pediatrics or in IBD, for example, we'd be happy if the compound worked as well as the Humira comparator, or even if it worked less. If it worked not at all, we would stop using it rapidly. So it comes down to, is there additional harm being done in pediatrics or in IBD patients that we're not aware of? That would be

the major concern. I think we talked at some length about that previously.

DR. SOLOMON: Okay. I can summarize if we're done with our conversation. It seems like we are. On this question number 3, regarding extrapolation, Dr. Waldman put out the straw man questioning the extrapolation to IBD, asking about mechanism of action and that being the cornerstone of being able to extrapolate. Dr. Miller and Dr. Mager thought that there was a lot of similarity and that the extrapolation was really okay.

Dr. Adler asked the question about structure and function and whether we understood how quaternary structure might impact function and slight differences, and there was some data brought forward by the FDA.

Dr. Curtis asked kind of rhetorically whether there were other studies that could be done to help with this extrapolation to IBD and really wasn't able to clearly articulate what those might be in this setting. I don't know if everybody

around the table completely agreed with that. I think some other issues were raised.

The question about dosing was raised, and we just heard that conversation in that Dr. Reimhold just talked about the adverse events that would be of concern because the efficacy would be clear pretty quickly and we would stop using it if that was the case.

Did I miss any other streams of conversation or comments that were made?

(No response.)

DR. SOLOMON: Okay. So we're moving on now to question 4, which is a voting question. And I'm going to read the question, and then I'm going to give you some instructions.

Does the totality of the evidence support licensure of ABP 501 as a biosimilar product to US-licensed Humira for the following indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure -- RA, JIA in patients 4 years of age and older, PsA, ankylosing spondylitis, adult Crohn's, adult

ulcerative colitis, and psoriasis? And we want people to explain the reason for the votes.

Are we going through the electronic voting? Yes. Okay. So just to give you some instructions about the electronic voting system, we'll be using an electronic system for the meeting. Once we begin the votes, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

So when it says you may press the corresponding, that's of your changed vote. So if you were a no and you want to go yes, you hold down yes, I assume. Did I read that correctly? Yes? Okay. Thank you.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen and the DFO will read the vote from the screen into the record. Next, we

will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed. So that's one question.

So if there are no comments concerning the wording of the question, we'll now begin the voting process. So we're voting on the package of indications. We're not voting on any specific indication. Just to clarify, if you don't believe in one of these indications, your vote would be a no; otherwise your vote would be a yes. Any questions or comments regarding the question?

(No response.)

DR. SOLOMON: Okay. So if there are no questions, then we'll proceed to the voting process.

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection,

the light may continue to flash. If you're unsure of your vote or you wish to change, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. SOLOMON: Okay. Everyone has voted and the voting is now complete, so we can take our fingers off the buttons I guess. Okay.

MS. CHOI: For the record, we have 26 yes, zero no, and zero abstentions.

DR. SOLOMON: I'm going to go around the room starting from the right, or do you have a list? I'm going to start at the voting end here. Dr. Curtis, you're not voting. Dr. Siegel?

DR. SIEGEL: Sure. Richard Siegel from NIH. So I voted yes. I think I discussed my thoughts on the Fc receptor binding and activity assays, which in my opinion are the best available predictors of efficacy and allowing extrapolation to IBD. And the clinical studies I thought were adequate in the two indications that they were tested for.

DR. NATHANSON: Jeff Nathanson. I voted

yes. The robust analytic data was obviously the foundation, and certainly the supporting clinical, and I felt very comfortable with it as well.

DR. SOLGA: Steve Solga. I voted yes. I thought the vote was easy, and I thought it was easy because the charge to the committee today was really quite narrow. Like February, we were asked to follow what the 351(k) pathway said and look at the data and compare them.

But like February, I've not seen such a disconnect between the charge to the committee and the concerns of the public, and I'd like to have that noted. And I've been on again/off again these committees for six years, and the disconnect is really quite remarkable.

The public brought up very many concerns in both written statements and oral statements, both February and today. It just wasn't today's committee's charge, but these are essential issues, and they need some forum to be aired out fully and completely.

That I can tell, this was passed in 2009.

And 2010 the FDA held a two-day public forum for solicitation of input, but that I can tell on Google, it's not happened since. That I can tell, it's the Senate HELP Committee that's charged with overseeing these issues, and they've heard from their constituents and from time to time have asked the FDA for a progress report.

In September of 2015, Dr. Woodcock spent a day there explaining the significant progress from the FDA. I would suggest that the 20 open public forum speakers today all write to Lamar Alexander, who's the chairman of this committee, and say, we want to come and have 90 minutes of your time to recite what we've recited today because we didn't get done what we needed to get done today for them.

DR. FEAGINS: Linda Feagins. I voted yes, and in my vote it was really focusing on answering the question that was put before us. And looking at the analytical data, it was very compelling that the drugs were highly similar. And then seeing the clinical efficacy in the diseases that were studied was reassuring.

DR. STREETT: This is Sarah Streett. I guess I struggled over it a little bit. I thought that the totality of the evidence, particularly for the indications that had small clinical trials, was very convincing and the science looked well done.

I agree with what Dr. Solga, said that there are other issues that we weren't charged to tackle but remain floating about and I think are really paramount. And I hope that we are more empowered to be involved in exploring them together going forward.

DR. ADLER: This is Jeremy Adler. I voted yes also. And my main concern was the lack of clinical data, both for inflammatory bowel disease, as well as for the pediatric indication.

That said, the evidence still was strong enough for me to vote yes. But I still feel, given that there's lack of clinical evidence, that it's important to have a specific, deliberate, prospective, post-marketing surveillance study. And I would suggest something that's not voluntary but more deliberate than that so that we can know

going forward, did we actually make the right decision? And I also agree with what Dr. Solga said as well.

DR. BERGFELD: Wilma Bergfeld. I voted yes, and I want to say I've been most impressed with the presentations both by the panel members, the FDA, and the presenting company.

I'd like to speak also as the chair of the Cosmetic Ingredient Review Committee, which is looking at cosmetic chemicals and the toxicology, and say they, too, are moving to structural analysis and less clinical analysis. So it seems to be the movement of the future with all the new technical advances, and I congratulate you.

I also was impressed with the public's presentation and I agree that all of their statements need to be considered. I've made note of them and would be happy to -- if you didn't record all that, I'd be happy to send you my records. So thank you.

DR. ROBINSON: June Robinson. I voted yes, because of the narrow constraints of a biosimilar

application. This does not seek interchangeability. And I await the FDA clarification as to the rules for interchangeability, and suggest that we would like to see this move forward with dispatch as it is an extreme concern of clinicians as this moves forward in the marketplace.

DR. MARGOLIS: My name is David Margolis. I also voted yes, again, at least because I thought that the information that we were given about biosimilarity in terms of the analytics was excellent. However, as a pharmacoepidemiologist, I also agree with the earlier statement that I find it shocking that in 2016 that we're still only relying on passive systems like Sentinel and MedWatch, and that we don't have mandatory post-marketing studies, not just for biologics, but also for drugs and devices that are approved on these sorts of pathways.

DR. GELLER: Nancy Geller. I voted yes, despite reservations about extrapolating from the data we had, which was very good, to the data we

don't have, and will never have.

MS. ARONSON: Diane Aronson. I voted yes, because I thought they were robust presentations, that ABP 501 is highly similar to Humira, and there's no clinical meaningful differences. I also was really supported by the FDA's presentations and clarifications.

DR. HORONJEFF: Jennifer Horonjeff. I also voted yes. And I think the package that was presented, I still had some questions there, but I think the robust discussion that we had certainly helped to convince me to vote yes.

But while I'm here on the record, I'd also like to echo the sentiment of those who gave testimony today and what had been brought up before, that I still think we have a disconnect with how this is being conveyed to consumers, and there's a lot of uncertainty on their end.

I certainly think -- I know that we're being charged to not talk about things like cost and other areas, but that's really the silo mentality which a patient never exists in, since they're

constantly having to deal with all these different things.

So I think we need to figure out a way to help bridge that gap so that they can better understand, because as one of the people giving a testimony today said, "As soon as we get the uptake of the patient, that's when we're going to succeed." So we really need to think about the consumer as well.

DR. OLIVER: Alyce Oliver. I voted yes. I felt like the totality of evidence supported licensure and also the extrapolation to the other indications. I want to support the public's concern about non-medical switching.

DR. MILLER: Don Miller. I voted yes. Again, we have this quandary that we're having our decisions clouded by public policy issues like non-medical switching. But Congress created the law and the pathway; FDA just has to enforce it and we have to vote based on that. So I think it was an easy decision to vote yes.

DR. BECKER: I'm Mara Becker. I voted yes.

I thought the Amgen package addressed the biosimilarity for ABP 501.

I'd like to echo Dr. Horonjeff's point about education. When you see how difficult it was for us to come to grips with understanding the purpose of and the pathway for biosimilarity and then try to disseminate that to the public so that they understand it, too, I think it's going to be really important moving forward, as we continue to be addressing these new agents, not only for acceptability and for safety, but for the public to understand the rationale and how they were approved.

DR. SOLOMON: I'm Dan Solomon, and I voted yes. To echo some of the points that have been made, it was an excellent packet, and the FDA did a very nice job of explaining how to interpret the information in this setting.

Concerns that were raised, which I want to emphasize, are the importance of post-marketing surveillance data. Here we have -- even though we may not have any specific concerns, we have a lack

of data, and those data are going to be collected in the ensuing months and years -- or they can be collected if the agency asks them to be collected -- and we can learn about the indications that we really were not presented information about.

The interchangeability is just a critical issue to the public. We have energized public sitting here today, and I think the agency can reach out and work with the public on an educational campaign to make sure that they understand what biosimilars are doing, what they can do, what they're not doing, because I think everybody in the public, as well as physicians, providers, assumes that if a biosimilar is approved, that it is interchangeable. But that's not really what we all voted on and that's not what the law says today.

I think the naming issue is tremendously important because of the post-marketing surveillance. I think the industry and the agency have to get together on those issues.

DR. JONAS: Beth Jonas. I voted yes. I was very comfortable with the analytic data that showed biosimilarity and with the clinical studies that we saw. So I was very comfortable with the extrapolation.

I share your concerns and everyone else's concerns about education. But I also want to mention that the payers are going to need to be educated also because oftentimes, the payers are the people who are making the decisions about the medications.

I think that's my primary concern, is to see, once the biosimilars are out there and we're using them and this idea of interchangeability and who's really making the decision. I think physicians should be making the decisions and not payers.

DR. REIMHOLD: Andreas Reimhold. I also voted yes. And again, the analytics and clinical trials were convincing and easy to accept. I was helped by the fact that the pediatricians and the GI specialists in the room were accepting of using

this kind of approach of dealing with the uncertainty of having a drug whose exact use and dosing may not be totally clear initially. But that's part of your field, I guess, and it's an uncertainty you've learned to accept.

So in terms of the interchangeability issue, I think the FDA will write a label for this drug, and it wouldn't be wrong to start very close to the first sentence and say, this is a biosimilar, not an interchangeable drug.

DR. WOLPAW: I'm Terry Wolpaw, and I voted yes. I voted yes because I felt that the analytic studies were extremely strong. I thought the presentation by both Amgen and the FDA were beautifully organized and clear, and thank you for that.

I also voted yes because I came to understand that one can take that kind of strength of analytic evidence and use that for extrapolation. I do think, for myself, I think on a committee like this, we should engage in continues quality improvement. And part of that is

the post -- the studies to learn how this kind of extrapolation worked as a committee so we can then take that to our next decision and be better at making that next decision.

DR. SCHER: Jose Scher. I also voted yes. Again, I think the robustness of the totality of the data superseded some of my reservations, particularly when it comes to immunogenicity. There's a signal there that I'm still not convinced that it will not have clinical efficacy issues down the road. But in the end, the safety profile appears to be highly robust. So that's that.

I also would like to think about ways to standardize these applications by other sponsors moving forward. It will clarify some of our uncertainty.

The other point being that if at all -- and I'm not so sure that this can be done -- but IBD studies, moving forward, from other sponsors would be helpful as a class, particularly for TNF blockers.

DR. BILKER: Warren Bilker. I voted yes

also. I feel that the studies clearly demonstrated biosimilarity for RA and psoriasis. I am, however, concerned about extrapolation and feel that it's critical to mandate post-marketing surveillance and active surveillance studies on the safety and efficacy of all the extrapolated indications for this and other biosimilars.

DR. HANCOCK: I'm William Hancock. I voted yes, again, on the strength of the analytical package, but also the very helpful comments from the FDA based on their extensive experience.

I think one challenge is communicating the analytical data. What was presented by the company and the FDA is just a tiny, tiny sliver of the vast reams of data, and if you're not in the field, you just don't understand the enormous amount of data that's provided by all of the analysis of all the lots, and all of their molecular properties. So that's hard to communicate, but important.

DR. HOHMAN: I'm Bob Hohman. I voted yes. I agree with my colleague here. And also I share -- I sympathize -- some of the reservations

that people had. But I think when you look at the package, Amgen did an excellent job answering all the criteria by the FDA and I really appreciate the FDA did an awesome job putting it all in perspective.

DR. BRITTAIN: Erica Brittain. I voted yes. The results in the two clinical trials that were done were impressive. Would I prefer to have randomized clinical trial data for each and every indication? Of course I would. But I think that the biosimilar paradigm wouldn't be feasible if that were required.

So even though I'm not really comfortable with the extrapolation, I'm relying on my colleagues on the panel who seem to think it's okay. So I hope you guys are right.

DR. WALDMAN: Scott Waldman. I voted yes. I voted yes because of the totality of the evidence. I think Amgen did a great job putting the package together. I think the FDA did a great job of analyzing that package and presenting it. I had and have some reservations about extrapolation,

but I thought the discussion and the massacre of my straw man --

(Laughter.)

DR. WALDMAN: -- was clarifying and overcame my reservations.

DR. MAGER: Don Mager. I voted yes. I don't think, as the last voting member here, I'd have much more to add. I'd like to commend the applicant for an excellent packet. And again, I'd like to thank the FDA on an excellent review and presentation and also for the discussion. You fielded quite a few difficult questions and provided excellent feedback.

The analytical data were the most compelling of the application. And frankly, I would be surprised if some of those minor things like glycosylation would match. I don't know much about the analytical component of it, but it seems like one of those things that aren't going to match in the future very much as well when you switch cell lines. So I'm not surprised. I'd be more surprised if it did match.

Then where those things would have an impact, the clinical studies clearly showed that this was a non-issue. There were no clinical meaningful differences there, and I was comfortable with the extrapolation based upon mechanisms controlling PK as well as the role of the analytical component addressing the presumable mechanisms of action.

I would like to encourage FDA also to take the charge at addressing a lot of the public concerns. The comments brought up by the public haven't changed since the first one that we reviewed. They're looking for answers and guidance for a lot of these things, and I think the FDA has a unique opportunity to step in and lead the discussion.

DR. SOLOMON: Would the FDA want to make any comments?

DR. NIKOLOV: I'll take this opportunity. First, I would really like to thank you for an excellent discussion. We appreciate this, and this is what we needed. We certainly appreciate

everyone's concerns and comments, and certainly the way Dr. Solga framed the disconnect between the charge and the concerns of the community. But we would still like to thank you for keeping focused on the issues that we have for discussion today.

I think we can assure all of you that all the issues that were brought up, broader policy and issues relevant to the community, will be a topic of our internal discussion and hopefully input from the community to make sure that these are addressed, so that we can get this pathway implemented the right way.

I would also to thank the FDA team for their preparation, and the sponsor. I would like to thank the advisory committee staff, who was really instrumental in making sure that this advisory committee was successful. I would like to thank the community also. With this, I don't have anything else to add.

Adjournment

DR. SOLOMON: Okay. I think this concludes our meeting today. I think many of you may be here

tomorrow. I don't know if we're supposed to leave our badges here, if we're going to be here tomorrow. Leave your badges, and then they'll be here when you come back.

Please take all personal belongings. The room is cleaned and meeting materials left on the table will be disposed of, and we will now adjourn. Thank you.

(Whereupon, at 4:44 p.m., the meeting was adjourned.)