FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE (AAC) MEETING

Wednesday, July 13, 2016

7:32 a.m. to 3:09 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

(7:32 a.m.)

Call to Order

Introduction of Committee

DR. SOLOMON: Good morning. I would 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 like to identify the FDA press contact, Theresa Eisenman. If you are present, please stand. There she is. Hi, Theresa.

My name is Daniel Solomon. I'm the acting chairperson of the Arthritis Advisory Committee, and I will be chairing this meeting. I'll 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, down at the end.

Sean, maybe you can start and we'll work our way around.

DR. CURTIS: Hi. Good morning. My name is Sean Curtis. I'm head of scientific affairs at

Merck, and I'm acting as the industry representative.

DR. YE: Hi. Good morning. My name is Yihong Ye, and I'm working at the National Institute of Diabetes, Digestive and Kidney Disease, and I'm a senior investigator there working on protein folding/misfolding.

DR. SHILOACH: Hi. My name is Joseph Shiloach. I'm working at the NIH at the NIDDK. And I'm in charge of the biotechnology core laboratory that we produce proteins and other biochemicals needed for clinical research and special studies.

DR. BERGFELD: I'm Wilma Bergfeld, dermatologist and dermatopathologist from the Cleveland Clinic.

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

DR. MARGOLIS: David Margolis, professor of dermatology and professor of epidemiology at the University of Pennsylvania.

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

DR. HORONJEFF: Jennifer Horonjeff, researcher and rheumatology at Colombia University Medical Center, and I'm also here as a consumer representative.

DR. OLIVER: Good morning. Alyce Oliver. I'm at the Medical College of Georgia. I'm an adult rheumatologist and medical director for ambulatory medicine.

DR. MILLER: I am Don Miller, professor of pharmacy practice at North Dakota State University.

DR. BECKER: Hi. I'm Mara Becker. I'm a pediatric rheumatologist and division director at Children's Mercy Hospital in Kansas City.

DR. SOLOMON: I'm Dan Solomon. I'm an adult rheumatologist at Brigham and Women's Hospital and professor of medicine at Harvard.

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

DR. JONAS: I'm Beth Jonas, associate professor of medicine in the Division of

Rheumatology, and director of the fellowship training program at the University of North Carolina in Chapel Hill.

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

DR. SCHER: Jose Scher, New York University of Rheumatology, director of the psoriatic arthritis center.

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

DR. HANCOCK: Good morning. William Hancock, professor of bioanalytical chemistry at Northeastern University, Barnett Institute.

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

DR. WALDMAN: Scott Waldman, professor of medicine and chair of pharmacology and experimental therapeutics at Thomas Jefferson University in Philadelphia.

DR. MAGER: Don Mager, a professor of

pharmaceutical sciences at the University of Buffalo.

DR. ADAMS: Peter Adams, product quality reviewer, Office of Biotechnology Product, FDA.

DR. KOZLOWSKI: Steve Kozlowski, director, Office of Biotechnology Products, CDER, FDA.

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

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

DR. CHRISTL: Leah Christl, associate director for therapeutic biologics in the Office of New Drugs, CDER, FDA.

DR. SOLOMON: Great. It's nice to have so many people back from yesterday. I think that will facilitate the conversation today.

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 will 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 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 at today's meetings, 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 biologics license application, BLA 761042, for GP2015, a proposed biosimilar to Amgen's Enbrel, etanercept, submitted by Sandoz. The proposed indications, 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 patients with moderately to severely active rheumatoid arthritis, in combination with methotrexate or used alone;

2) reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older;

3) reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis and improving physical function in patients with psoriatic arthritis in combination with methotrexate in patients who do not respond adequately to methotrexate alone;

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

5) treatment of adult patients 18 years or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

This is a particular matters meeting during which specific matters related to Sandoz'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 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's 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 financial imputed 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 an overview of the 351(k) regulatory pathway from Dr. Leah Christl.

Presentation - Leah Christl

DR. CHRISTL: Good morning. My name is Leah Christl, and I'm going to take time to provide you with a regulatory overview of the biosimilar pathway. I apologize in advance for those who had to sit through this presentation yesterday, but this is a distinct meeting from the meeting yesterday, and we do have a change in the committee membership, as well as possibly some of the audience attendees. So we felt that it was important to go through this again, and also the committee may have some clarifying questions as well regarding the pathway for those who participated yesterday.

I'll go through the background of the

regulatory pathway, talk about some definitions to give some clarity about the terminology, talk about the general requirements for the approval pathway that are outlined in the law, and then we'll talk a little bit about the development concepts around biosimilars.

The Biologics Price Competition and Innovation Act of 2009, or the BPCI Act, was passed as part of health reform in the Affordable Care Act on March 23rd of 2010. And what it did is that it created an abbreviated licensure pathway for biologic products that are shown to be biosimilar to, or interchangeable with, an FDA licensed reference product. And we'll talk a little bit about what each of those terms mean.

What do we mean by an abbreviated approval pathway or abbreviated licensure pathway? The Act states that a biologic product that is demonstrated to be highly similar to an FDA licensed biologic 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 for the labeled conditions of use.

This licensure pathway permits a biosimilar biologic product to be licensed under 351(k) of the Public Health Service Act based on less than a full complement of product-specific preclinical and clinical data.

This is what's meant by the abbreviated licensure pathway. It's the concept of that reliance on what's known about the reference product such that you can have less than a full complement of product specific preclinical and clinical data about the proposed product.

What do we mean by biosimilarity? Biosimilarity is defined to mean that the biologic 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 proposed product and the reference product in terms of safety, purity, and potency of the product.

When we talk about safety, purity, and potency, it's the description in the Public Health Service Act, but in more lay terms, we're really talking about safety and efficacy of the product. It's just we use different terminology.

What do we mean by reference product? Reference product means the single biological product licensed under a Section 351(a) of the Public Health Service Act, against which a biological product is evaluated in an application submitted under Section 351(k) of the PHS Act. And (a)s and (k)s are very regulatory terms, so we'll talk a little bit about what those mean.

An application that's submitted under Section 351(a) of the Public Health Service Act is a standalone application that contains all the information and data that are necessary to demonstrate that that proposed product is safe, pure and potent.

In contrast, an application that's submitted under Section 351(k), so again this would be for a biosimilar product, needs to demonstrate that the

proposed product is biosimilar to the reference product. For licensure, a 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.

The standard for approval of originator products, or these standalone products under 351(a), biosimilar products under 351(k), is that both must demonstrate that they're safe, pure, and potent for the conditions of use that are sought for licensure. However, the data packages to support this finding will differ between the pathways between the standalone and the biosimilar marketing application. And we'll talk a little bit more in future slides about the content of those data packages and how they differ.

While the subject of today's meeting is not a proposed interchangeable product, it is a proposed biosimilar product. In the context of giving a regulatory overview, we think it's

important for folks to know the definition for interchangeable as well. So again, products can be biosimilar to, or interchangeable with, an FDA licensed reference product.

Interchangeability is defined in the Act to mean that the biologic product is biosimilar to the reference product, so it meets that standard of being highly similar with no clinically meaningful differences.

In addition, it can be expected to produce the same clinical result as the reference product in any given patient. And for a product that's 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 product.

And that concept of substitution is specific to interchangeable products. The Act does not contemplate this for biosimilar products; it's only for interchangeable products.

The Act describes general requirements in terms of the information that a biosimilar application must contain. So it needs to contain information that demonstrates that that product is biosimilar to the reference product; also, that 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, such as indications, populations, proposed in labeling, need to have been previously approved for the reference product. It has the same route of administration, dosage form, and strength as the reference product. And that the manufacturing process and the facility meet the FDA's standards for biological products such that the product continues to be safe, pure, and potent.

The types of data that would be submitted in an application for a biosimilar product are also discussed in the BPCI Act. So an application would include, among other things, information demonstrating biosimilarity based upon data derived from analytical studies, animal studies, and clinical study or studies.

It states that 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 which 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.

The Act goes on to state that FDA may determine in its discretion that one of the data

elements described above is unnecessary in a 351(k) application, and we'll talk a little bit more about that in future slides when we talk about some of the development concepts.

While biosimilarity is demonstrated to the US-licensed reference product, FDA has taken the scientific position, as articulated in the guidance, that data from animal studies and certain clinical studies comparing the proposed biosimilar product with a non-US-licensed comparator, may be used to support a demonstration of biosimilarity to a reference product.

The sponsor in this case should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the US-licensed reference product.

What this means is that the sponsor provides data to show that the lots of the non-US-licensed comparator would be representative of an outcome if the U.S. reference product was used. We're not

making a finding that the U.S. and non-U.S. products are the same. It's about justifying the relevance of that data and making a connect between the non-US-licensed comparator and the US-licensed reference product in terms of the representative nature of the data in terms of a demonstration of biosimilarity.

The type of bridging data that would be needed to be provided by the sponsor would include direct physical/chemical comparison of all three products. It would likely include a three-way bridging clinical, clinical PK, and/or PD study. And all three pairwise comparisons should 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 provide appropriate justification in terms of supporting the relevance of that data that's generated with a non-US licensed comparator.

Now we'll move into an overview of the approach to the development of biosimilars. And as

I noted yesterday, we find it easier to move through this information instead of just regurgitating the guidance to focus on some key concepts around development of these products.

The first key concept is that the goals of a standalone and biosimilar development program are different. A standalone development program, which again is under 351(a) of the PHS Act, the goal of that development program is to establish the safety and efficacy of the new product.

Drug development would start with preclinical research, moves on to phase 1, phase 2, clinical studies, and then culminates in phase 3 pivotal clinical trials to demonstrate safety and efficacy for the proposed conditions of use. This is the model of drug development that most individuals are familiar with.

In contrast, the abbreviated licensure pathway, which is again under 351(k) of the PHS Act, the goal of that development program is to demonstrate biosimilarity between the proposed product and the reference product. The goal of a

biosimilar development program is not to independently establish the safety and effectiveness of the proposed product. The reference product already did that in their studies in terms of those pivotal clinical studies to demonstrate safety and efficacy. The goal for a biosimilar development program is to demonstrate that they're biosimilar to the reference product.

This abbreviated pathway means that the biosimilar product can be approved based on less than a full complement of the product specific preclinical and clinical data because there can be reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product. This approach avoids unnecessary expensive and unethical duplication of studies and it allows safe and effective products to be made available to patients.

Although the contents of the development program package, as you can see here, the types of data in terms of analytical and non-clinical, clinical pharmacology, and clinical, are generally

similar. The emphasis on each of those data elements is different between the two development pathways, representing the different paradigm in drug development.

The data package required for approval of a biosimilar product is quite extensive. It's the pathway that's abbreviated in terms of the route to licensure. It's not the data package that is abbreviated. Again, it is quite extensive, It's just a different type of data.

The second key concept involves the approach to developing the data to support a demonstration of biosimilarity. FDA has outlined in guidance a stepwise approach to generating this data in support of a demonstration of biosimilarity. And if you remember from the previous slide, that pyramid approach with the analytical data being the foundation and then moving up through non-clinical, clinical pharmacology, and eventually to additional clinical studies.

What this is, is a stepwise approach of generating data beginning with that analytical

foundation. What a sponsor needs to do is evaluate residual uncertainty at each step as they're generating data, and it's ultimately the totality of the evidence that supports a demonstration of biosimilarity.

So sponsors apply a stepwise approach to data generation in the evaluation of residual uncertainty about biosimilarity at each step of development as they generate data. And the questions that come up that need to be addressed are what differences have been observed and what's the potential impact of those differences?

So if there's differences observed in the analytical similarity data, what do we think the potential impacts of those differences could be, and then how do you evaluate the impact of those differences? What are the studies that are the best studies to look at the impact of the differences?

There's no one pivotal study that demonstrates biosimilarity, so again folks are used to in standalone drug development that there's

pivotal phase 3 studies to demonstrate safety and efficacy. Again, there's no one pivotal study that demonstrates biosimilarity; it's that totality of the evidence.

The third key concept is around the analytical similarity data. And again, this is the foundation of the biosimilar development program, and this involves extensive structural and functional characterization of both the reference product and the proposed product.

A comparative assessment of the attributes needs to occur on an analytical level looking at structural and functional attributes, and these can include a number of things, including amino acid, heterogeneity, glycosylation, bioactivity. 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.

So it's important for the sponsor as well as the agency to understand the molecule and the function, and to identify the critical quality

attributes that are involved with the function of that molecule, the biological function of that molecule.

In order to generate this data, the sponsor will first characterize the reference product quality characteristics and product variability. Then they will design a manufacturing process for the proposed biosimilar product to produce a product with minimal to no differences in product quality characteristics compared to the reference product.

They need to identify and evaluate the potential impact of any differences that are observed, and then determine what study or studies will address the residual uncertainty to answer those outstanding questions.

So it's important, again, 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 from the quality data.

FDA has also taken a scientific approach of applying a statistical analysis to the analytical similarity data. So the statistical analysis of these data are conducted to support a demonstration of highly similar. It's not a pass/fail system; it's part of the demonstration of highly similar.

So the quality attributes are ranked based on criticality with regarding to their potential impact on activity, PK or PD, safety, immunogenicity, and other factors. The data are then analyzed by various testing methodologies, which could include equivalence testing for certain highly critical attributes that are involved with the function of the molecule; quality range methodology for other critical to low critical quality attributes; and then raw graphical comparisons for other attributes that are either lower ranked in criticality or not amenable to other testing methodologies, such as amino acid sequence, which is a highly critical attribute, however it's not amenable to any sort of testing methodology. It either is or isn't the same.

In terms of the animal data, animal toxicity data can be useful when there are uncertainties remaining about the safety of the proposed product prior to initiating clinical studies. However, the scope and extent of animal studies, including such an assessment of toxicity, will depend on publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed product, and the extent of any know similarities or differences between the two products.

This is a place where I had mentioned before the FDA may, in its discretion, determine that one of those data elements is unnecessary. We really look at the animal toxicity data, and any other animal studies, to support what we refer to as a safe-to-proceed decision in terms of initiating clinical studies. And that assessment depends on the amount of analytical similarity data that a sponsor submits to the agency at the time that they initiate clinical studies, and if there's any differences observed between the products and if

there's uncertainty in the realm of safety. In some cases, from a similarity aspect, a comparison of PK or PD in an animal model may also be useful.

The fourth key concept involves the role of the clinical studies in a biosimilar development program. The nature and scope of clinical studies will depend on the extent of residual uncertainty about biosimilarity between the products after conducting the structural and functional characterization, and where relevant, animal studies. So again, it's that stepwise approach where you're moving up that pyramid with the base being the analytical comparison.

As a scientific matter, FDA does expect an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and the reference product. As a scientific matter, at least one clinical study that includes a comparison of the immunogenicity of the proposed product and the reference product is also expected.

When we talk about clinical studies for biosimilars, we mean any studies in humans, so

these can include a clinical pharmacology study in addition to a more traditional clinical safety or efficacy study. We always encourage sponsors to collect immunogenicity and other safety data in any clinical study that they use because, again, we're looking at that totality of the evidence.

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

Again, it's moving up that pyramid with this concept of additional clinical data being at the top of that pyramid as you're moving through generating data, looking at what residual uncertainty you have about biosimilarity.

More specifically in terms of the types of clinical data, PK and/or PD data is generally

considered to be the most sensitive clinical study or assay in which to assess for differences between the products. Again, it's not the responsibility of the biosimilar applicant to determine the PK profile of its own product, choose clinical doses; the reference product already did that.

Here we're looking at comparative PK and looking at PK and/or PD similarity. Demonstrating PK similarity should be done in an adequately sensitive population to detect any differences between the products, should they exist. And for PD, the use of similar PD using PD measures that reflect the mechanism of action, or reflects biological activity of the drug, should be conducted.

Not all products will have a good PD measure, some do and some don't, and this concept of whether or not there is a good PD measure or endpoint can play into the concept of whether or not there's residual uncertainty about no clinically meaningful differences in addition to the demonstration of biosimilarity.

PK and PD similarity data will support a demonstration of biosimilarity with the assumption that similar exposure and pharmacodynamic response, if it's applicable for the product, will provide similar efficacy and safety. In other words, an exposure response relationship exists for the product.

For a comparative clinical study, this study, if it's deemed necessary to be conducted to address residual uncertainty about biosimilarity, again should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product. Therefore the population, endpoint, sample size, and study duration should be adequately sensitive to detect differences between the products should they exist.

Typically, FDA looks for an equivalence design. Again, it's the concept of no clinically meaningful differences, so we look at an equivalence design that wouldn't normally be recommended. But for certain products, other

designs may be justified depending on product-specific and program-specific considerations. Again, if a comparative clinical study is conducted, FDA would expect that there is an assessment of safety and immunogenicity that is a part of this study.

Once the sponsor generates all of this data that we've talked about -- the analytical similarity data; comparative animal studies, if they're deemed necessary; comparative PK, PD if it's relevant; and possibly a comparative clinical study; and then also comparative immunogenicity data -- they have all of this data that's supporting the demonstration of biosimilarity.

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's intended to support a demonstration of biosimilarity in one condition of use, such as if they conducted a comparative clinical study in one indication, to other conditions of use for which the reference

product is licensed and for which the biosimilar is seeking licensure. In this case, a sponsor would need to provide scientific justification for extrapolating data.

FDA has outlined in guidance a number of factors or issues that need to be considered in the context of the scientific justification to support extrapolation. This can include the mechanism of action in each condition of use for which a licensure is sought; the PK and biodistribution of the product in the different patient populations; the immunogenicity of the product in different patient populations; and then any differences in expected toxicities in each condition of use in the patient population.

Differences between the conditions of use do not preclude extrapolation. What it means in terms of providing a scientific justification is that those factors and issues need to be addressed with information, and sometimes data. That data is not always going to be clinical data. It could be functional data looking at the different mechanisms

of action to support the concept of extrapolation.

The sponsor needs to ensure that that totality of the evidence, including the scientific justification for extrapolation, supports their approach; and again their total data package in the context of the totality of the evidence supports a demonstration of biosimilarity for all the conditions of use for which they're seeking licensure.

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 biosimilar product and the reference product.

Approval of a proposed biosimilar product is based on the integration of various information and the totality of the evidence submitted by the biosimilar sponsor to provide an overall assessment that the proposed product is biosimilar to the reference product.

At this point, I thank you for your

attention, and I am happy to take clarifying questions from the committee if there are any.

Clarifying Questions to the FDA

DR. SOLOMON: Thank you. That was very helpful. Are there clarifying questions from the committee?

One point that I'd ask you about is the interchangeability question, and is there a guidance document yet on interchangeability?

DR. CHRISTL: Right. FDA is working on a guidance document for interchangeability. It is on our guidance agenda for this calendar year. And we know it's considered most valuable guidance by sponsors as well as the prescribing community and patients. It's also most valuable guidance I would say for the agency as well. So we are working on that, and we hope that that will issue in this calendar year.

DR. SOLOMON: Great. Any other clarifying questions?

(No audible response.)

DR. SOLOMON: I'll ask one more. You

mentioned the concept of safe-to-proceed decision. And I guess while I know this is background information, I'm thinking about other presentations. And it's not entirely clear always those background decisions that are being made by the agency and whether those come into play in a specific application.

I don't know if you can comment on that, how that might have come into play in what we're going to talk about today.

DR. CHRISTL: Right. We have a very iterative process with sponsors in terms of the development of biosimilars. We have a separate user fee program that involves different types of meetings, so we have an extremely iterative process to support this concept of the stepwise evidence development.

Sponsors will start generating data, will bring information to us, ask questions about proceeding through their development program. We'll talk about what residual uncertainty is and help them to target their program such that they're

not doing unnecessary studies and really focusing on what it is that they need to do.

So certainly those conversations in the development space, FDA recommendations about what studies are necessary, certainly come into play as we look at the totality of the data to support licensure, whether or not our recommendations were followed, whether or not the data supports a demonstration of biosimilarity. We do think about our interactions and the history of that application as we move through the review of the pending licensure application in front of the FDA.

DR. SOLOMON: Thank you.

Any other questions?

(No response.)

DR. SOLOMON: I wanted to ask Dr. Siegel, who came in late, to introduce himself.

DR. SIEGEL: I have the shortest to go, but sorry about that. Anyway, yes. I'm Richard Siegel. I work at the NIH. I am the clinical director of the NIAMS, whose portfolio includes arthritis and does primarily rheumatology research.

And my lab studies are TNF, super family, cytokines, biology, and signaling.

DR. SOLOMON: Great. Thank you.

Thank you, Dr. Christl.

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

FDA Introductory Remarks - Nikolay Nikolov

DR. NIKOLOV: Good morning, everyone. The fact that there were not that many questions to Dr. Christl, I'll take it as a good sign. But I think we'll be certainly open to address any questions during the day in the discussion.

I would like to welcome you to the Arthritis Advisory Committee meeting for the 351(k) biologic license application for GP2015, a proposed biosimilar to US-licensed Enbrel.

My name is Nicolay Nikolov. I am 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 out of your busy schedules to come

in and provide your expertise.

In the next few slides, I will provide an overview of GP2015 development program in the context of the abbreviated licensure pathway that Dr. Christl described and summarized before me.

The applicant, Sandoz, has submitted a biologics license application, or a BLA, under Section 351(k) of the Public Health Service Act for GP2015, a proposed biosimilar to US-licensed Enbrel. GP2015 is being developed for the same indications for which U.S. Enbrel is licensed, as listed on this slide.

To support this application, Sandoz provided extensive analytical data intended to support:

1) a demonstration that GP2015 and US-licensed Enbrel are highly similar; and

2) a demonstration that GP2015 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 differences between GP2015

and US-licensed Enbrel, Sandoz provided data intended to demonstrate:

1) similarity in exposure in healthy subjects;

2) similarity in efficacy and safety in patients with plaque psoriasis; and

3) similarity in immunogenicity between GP2015 and Enbrel in patients with plaque psoriasis in healthy subjects, as well as in patients who underwent a transition from Enbrel to GP2015.

This slide summarizes the clinical development program for GP2015 and key design aspects of the clinical studies supporting the application. The first three studies are single-dose PK studies, 101, 102, and 104, and the cross-study report 105 provided the data to establish PK similarity between GP2015 and US-licensed Enbrel and the PK component of the scientific bridge to justify the relevance of the clinical data from the comparative clinical study 302, which was conducted with European Union or EU-approved Enbrel as a comparator.

Study 302 had two treatment periods. Treatment period 1, which is week 1 to week 12, provided the primary comparative clinical safety, efficacy and immunogenicity data between GP2015 and EU-approved Enbrel.

Treatment period 2, which is week 12 to week 30, also provided safety and immunogenicity data in the setting of patients undergoing transition from EU-Enbrel to GP2015 at week 12. This information is relevant and important to ensure that if approved as a biosimilar, GP2015 could be administered safely to patients who may have been previously exposed to Enbrel.

As discussed by Dr. Leah Christl, an applicant needs to provide information to demonstrate biosimilarity based on a comparison between the proposed biosimilar product with the reference product. As noted in the previous slide, the GP2015 comparative clinical study used a non-US-licensed comparator, specifically EU-approved Enbrel.

The FDA has determined that in cases like

this, the applicant must, as a scientific matter, provide adequate data or information to scientifically justify the relevance of these comparative data to the 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 non-US-licensed Enbrel, Sandoz provided extensive analytical bridging data that directly compared all three products, and conducted three clinical PK studies and one cross-study comparison to provide the exposure bridging data between GP2015, US-licensed Enbrel and EU-approved Enbrel 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 indication.

Consistent with the 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 are no clinically meaningful differences for the additional indications sought for licensure.

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

1) whether the evidence from analytical studies supports a demonstration that GP2015 is highly similar to the US-licensed Enbrel;

2) whether clinically meaningful differences exist between GP2015 and US-licensed Enbrel in the studied indication of plaque psoriasis; and

3) whether the totality of the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel

for the additional indications for which U.S. Enbrel is licensed and Sandoz is seeking licensure of GP2015.

Following the discussion, the committee will be asked to vote on one question, similar to yesterday's advisory committee. The question is, does the totality of the evidence support licensure of GP2015 as a biosimilar to US-licensed Enbrel for the following indications for which U.S. Enbrel is licensed and for which Sandoz is seeking licensure: rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

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 with diverse expertise relevant to product quality, clinical pharmacology, immunology, biostatistics, and dermatology, in addition to the standing arthritis advisory committee, which we believe will foster a very productive discussion today, similar to yesterday.

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

DR. SOLOMON: Are there any questions for Dr. Nikolov?

(No response.)

DR. SOLOMON: Okay. Thank you.

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 Sandoz's presentations.

Applicant Presentation - Mark, McCamish

DR. McCAMISH: Thank you, Dr. Solomon. It's a privilege to be here today to observe you setting history while you review two biosimilar applications in a 48-hour period. If they are approved, it will double the number of biosimilars available to the U.S. population, which is really one of our passions.

My name is Mark McCamish, and I am the global head of development for Novartis biosimilar activities that are located in Sandoz. I'm a physician/scientist by training, had a traditional academic practice for about a decade at the University of California Davis and Ohio State University, prior to transitioning into industry

for the past two decades.

The last decade, I focused on biosimilars as I developed a passion for really addressing access issues that we've run into. And I have to share openly, and being here yesterday and seeing you struggle with some of the concepts that are there, I've had 10 years to learn the concepts. And I had no clue about the importance of analytical characterization to the product 10 years ago, and it's really become a fascinating experience over time to see the importance about that.

So I have modified my introductory presentation to try to share with you some of the learnings that I've had during this process because I recognize some of the frustration you experienced yesterday in trying to deal with some of these concepts. Then I'll use that to introduce our product, GP2015, as we move forward.

You've seen that the totality of evidence, this topic we talked about, totality of evidence, demonstrates that GP2015 is similar to the US-licensed Enbrel. FDA and Sandoz briefing books

concluded this, that there's extensive analytical data that demonstrates high similarity. That's the regulatory term. It's also confirmed the relevance of the EU and U.S. product.

This question came up yesterday. Is the U.S. product biosimilar to the EU product? Is the U.S. product interchangeable with the EU product? What we're required as a sponsor is, by statute, to compare to the U.S. reference product. However, you recognize that we utilize a global program, and therefore we utilize European as well as U.S. reference product. It's up to us to show that those products are essentially the same, and can be used in a clinical trial.

What we've shown analytically, if you were to purchase a pre-filled syringe of this product in Europe and purchase it in the U.S., as long as you didn't tell us the price, we would not be able to tell you the difference between the products analytically. They are indistinguishable analytically. So that's what we're doing in terms of bridging between the U.S. and the EU reference

product.

We've also used a clinical program, as designed, as essentially a whole-body bioassay to test whether our product is the same as the reference product. And we demonstrated no clinically meaningful differences, and that the transition that FDA asked for, moving a patient from the referenced product to GP2015, was not associated with untoward events.

So this extensive package that we talked about really addresses the scientific consideration for extrapolation, and I'll talk about that in terms of the data we have. It's this totality of evidence that supports extrapolation, not any one study, not any one component, but a total evaluation of our molecule, GP2015, versus etanercept, Enbrel, and showing that those are highly similar. And if it's the same product, essentially the same product, then you have evidence that you can use that in all approved indications, and the confirmatory clinical study helps with that information as part of this

totality of the package.

Just as you were pioneering biosimilars in the past 48 hours, Sandoz has been a pioneer in the development of products for biosimilars. We've had an extensive in-house biologic drug development experience for over 30 years, and we've been focused on biosimilars for the past 20 years.

This has led to multiple firsts. We were the first ever biosimilar to be approved. That was in Europe, 2006, rapidly followed by two additional biosimilars. We were the first biosimilar to be approved in Australia, first in Canada, first in Japan, last year the first approved in the U.S., and to date the only biosimilar on the U.S. market.

Sandoz biosimilars are sold in more than 60 countries. We've generated 250 million patient days experience with our biosimilars. We've already proven that this has an impact on patient access, which again is what drives us. So it's this unmet medical need, our passion directed at improving patient access, that's the foundation of the development program at Sandoz.

Enbrel is a wonderful product. It's been life changing. It's changed the practice of medicine. The challenge is that many patients in the U.S. still remain unable to access this easily, and there are many barriers that have to be negotiated to get access. So GP2015 is a proposed biosimilar to Enbrel, and it's our desire that this will expand patient access, provide competition, and reduce the burden on the U.S. healthcare system.

The proposed indications for GP2015 are identical to those of U.S. Enbrel listed here: RA, JIA, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis. We justify this, again getting back to this extrapolation principle, based on FDA's guidance, and also based on years of experience that FDA's had in reviewing similar types of information from manufacturing changes.

Now as you know, etanercept is a wonderfully designed approach to capture TNF. So it's the extracellular ligand-binding protein of the human P75 receptor, bound to the crystallizable fraction

of an IgG1. And this is created basically as a competitive inhibitor of soluble TNF alpha as it binds to this fusion protein.

GP2015 will have comparable dosage forms to Enbrel, a 25-milligram prefilled syringe, a 50-milligram prefilled syringe, and a 50-milligram auto injector. It's to be used in the same administration sub-Q once or twice a week depending on the indication.

This slide shows that we have had patient input here, how could we address patient needs, bringing out basically the same product? One way is in the device. So you can see in the prefilled syringe on the left-hand side, we put in an enlarged finger flange because patients with RA have dexterity issues, and the larger finger flange was very helpful in terms of their self-injection.

On the right-hand side, you see the auto injector. And if you look to the lower right-hand side, you'll see the shape. It's a triangular shape. It's not a traditional circular shape. And again, working with patients with RA, we found that

a different shape, a triangular shape, helps them with the dexterity issues, as well as this 2-step injection so that they don't have to move their thumb from the circular part of an auto injector up to the top to click to activate this. So again, trying to meet the patients' needs.

The development of a biosimilar, as you have learned, requires a paradigm shift. And this paradigm shift will need to happen in the community of all clinicians as well. On the left-hand side, it's an upside down pyramid where the analytics at the bottom for an original drug development program, a novel drug, the analytics simply describe the drug.

On the top part, the clinical aspects of this program are what the physicians generally focus on. How is it used? What's the indication? What's the dosage? What are the adverse events, et cetera? All defined by clinical trials, often two clinical trials in each indication.

But the development of a biosimilar turns the world upside down. With biosimilar

development, the analytical is the base of making this judgment of high degree of similarity. Is this product essentially the same?

The clinical, on top, is essentially a whole-body bioassay to try to address that sameness of the molecule. And this will be an ongoing challenge for us in communicating to clinicians this paradigm shift.

Now Sandoz had developed a 5-step approach for development of a biosimilar. It starts with target definition. I can't emphasize how important this is, and I've got a slide to document this. We have to understand the reference product. We have to be an expert in the reference product. So we need to understand the target molecule and its variability over time.

As you see, and as you learned yesterday, the reference product is not identical to itself over time. So we have to understand what are the differences in the reference product so that we can map those differences, and then we have this targeted, directed development program focused on

ensuring that our product is essentially the same, falls within the variability of the reference product.

Then the characterization that you've heard about yesterday, and we'll go through today, establishes that similarity based on not only physical/chemical, but the biological and the functional characteristics that these are essentially the same.

The regulatory interactions, as Dr. Christl mentioned, is an iterative approach, not only with the U.S. FDA, but with EMA and other regulatory authorities. So we interact with them, sharing with them our information, and then we work with them to design the confirmatory clinical trial.

Here we have a single clinical trial, which is focused at confirming the sameness of this molecule. And psoriasis is the most sensitive indication whereby if there were changes, differences, in the molecule, the psoriasis study is the best way of picking up those differences. So that's why we used it.

We're not experts in these therapeutic areas. So we have to look at this. We get outside experts to comment, but that's the approach we take. So the totality of this data demonstrates that sameness.

The extrapolation concept that you all were talking about yesterday is for molecule to molecule. It's our job, the sponsor's job, to provide copious information that shows that our molecule is essentially the same, proper regulatory term, highly similar, to the reference product.

If our product, GP2015, is essentially the same to Enbrel, it will work the same in these indications. You're extrapolating from one molecule to the other, not from a disease to a disease.

Clinicians, you are all aware that there are drugs that work in psoriasis that won't work in rheumatoid arthritis, and there are drugs that work in rheumatoid arthritis that won't work in psoriasis. So to ask you, based on a single trial in psoriasis, to extrapolate from that trial in

psoriasis to other indications, is not feasible, because you know that in itself is not inherently convincing.

However, if the psoriasis trial is the final pinnacle of evidence that these molecules are the same, then you're extrapolating from one indication to the other because of the sameness of the molecule.

This regulatory concept of sameness, let me just take a minute to review. So regulatory concept of sameness started in the middle '80s with generics, and it's fairly straightforward to understand because you can create an identical copy of the generic. It is chemically synthesized.

When you prove that it's an identical copy, then all you have to do clinically is show that the formulation, whatever your formulation is, delivers that identical molecule in the same way. Then it's approved as identical, and you can extrapolate to indications.

Now more recently there have been complex generics that are a distribution of molecules.

Even with generics, with those complex ones, you cannot say your molecule is identical to the reference. You have to show that your distribution is the same as the reference.

As we've gone to biologics, in the mid 90's, there was an understanding that when you launch a biologic, because of patient needs, the sponsor has to scale up those manufacturing capabilities. To scale it up, there are changes that happen with the molecule. Now these are not huge changes. They can be very, very minor changes, but they're changes that you can pick up analytically. And it's up to the reference sponsor to come to an agency and say, okay, we scaled up this process, here's the pre-manufacturing change process, here's the post-manufacturing process, and all this analytical data show that it's highly similar.

So comparability on the lower part of this quadrant shows this highly similar definition, highly similar quality attributes.

If you transition to biosimilarity, these same concepts have evolved in terms of developing a

biosimilar. The difference is, it's a different sponsor, a different manufacturer making the product and having to prove through this same context, this highly similar, that their product is essentially the same.

Now, the regulatory term in the U.S. is "highly similar." In the lower part of this last quadrant, you can see how the European Medicine Agency has defined it in their Q&A document to help clinicians. They realized that highly similar and biosimilar communicate to a physician there's something different with this because you don't say bioidentical, you don't say biogeneric, you say biosimilar.

So they came up with this term, it says the active substance is essentially the same biologic substance, though there may be minor differences due to their complex nature and manufacturing process. So I'll be using the term "essentially the same" to connote that's what we're trying to do; we're trying to provide all of the information from a regulatory perspective to show that this

molecule is highly similar, essentially the same, and will function the same.

The next slide I'll talk about emphasizes this comparability. This slide will talk about what was done with Enbrel. So this is a focus on Enbrel, not biosimilarity. This slide was taken from a publication by Martin Schiestl, who will be talking next about the analytical data. And we noticed as we were developing the product over years, that there was a shift in the product.

As Dr. Kozlowski mentioned yesterday, this information is not publicly available in the U.S. Sometimes it's available in Europe through a European public assessment report, but analytically we could pick up a difference in the molecule.

This shows the change in a G2F glycosylation outlined in that little square at the right. We could see that there was a shift between a 50 percent enrichment and a 30 percent enrichment. Then, I had a publication a couple of years later where we showed where those batches came from. So the colors show U.S./EU batches, and you can see

that the European batches started out and they shifted, and then the U.S. batches shifted.

We are in this post-modification period, so the products we purchase are similar to the one with a 30 percent enrichment. My point here is that the process for showing that this product was essentially the same, the sponsor brings the data to the regulatory authority, here's what our product was before, here's what it is after, and provides all the analytical data, plus rationale that this particular product change is not clinically relevant.

This G2F is known to not be relevant to immunogenicity, binding, aggregation, et cetera. With that data, then the regulatory authority approves the post-manufacturing change as the same. Same label. In this case, no clinical trials, and no clinical trials in all indications, because it's the concept that the analytics will provide you reassurance that the molecule performs in the same way. Biosimilars, on the other hand, follow this process, but by regulatory statutes are required to

do clinical trials that are there.

So this was used, same label, and you can see during that period of 2010 and 2011, both products on the market at the same time, same label, you wouldn't know which one it was, but there's judgment that they respond the same. And that's a key thing to understand.

In moving this forward, the totality of data is how we show extrapolation. If you show the structural attributes are highly similar, biologic functions are highly similar, non-clinical tox is highly similar, human PK/PD bioequivalence, psoriasis using it as a sensitive marker to do a whole-body bioanalysis that this is the same molecule, shows equivalent efficacy, that is the totality of the data to show that the molecule is essentially the same, and that helps in terms of the extrapolation that scientifically justify to the other indications.

As we walk through today, we'll be telling you about the data in a similar fashion, the analytics, the PK, the clinical, all focused on

this totality of data that then justifies that the molecules are essentially the same, highly similar, that extrapolation can be justified in doing this.

Martin Schiestl, who is a real expert in this area, will walk you through the analytical. We'll have Oliver von Richter walk you through the non-clinical and PK. We'll have Malte Peters walk you through the clinical confirmation with the psoriasis trial. Then we have Dr. Jonathan Kay that will give us some of his perspectives of the use in practice. And then I'll conclude the sponsor presentation and wrap it up in two slides.

Now I said we're not experts in this therapeutic area, so we did bring Dr. Kay, who is a professor of medicine at University of Massachusetts, and Craig Leonardi, who is an adjunct professor of dermatology, but really a leader in the field for dermatology and psoriasis. And he's been the steering committee and the head of our steering committee for Sandoz for this program. So they are available to ask and answer questions as well.

With that, I'll transition on to Martin, and I do thank you for your time.

Applicant Presentation - Martin Schiestl

DR. SCHIESTL: Thank you. I'm Martin Schiestl working as the chief science officer for Sandoz Biopharmaceuticals. And within Sandoz, I have been now working for 20 years on the development of these biosimilar products.

My presentation will focus on the analytical piece of this pyramid, which sets the foundation for demonstrating biosimilarity. It covers all the structural and functional comparisons between Enbrel and GP2015. And I will also briefly describe how we developed our biosimilar, introduced a molecule, and then share the analytical results of our similarity assessment.

We systematically developed GP2015 to match Enbrel. In the first step, we defined our target by analyzing numerous batches of Enbrel to really understand the molecule, its batch-to-batch consistency, and its variability over time. This variability defines the goalpost for our own

development program.

We also leveraged our understanding of how different molecular attributes impact the clinical safety and efficacy of the product, and we put special attention to those attributes that we know matter clinically. Then we developed the manufacturing process to meet this target.

This requires multiple repetitions to fine-tune each step in manufacturing, like the cell line, the bioprocessing, the protein purification, and the final drug product manufacturing. Finally, once we had optimized the product, we tested it for similarity at all levels.

Now the 2015 manufacturing process is validated and designed to deliver the biosimilar product consistently also in the long term. And here you see the process scheme starting with the cell bank vial on the left, and the bioprocess, the subsequent protein purification which delivers the drug substance, which is then formulated and filled to the drug product syringes.

All of these steps are tightly controlled.

For example, incoming raw materials are specified and tested. We also have controls implicit by the process design. For example, the design of the master cell line or the way we establish the purification step to clear the product from certain impurities.

We also control process parameters and test in-process samples from the start to the end. And we perform release testing not only of the final syringes, but also of the drug substance and the cell harvest. Finally, all of these controls are embedded in our quality system, which is compliant of good manufacturing practices and governed by our quality assurance, and it's also inspected by FDA in regular intervals.

This control system is a state of the art and fulfills all the regulatory requirements for reproducible manufacturing so that every manufactured batch, also batches which are produced in the future, have the same clinical properties.

Now turning to the molecule. Here is again the structure of this etanercept, the active

ingredient in GP2015, and this is produced using a Chinese hamster ovary cell line. It's well characterized and manufactured to match the structure of Enbrel. It's a dimeric fusion protein consisting of the human TNF receptor, which is linked to the Fc part of an antibody, and it has multiple glycosylation sites and disulfide bonds.

When we developed GP2015, we optimized more than 40 molecular attributes, or quality attributes as it is the regulatory term which we used to match Enbrel. They start with the amino acid sequence, which basically defines the molecule.

Here it is a clear regulatory requirement that for a biosimilar, the amino acid sequence needs to be identical to the reference product. If there is even one out of the more than 900 amino acids in Enbrel which is not the same, the product wouldn't be approved as a biosimilar product.

Next is the higher order of 3-dimensional structure, which also needs to be the same in order to illicit the same biological functions. Then we looked at all the protein modifications, like

glycosylation and other protein variants. We then looked at impurities like aggregates and fragments, and we also looked then at all the biological functions.

So all together we have conducted tens of thousands of measurements over the past couple of years, but for timing reasons, we will focus only on those data today, which are most important for the biosimilarity assessment.

But given those many attributes, how do we know which of them matter clinically? To answer this question, we used a systematic risk assessment, an approach which is also now standard in the biopharma industry and also regulatory expectation by the FDA.

We looked at the more than 40 molecular attributes plus those which were related to the process materials and to the excipients. For each of those attributes, we assessed the impact with regard to immunogenicity, safety, pharmacokinetics, and efficacy, and used all this existing product knowledge from literature, also our in-house

studies and from related molecules, to end up with a criticality ranking of all attributes from the important ones, with a very high criticality -- you'll see them here in red at the top -- down to those which have a very low criticality, shown here in green.

In this table, you see how many attributes of GP2015 fall into each criticality category, and on the right you see some examples of these attributes. By using this information, we then optimized our manufacturing to focus most of our attention on the attributes in the red and orange boxes, but certainly we also took care of the others as well.

To provide you now with a closer look, in the top two rows, I've marked some of the highly critical attributes, like TNF alpha neutralization and the higher order structure, which are important for etanercept. In a moment I will show you also the comparative data we used to assess the similarity of these attributes between Enbrel and GP2015.

In order to analyze such complex molecules, we need powerful analytical tools which have become available in recent years. Here you see just as an example the mass spectrometry and how this evolved in 20 years since 1990. Within this time span, the detection limit has increased by a factor of 10 million, so it improved from 100 picamoles down to 10 attomoles.

To put this in context, imagine that in 1990 they were able to detect a certain amount of protein in one glass of water, and today we could detect the same amount of protein in an Olympic size swimming pool. And it's this evolving technology which greatly improved our ability to characterize proteins and which allows us today to develop biosimilars to such complex molecules like etanercept.

Now I'd like to turn to our analytical comparative data package, and the database used to determine biosimilarity is huge. We analyzed more than 80 batches of Enbrel bought over several years in Europe and in U.S., and compared them with

GP2015. And as Mark pointed, out, we also compared the Enbrel batches sourced in both regions to determine their similarity to each other, and determined that these products are really the same, because in our global program we used both Enbrel U.S. and Enbrel EU in our clinical studies.

Here you see the table I will use to guide you through our data. It contains those attributes which are most important to demonstrate biosimilar for this molecule, and I will provide examples of each. In addition, the table also includes stability behavior, which means how stable the drug is over time. This is an additional element for the similarity assessment.

Now first let's consider the primary structure, which is the linear sequence of the amino acids. As I mentioned before, this needs to be identical for a biosimilar. The amino acid chains fold then to the higher order of 3-dimensional structure, and it's actually the folded protein which interacts with the TNF, like a key that fits precisely into its keyhole. This

folded protein is responsible for the biological function. So the trick of the same functions is the higher order structure also needs to be essentially the same.

We matched the primary structure using peptide maps. And to conduct this assessment, the molecule is cut into different pieces by its specific enzyme, and the resulting fragments are separated by chromatography. Here you see the chromatograms for GP2015, Enbrel U.S. and Enbrel EU, which all show a very nice match to each other.

But we didn't just compare those peak patterns visually. We also analyzed and sequenced each peak you see here by using mass spectrometry, and by this we got the exact amino acid sequence. And by doing this with four different enzymes, we generated overlapping peptide maps. So they overlap from the amino acid sequence, so they covered the complete sequence of this molecule. So we were able to experimentally confirm the 100 percent identity of the amino acid sequence

between GP2015 and Enbrel.

Now to test similarity of the higher order structure, we looked at the molecule from several different angles and using a panel of different methods, and the collective results from all of these tests provide a comprehensive picture of the folding overall.

One of these methods is FTIR spectroscopy, and here is an overlay from the FTIR spectra from different batches of Enbrel and GP2015. What appears here is one single curve is in fact an overlay of 14 batches. You see here in this method, the spectra are indistinguishable between Enbrel and GP2015.

We also crystallized the receptor portions of Enbrel and GP2015 bound to TNF alpha and measured their folding using x-ray crystallography. And here we have a video which shows the result of these measurements. On the left it's Enbrel bound to TNF, and the on the other side is GP2015.

An x-ray has the advantage of allowing us to measure the folding down to the atomic level. As

you can see, there is a perfect overlap of the 3D structures between the two molecules bound to TNF.

Also all the other methods here applied, like hydrogen/deuterium exchange, circular dichroism and NMR, differential scanning calorimetry, also showed indistinguishable higher order structure. It was not surprisingly both Enbrel U.S. and Enbrel EU also showed the same results.

Now let's turn to the functional properties. This slide illustrates the clinical mode of action. TNF binds to its receptor on the cell membranes, which induces all the downstream effects that are important for the information. Etanercept binds and neutralizes the soluble TNF so that it cannot bind to the TNF receptor anymore, and the downstream effects are blocked. This is the same mode of action for all indications of this product.

We are measuring this neutralization of TNF alpha using a cell-based bioassay, which mimics the mode of action. When TNF binds to the receptor on the cells in this bioassay system, it also

stimulates a gene expression.

Etanercept neutralizes the TNF, which leads to a dose-dependent suppression of this activity. So by this we were able to measure very sensitively and quantitatively the bioactivity for this molecule.

Here you see the results. The red circles at the top show the distribution of the bioactivity of Enbrel EU, and each point is the value of one batch. The white circles show the values for Enbrel U.S., and blue shows GP2015.

As you can see, the bioactivity of the different GP2015 batches lies fully within the range of Enbrel U.S. and EU, so the criterion for similarity is fully met. In addition, we also see that we are producing GP2015 with a very high degree of consistency.

Now, here you see the same results as on the slide before, but also how those results are distributed over time. Here on the left, these are the batches and the values for Enbrel U.S. and Enbrel EU, so sorted by their expiration date. And

each of those batches was sold from the market, so therefore each of those batches represent acceptable quality or Enbrel quality, which has been used to treat patients.

We identified the range of variability in TNF alpha neutralization of Enbrel to be between 76 and 118 percent neutralizing activity. GP2015, as you see here, falls neatly within this range.

Now, the FDA asked us also to do statistical equivalence testing, which is a comparison of the means. But you'll notice that when we looked at some of the newer batches of Enbrel, we see more of those at the lower end of the scale. So they were still within the overall range, but this changed the mean over time. So therefore, GP2015 was statistically equivalent to Enbrel batches only until to an expiration date of 2014, but not if you included the newer batches.

Now, as Dr. Leah Christl pointed out, this statistical equivalence testing is not intended as a pass/fail criteria for biosimilarity. It's intended to facilitate a biosimilarity assessment.

Also if you look at the data, everything is perfectly fine with GP2015 because we can produce very stable with very small variability, but certainly it's a duty of a biosimilar manufacturer to really understand the reference product, so we took a closer look at this phenomenon, and on the next slides we show the results of this.

When we looked at the factors that determine the bioactivity, we found that this was related to the disulfide bond structure of the molecule. Those disulfide bonds, they connect to cysteines in a sequence, and by this they lock the 3-dimensional structure of the molecule.

Here on the left you see an illustration of a portion of the etanercept structure with the correct disulfide bonding, and this form is fully biologically active. However, the etanercept contains also low level of impurities, which have incorrect disulfide bonding. On the right, you see an example of the same sequence with such an incorrect disulfide bond variant, which we have found and determined in etanercept. And this leads

to an alt protein folding, and in this form the molecule is not able to induce neutralizing activity anymore.

The amount of incorrect disulfide bond variants correlates with the TNF alpha neutralization activity. We measured different batches of Enbrel, GP2015, process intermediates, and also waste fractions from our process development with the higher amounts of these impurities and found this very clear structure functional relationship.

The newer batches of Enbrel had more of those incorrect disulfide bond variants, which explains the lower TNF alpha neutralization activity. On the other side you see a consistently low level of these impurities in GP2015 because we tightly control for them in our manufacturing process.

Now the next question was, what is the relevance of these incorrect disulfide bond variants? And what we found is that they have no physiological impact. This is because while they

are detectable in vitro, under physiological conditions, they refold back into the fully active structure.

How do we know this? We incubated Enbrel samples in a system that is designed to mimic the physiological conditions that occur when the molecule is injected into patients. Upon injection, the molecule is exposed to chemical conditions in the bloodstream that allow the opening and reconnecting of disulfide bonds, or in chemical terms, this is called reduction and oxidation.

We used a well-established redox system to mimic these conditions -- the redox potentially in the in vivo is very low, but it's still suitable and able to open and reconnect labeled disulfide bonds. What we saw is that the incorrect disulfide bonds variants reverted back to the most ever correct folding. When they revert back, the TNF alpha neutralization is fully restored.

We performed these redox experiments on a number of samples, and here is, just as an example,

two batches of Enbrel U.S. that we studied. When incubated under simulated physiological conditions, the amount of the incorrect disulfide bond variants is reduced, and the neutralization activity is restored; in this case, from approximately 80 to close 100 percent. This means that when Enbrel is applied and injected, the incorrect disulfide bonds variants can quickly fold back to the fully active molecule.

All of our redox experiments validated this structure functional relationship you see here again, and therefore we could use this model also to adjust for the TNF alpha activity for all batches. And when we did this, we were also able to fulfill the formal statistical equivalence testing criteria as shown here.

This figure shows that the difference of the means, including the 90 percent confidence interval, lies within the equivalence acceptance criteria. This is consistent also with the FDA's own evaluation, which is displayed in the FDA briefing document.

We have shown that GP2015 is not just within the range of variability; it's also statistically equivalent to the Enbrel in terms of TNF alpha neutralization. But in addition, we also checked for a number of other functions related to the receptor portion of etanercept, so the functional part of the molecule that is relevant for the clinical mode of action.

These are TNF alpha binding, TNF beta neutralization, and inhibition of TNF alpha mediated to apoptosis, and for all of these functions, we found that GP2015 is highly similar to Enbrel. These results are described in greater detail in the briefing documents.

Another important attribute is the protein content as it defines how much etanercept is given to the patient. Here again you see the data for Enbrel EU, Enbrel U.S., and GP2015. From the very characteristic impurity profiles I'll be showing you later, we also can conclude this bridge and to show that Enbrel U.S. and Enbrel EU are, in fact, the same product. We can compare GP2105 with the

combined ranges of Enbrel EU and U.S., and GP2015 lies fully within this range. This confirms the similarity in protein content.

Binding to the FcRN receptor is another important feature of this molecule as it has an impact on clearance, the in vivo half-life, and therefore also the pharmacokinetics. Here you see the KD value of this, which is a measure of the binding of the different batches. These show that the FcRN binding properties are comparable between GP2015, Enbrel sourced in the U.S., and Enbrel sourced in the EU.

Now let's take a look at the product related impurities which should be kept as low as possible. These include those variants of incorrect disulfide bonds, which I mentioned earlier; the alpha galactosylation, which is a risk factor for immunogenicity; clipped degradation products, which have a lower bioactivity; and aggregates, which are considered as a risk factor for immunogenicity.

Here on the left are the data for the amounts of alpha galactosylation for the different

batches. The filled red dots are Enbrel EU, the non-filled ones are Enbrel U.S., and blue is GP2015. On the right side you see the amounts for the aggregates, and you can see two things.

First, the values for GP2015 are nicely below the upper limit of Enbrel, so this is the criteria also for biosimilarity. Second, the data clearly demonstrate also the sameness of Enbrel EU and Enbrel U.S.

As noted in our briefing document, we observed also the same conclusions and the same results for the degradation products and incorrect disulfide bond variants, so this means the criterion for biosimilarity is clearly met for these quality attributes.

Finally, we compared the stability profiles, both at intended storage conditions, such as storage in a refrigerator, and in accelerated and stressed conditions, such as at high temperatures. Here you see the data for intended conditions and how the low molecular weights species -- so these are degradation products -- increase over time for

different batches of GP2015 and Enbrel.

These data are important because the formation of those clipped variants is the primary degradation pathway for etanercept when stored in the fridge. In other words, this is what limits the shelf life or expiration date of this product. And here you can see the slopes are pretty comparable, as should be in the case for a biosimilar.

To conclude the analytical presentation, we have confirmed the very high degree of similarity between GP2015 and Enbrel. The primary structure is 100 percent identical; the higher order structure is indistinguishable; the bioactivity is the same; the product related impurities are similar and low, and the stability behavior is comparable. In addition, we have shown that Enbrel U.S. and Enbrel EU are indistinguishable.

Given these data, we have demonstrated that the active ingredient in GP2015 and Enbrel is essentially the same molecule. This leaves then very little uncertainty to be addressed by the

non-clinical and the clinical data package. So with this, I would like to turn over the podium to my colleague, Oliver von Richter, to present the non-clinical and PK data. Oliver?

Applicant Presentation - Oliver von Richter

DR. VON RICHTER: Thank you, Martin.

Good morning. I am Oliver von Richter. I'm a clinical pharmacologist at Sandoz with more than 15 years of experience in non-clinical and early clinical development. It is my great pleasure to guide you through our next component of our biosimilar development program, namely the non-clinical and pharmacokinetic characterization of GP2015 and comparison to Enbrel.

I would like to start with a non-clinical program. Here we have to keep in mind that the scope and extent of animal studies in a biosimilar development program are different than for the development of an originator. It is not about evaluating the safety profile of a new molecule, but about determining similarity and addressing residual uncertainty following the analytical

comparability studies that Dr. Schiestl has just reviewed.

For GP2015, there was very little uncertainty about the similarity of the molecules given the highly similar analytical data. The non-clinical program comprised assessments of pharmacodynamics, pharmacokinetics, and toxicity, including immunogenicity and local tolerance.

In addition, since we had to use a different formulation for GP2015 than Enbrel, due to intellectual property restrictions, the selection of the most appropriate formulation was supported by an animal PK study.

We'll now provide you with an overview of the animal studies we conducted. The detailed results were provided in our briefing document. In terms of pharmacodynamics, we used a human TNF alpha transgenic mouse model, which is a well-established model to assess and compare the efficacy of our treatments.

Based on pilot study 004, we selected a dose of 10 milligram per kilogram administered IP. It's

the most sensitive setting for the comparator study 007. In this study, both GP2015 and Enbrel elicited a similar response in inhibiting arthritis disease progression.

Regarding pharmacokinetics, we performed two different studies in rabbits. In the first PK study we looked at different formulations for GP2015 in comparison with Enbrel. The formulation selected, based on this pilot study, was a lysine/citrate formulation which then showed a similar PK profile to Enbrel in the comparative PK study, the 006 study. Toxicology was assessed in cynomolgus monkeys using repeated dosing over 4 weeks. The observed science was similar in both treatment groups.

Given the similar profile of GP2015 and Enbrel demonstrated in the non-clinical studies, I would like to move on to the pharmacokinetic characterization of GP2015 in humans. This was mainly based on PK bioequivalent studies in healthy volunteers and supplemented with supportive PK data in psoriasis patients.

Our PK data comes from five studies, including the pivotal PK study 102. It is a randomized, double-blind, two-way crossover study, which compared GP2015 to US-licensed Enbrel in 57 healthy volunteers. There are two more PK studies in healthy volunteers using European authorized, referred to as Enbrel EU, as the comparator product.

Study 101 is a sister study to 102 and was used to support the scientific bridge between the U.S. and the European reference product in a cross-study comparison. In study 101, the lower bound of the 90 percent confidence interval for AUC was outside the bioequivalence limits. Following a thorough root cause analysis and consultation with European regulators, we conducted study 104 to confirm bioequivalence of GP2015 to Enbrel EU.

In addition, we have a number of supportive PK studies. Study 103 assessed bioequivalence between the two proposed delivery devices: the auto injector and the pre-filled syringe. Then finally, we also collected PK trough data over

12 weeks in 147 psoriasis patients. You will see more details about this study later.

I will now focus on the studies that are pertinent to the U.S. filing. All of our PK studies in healthy volunteers shared a common design over crossover studies, meaning that we compared different products within individual subjects.

Single doses were applied on day zero of each period and subjects stayed in the clinic for 3 to 8 days, depending on the study. The study also included an adequate washout period between the two treatment periods of at least 35 days. That is approximately 9 times the elimination half-life of etanercept, prior to crossing over to the other product.

This slide depicts the subjects' disposition in our healthy volunteer studies. Overall, a total of 216 healthy subjects were enrolled, and only 8 subjects, that is 3.7 percent, withdrawn from the studies. Out of 216 healthy subjects, only 1 subject had to be excluded from the PK population

in study 103 due to high pre-dose values in the second treatment period. This shows that the length of the washout period was adequate.

Now let's look at our pivotal study 102, where we compared GP2015 with US-licensed Enbrel, referred to as Enbrel U.S. The primary objective of the study was to determine the bioequivalence between GP2015 and Enbrel U.S. in terms of the PK parameters, AUC-last and the maximum serum concentration Cmax, following a single subcutaneous injection of 50 milligram.

The secondary objectives were the additional standard PK parameters as well as immunogenicity, safety, and local tolerance. The data on GP2015 immunogenicity will be discussed in the next presentation.

Here we see the time course of the mean serum concentrations following the single-dose administration of both products, up to 18 days after the subcutaneous administration. The profiles of GP2015 and Enbrel U.S. were similar.

The statistical evaluation of study 102

demonstrates bioequivalence between GP2015 and Enbrel U.S. On the left, we see the geometric means for the respective PK parameters. On the right, we see the graphical display of the corresponding point estimates, namely the geometric mean ratios for GP2015 over Enbrel, along with 90 percent confidence intervals, which are depicted as horizontal bars.

The dashed vertical lines represent the acceptance range for bioequivalence, ranging from 0.8 to 1.25, as defined by the FDA in their guidance on bioequivalence testing. If we look at the point estimates and the 90 percent confidence intervals, we see that these are well contained within the prespecified bioequivalence margins of 0.8 to 1.25.

I would now like to address how the PK data from studies 101 and 102 were used to support the scientific bridge between Enbrel U.S. and Enbrel EU. The reason why we look at the scientific bridge is that we used Enbrel EU and the comparator studies of our non-clinical program, and in the

confirmatory efficacy and safety study in psoriasis patients.

The scientific bridge between the U.S. and EU batches makes those data applicable for our U.S. application. The bridge is built primarily on the extensive analytical and biological characterization, which was presented earlier by Dr. Schiestl. You will recall that it showed the two Enbrel products are essentially the same.

The PK bridge, presented in report 105, is based on this cross-study comparison of Enbrel EU data taken from study 101, with Enbrel U.S. data taken from study 102. Both study protocols included a prespecified comparison of those PK parameters between Enbrel U.S. and Enbrel EU to establish bioequivalence between these two products. Both studies were identical in their design and were run back to back at the same site.

Here we see the respective mean serum concentrations. You see a slightly lower exposure with the European reference product. If we look at the point estimates and the 90 percent confidence

intervals, we see that these data are completely contained within the prespecified bioequivalence margins of 0.8 to 1.25. These data, in addition to the extensive analytical comparison, further support the scientific bridge to prove the similarity between Enbrel EU and Enbrel U.S. As a result, all data generated Enbrel EU as the reference product are justified for U.S. filing.

Now let's look more closely at study 103. This was the healthy volunteer trial designed to test the bioequivalence of GP2015 administered with the pre-filled syringe and the auto injector, based on AUC-last, AUC-infinity, and the maximum serum concentration Cmax.

The secondary objectives which were defined based on interactions with the FDA, were to compare these parameters within a population with a wide range of body weights, and showing that the two devices will not differ in the delivery depending on the body weight of a patient. In addition to the PK parameters, we also looked at safety, tolerability, and local tolerance.

If we look at the mean serum concentrations over time following administration with either device, you see two superimposable curves. This shows that the delivery of GP2015 from the two devices is indeed the same.

Here is the statistical analysis of those data. All point estimates are close to 1.0, and we have tight confidence intervals which are clearly contained within the predefined margins of 0.8 to 1.25.

In addition to the PK assessment in healthy volunteers, we also evaluated serum trough levels in the context of the confirmatory efficacy and safety study comparing GP2015 and Enbrel in psoriasis patients. We implemented a PK substudy in 147 of these patients where we compared their trough serum concentrations over 12 weeks.

We collected blood samples at day 1 prior to dosing, and then sampled trough levels at weeks 2, 4, 8, and 12. All of these assessments were done descriptively.

When we look at the time course of the mean

trough concentrations, we see that the GP2015 and Enbrel levels, as well as their variability, were similar across both treatment groups. It is important to note that patients were treated twice weekly, and that the trough levels at week 2 are based on multiple, namely 3, administered doses. Therefore, you see essentially what would be expected. Steady state trough levels are reached at week 2, and they remain constant until the end of the PK observation period at week 12.

This concludes the presentation of the PK results we have generated in the GP2015 development program. We have shown that GP2015 is bioequivalent to Enbrel in the healthy volunteer studies, and that the pre-filled syringe and the auto injector are equally suitable for administering GP2015.

Enbrel U.S. and Enbrel EU are one Enbrel from an analytical and PK perspective. The PK substudy in psoriasis patients has shown similar trough serum concentration in both groups. So overall, the PK assessment contribute to the

totality of the evidence supporting biosimilarity.

In summary, with all the data that I have presented, you see that we have addressed two more levels in the pyramid. At the non-clinical level, we have established a similar PD and PK, as well as toxicity. And at the human PK level, we have shown similar PK of GP2015 versus Enbrel in healthy volunteers and psoriasis patients.

Now to complete our analysis, I would like to invite my colleague, Dr. Malte Peters, to guide you through our confirmatory efficacy and safety study.

Applicant Presentation - Malte Peters

DR. PETERS: Thank you, Oliver.

Good morning. My name is Malte Peters. I'm the global head of clinical development in Sandoz's biopharmaceuticals business unit. I am a physician scientist by training, and I treated patients with immune disorders and cancer during my academic appointments.

Today I'm going to show you the clinical confirmation data of GP2015 equivalence to Enbrel.

I will provide you with an overview of our GP2015 program, will explain the design of our confirmatory safety and efficacy study, which is termed GP15-302. Of course, I will show you the efficacy, safety, and immunogenicity results, and I will provide you with some summary and concluding remarks.

The clinical confirmation represents the tip of the pyramid, which you have seen so many times today. The pyramid is our attempt to graphically display the totality of the evidence concept, which has been introduced by Dr. McCamish to you earlier today. It's important to remember that all four parameters listed here, the analytical, non-clinical, pharmacokinetic, and clinical datasets, are equally important to corroborate the totality of evidence concept.

I will focus now, in the next couple of minutes, on our confirmatory efficacy and safety study, which has been performed in patients with plaque type psoriasis. In this study, GP2015 was compared to the EU-approved version of Enbrel. 531

patients were randomized, the study duration was 52 weeks, and a dose of 50 milligram twice weekly was used for the first 12 weeks of treatment, and 50 milligrams weekly thereafter. The compounds were administered in a subcutaneous fashion.

Tumor necrosis factor alpha is in the center of a pathophysiological cascade, which was pertinent to all of the indications that are listed on this slide for which Enbrel is approved. Downstream signaling of tumor necrosis factor alpha includes invasion of inflammatory cells, which in turn lead to increase in concentration of chemokines and cytokines, amongst which is also tumor necrosis factor alpha. That's why the brocade of tumor necrosis factor alpha is essential to interrupt this vicious circle.

Why have we conducted our study in psoriasis? Psoriasis represents the most sensitive indication to detect potential differences in efficacy and safety between GP2015 and Enbrel, and there are three important considerations regarding this point.

First of all, there's an adequately large effect size in psoriasis. Secondly, Enbrel is used as monotherapy in psoriasis, which reduces confounding factors, for example coming from immunosuppressive therapy such as methotrexate treatment.

Lastly, the dose of 50 milligram, which is used in psoriasis, lies in the linear phase of the dose response curve. That's important because it increases the probability of detecting differences between the proposed biosimilar, in this case GP2015, and Enbrel, should these exist. And lastly, of course, well known FDA-approved Enbrel for adult patients with psoriasis in 2004.

The study objectives of our study GP15-302 are listed here. First, we wanted to demonstrate equivalence and efficacy, and similarity in the safety profiles of GP2015 and Enbrel in patients with psoriasis.

Secondly, we wanted to compare long-term efficacy, safety, and immunogenicity in patients who received continued treatment with GP2015 or

Enbrel.

Thirdly, we wanted to evaluate the effect of repeated switching between GP2015 and Enbrel on efficacy, safety, and immunogenicity. And Dr. von Richter has already presented to you the pharmacokinetic results pertinent to the fourth objective with respect to PK parameters.

Patients with moderate to severe form of psoriasis were eligible for our trial. In our trial, we defined moderate or severe form of psoriasis by a PASI score of at least 10, and an IGA score of at least 3, and a body surface area affected of at least 10 percent.

Patients had to have previous photo therapy, or systemic therapy, for psoriasis, or had to be candidates for such a therapy in the eyes of the investigator. Patients could not participate in our study if they had other forms of psoriasis than plaque type.

Certain medications, certain immunomodulatory medications for psoriasis and other diseases, were prohibited. Previous exposure

to etanercept was not allowed. Patients could not have active ongoing inflammatory diseases other than psoriasis, nor a history of ongoing, chronic or recurrent infectious diseases, including tuberculosis.

We selected a novel study design with multiple treatment periods in order to achieve the objectives of our study. There were four treatment periods: a screening period; treatment period 1; treatment period 2; and an extension period. The extension period has been included based on discussions with European health authorities.

At the time of the submission of our file to FDA, this data was not mature. Therefore, in today's presentation, I will focus exclusively on treatment period 1 and treatment period 2. At the end of treatment period 1, our primary endpoint was assessed, which was PASI 75 score, and I will come back to this in a moment.

Now let's focus on treatment period 1. This treatment period ranged between week zero and week 12. During this treatment period, patients

were randomized in a one-to-one fashion between GP2015 and Enbrel. The objective of this treatment period was to demonstrate equivalence in efficacy and similarity in the safety and immunogenicity profiles of GP2015 and Enbrel in patients with psoriasis.

At the end of treatment period 1, patients were assessed for the PASI score and could be re-randomized into treatment period 2 provided they had a PASI score of at least 50.

In treatment period 2, there were 4 treatment arms, consisting of either continuous treatment with GP2015, designated by the continuous blue line, or continuous treatment with Enbrel, designated by the continuous red line. Patients could also be randomized into arms where they underwent switched treatments between GP2015 and Enbrel, as shown by the two arrows in the middle with the alternating colors.

This treatment period ranged between week 12 and week 30, and there were two objectives during this treatment period. First, to compare efficacy,

safety and immunogenicity between the patients randomized to the continued treatment arms shown at the top and the bottom of this diagram. The second objective was to compare continued treatments with treatments consisting of repeated switches between GP2015 and Enbrel.

The statistical requirements for our study was based on scientific considerations based on published data and the literature. The primary endpoint was considered to be met if the 95 percent confidence interval for difference between treatment groups and PASI 75 at week 12 fell within the prespecified equivalence margin of 18 percent. A 90 percent power assumption was used for the sample size calculation.

The key secondary endpoints were considered to be met if the longitudinal analysis of the percent change of PASI score from baseline to week 12 fell within the prespecified equivalence margin of 15 percent, and we used two different statistical approaches, and I will come back to this in a moment.

The fact that the prespecified equivalence margin for the key secondary endpoints were slightly narrower compared to the primary endpoint was due to the fact that the secondary endpoints were considered to be slightly more sensitive.

The primary analysis set was the per-protocol set in our trial. However, supportive analysis using the full-analysis set were also performed.

774 patients were screened in our trial; 531 patients were randomized, constituting the safety, full analysis, and immunogenicity set. Thirty-one patients had major protocol deviations, who did not already discontinue treatment in treatment period 1, and 20 patients discontinued treatment in treatment period 1. That left us with a per-protocol set of 480 patients.

It's important to know that the majority of patients was actually able to be re-randomized into treatment period 2, and the respective numbers are shown in the dark blue boxes. 497 patients constituted the safety and immunogenicity set for

treatment period 2, and the per-protocol set in treatment period 2 consisted of 446 patients. Patients were randomized at 71 sites across 12 European countries and South Africa.

The patient demographics and baseline characteristics were very well balanced between the two treatment groups consisting of GP2015 and Enbrel. This statement is true for age, sex, race, weight, and body mass index.

The patient disease history parameters were also very well balanced between the two treatment groups of GP2015 and Enbrel. The mean time since initial diagnosis was in the range of 17 to 18 years in both patient populations. Twenty percent of patients suffered from psoriatic arthritis.

The majority of patients had no prior systemic therapy, and a moderate form of psoriasis, as shown by the IGA score of 3. The mean PASI score at baseline was 22.5 in both treatment arms. The mean percent of the body surface area affected was 30.5 and 30.9 percent, respectively.

The patient disease history and the patient demographics were also analyzed in the per-protocol set, and were highly similar and also well balanced. We have shown you the full-analysis set on this slide and on the previous slide.

Now let's turn to the efficacy results of treatment period 1. We used the psoriasis area and severity index scoring system, or PASI scoring system, in our study. The PASI scoring system has been established in 1978, and is since used in virtually every clinical trial which assesses patients with psoriasis in a clinical trial.

The PASI scoring system assesses four different areas of the body: the head, the trunk, the upper limbs, and the lower limbs. In each of these areas, four different assessments are made: the percentage of the body surface area affected is assessed, the degree of erythema, induration, and desquamation are also assessed. The maximum possible PASI score is 72.

Now let's take a moment and think about the patients we're talking about here today, patients

with psoriasis. Psoriasis affects 2 percent of the world population. Psoriatic lesions are painful and are itching, and patients often are discriminated against because psoriasis is a stigmatizing disease.

This photograph is taken from one of the earlier publications of Dr. Leonardi, who is with us today. The photograph on the left side represents a patient with a PASI score of 22.7. Twelve weeks upon treatment, the PASI score decreases to 6.3. This is an improvement of 72 percent.

Twenty-four weeks after initiation of treatment with Enbrel, this patient had a reduction in PASI score to 3.8. That's a reduction of 83 percent. So you can easily appreciate that a PASI score of 50, 75, and 90 describes a 50 percent, or 75 percent, or 90 percent improvement in PASI score.

Now what's important to note here, if you look at the middle photograph, despite the fact that this patient had a 72 percent improvement in

PASI score, this patient would still not have been counted as a PASI 75 responder.

The primary endpoint in study GP15-302 has been met. GP2015 and Enbrel are equivalent. The table at the upper half of the slide shows you the adjusted PASI 75 response rates measured at week 12. 73.4 percent of patients treated with GP2015 had a PASI 75 response at week 12 as opposed to 75.7 percent for patients treated with Enbrel. That's a difference of 2.3 percent.

The respective results of our statistical analysis are shown at the bottom part of the slide. The upper bar demonstrates the 95 percent confidence interval as defined in the protocol. The lower bar shows you the 90 percent confidence interval as requested by FDA. And you can see that the upper and lower boundaries of these two confidence intervals fall very well within the prespecified equivalence margins of minus 18 to plus 18 percent.

Here's additional data with respect to the response rate, which we assessed during treatment

period 1. You can see the respective results for the PASI 50, 75, and 90 scores. And you can easily see that the results assessed for patients receiving GP2015 and Enbrel are highly similar as the two curves are always almost superimposable.

The key secondary endpoints assessed in our trial were also met. You can see on the left side the difference in percent change from baseline in PASI score up to week 12. We applied two statistical instruments, namely the averaged treatment effect, or ATE, as well as the mixed model repeated measures, or MMRM method.

So what are these methods? While the PASI 75 score at week 12 represents one single assessment of psoriasis at a single given time point, these two methods are a longitudinal assessment over time. They can essentially be compared with an area under the curve graphical display, which you often see in clinical pharmacology trials. The upper and lower boundaries for both statistical assessments, ATE and MMRM, fell very well within the prespecified

equivalence margins of minus 15 to plus 15.

We also utilized the investigator's global assessment rating scale. Remember that to be eligible for our trial, patients had to have an IGA score of 3 or 4, which designates a moderate or severe form of psoriasis. We then assessed the proportion of patients who received a complete or almost complete clearance of their psoriatic lesions during treatment. In other words, we counted the number of patients who changed their IGA score from 3 or 4 to zero or 1.

Here are the results. There was a marked and similar improvement of IGA scores achieved in both treatment arms consisting of GP2015 and Enbrel. At week 12, 10 percent of patients had a complete or almost complete clearance of their psoriatic lesions. This number increased to roughly 30 percent at week 8, and at week 12, more than 50 percent of patients had completely, or almost completely, cleared their psoriatic lesions.

Now let's turn to the safety results in treatment period 1. The exposure to study drug was

highly similar between patients treated with GP2015 and Enbrel. The mean duration of exposure was 80.6 days for patients treated with GP2015, and 79.2 percent for patients treated with Enbrel.

What's also important to see on this slide is that more than 90 percent of patients either did not miss a single dose, or only one dose, speaking to the high clinical compliance that was observed in our study, and that was true for both treatment arms.

The treatment-emergent adverse events observed in treatment period 1 were very well balanced between the two treatment arms consisting of GP2015 and Enbrel. If you just look at the first line, the percentage of patients in whom at least one adverse event was recorded was 37.5 percent for patients treated with GP2015, as opposed to 36 percent for patients treated with Enbrel.

The other safety parameters that we assessed during the course of our trial, which are listed on this slide, were also very well balanced. And this

is also true for the number of patients who had to discontinue or interrupt study treatments due to adverse events.

There was a slight numerical difference with respect to adverse events of special interest, which we deducted from the prescribing information of Enbrel, and I will come back to this in a moment. One patient died during the course of treatment in the Enbrel group. This patient had a cardiopulmonary arrest, which was not considered to be related to study treatment.

The treatment-emergent adverse events, which were reported at an incidence of greater than 1 percent regardless of study drug relationship, were very well balanced between the two treatment arms consisting of GP2015 and Enbrel. The forest plot on the right side shows you the details.

If the symbols are found on the right side of the dashed line, the incidence of the adverse events are higher in patients treated with GP2015. If the symbols are on the left side, the incidence is higher in patients who are treated with Enbrel.

Overall, there's no particular pattern, and the incidences oscillate basically around the midpoint.

Here's more detail related to the treatment-emergent adverse events of special interested listed by system organ class and preferred terms. While there were some numerical differences between the two treatment groups, the infections were mainly benign and local infections. We recorded benign neoplasms, as listed on this slide. Benign lesions included a skin papilloma and a lipoma.

There was one patient in whom a colon neoplasm was recorded. This was a patient with a tubulovillous adenoma. One patient had a malignant melanoma in situ. This lesion was removed before initiation of study treatment, and this patient discontinued the study. Another patient had a melanocytic nevus. This lesion was removed at day 28 of treatment, and his patient continued treatment.

Overall, these are single events in different system organ classes, and there's no

specific or significant safety pattern that can be deducted from this analysis.

Let's now look at the efficacy results of treatment period 2. Treatment period 2 had two different objectives. Let's look at the first objective first to compare efficacy, safety, and immunogenicity between the two continued treatment arms, which are shown by the continuous blue line and the continuous red line.

Here are the results, the PASI 50, 75, and 90 scores for patients treated with Enbrel. If we now overlay the respective results for patients who received GP2015 during this treatment period, the two curves are virtually superimposable.

The second objective of treatment period 2 was to compare efficacy, safety, and immunogenicity between patients who received continuous treatment, as shown by the purple colored arrows, and patients who received undergoing repeated switches between GP2015 and Enbrel, as shown by the two green arrows in the middle portion of the slide.

Here are the results for the PASI 50, 75,

and 90 scores for those patients who received continuous treatment with either GP2015 or Enbrel. Again, we now overlay the respective results for patients who received switch treatment between GP2015 and Enbrel. And you can see that both curves are superimposable. This indicates that switching between GP2015 and Enbrel had no impact on clinical efficacy.

Of course we were interested in the safety profiles during this treatment period. We first looked at the comparison of those patients who received continuous treatment of GP2015 or Enbrel. The results are very well balanced between these two treatment groups.

If you just look at the first line, the percentage of patients in whom at least one adverse event was reported was 31.3 percent for those patients receiving continuous treatment with GP2015, as opposed to 34.4 percent for those patients who received continuous treatment with Enbrel.

The other parameters listed on this slide

were also very well balanced. And I spoke already to the differences with respect to the adverse events of special interest.

Here we analyzed the overall treatment-emergent adverse events by pooled treatment groups consisting of either continuous treatment with either GP2015 or Enbrel, or of switched treatments between GP2015 and Enbrel. The results are very well balanced between these two treatment groups.

Again, if you just take the first line of this table, the percentage of patients in whom at least one adverse event was recorded was 32.9 percent for those patients who received continuous treatment, as opposed to 34.2 percent for those patients in whom treatment was switched between GP2015 and Enbrel. Now this is important because it shows that switching back and forth between GP2015 and Enbrel has no impact on patient safety.

In the last couple of minutes, I would like to quickly touch on the immunogenicity assessments

that were conducted in our trial. We implemented a 3-step procedure with respect to screening, confirmatory, and neutralization assay. It was a conservative one assay approach for the detection of anti-drug antibody using GP2015 as a catcher and detection agent.

An ECL bridging immunogenicity assay for screening and confirmation was conducted, which had a high assay sensitivity of 116.5 nanogram per milliliter. The assay had a high drug tolerance level, which ensured that detection of anti-drug antibodies was possible, even with trough levels measured in this study of up to 15,000 nanogram per milliliter.

The suitability of this method to detect anti-drug antibodies against GP2015 and the originator compound was demonstrated in a validation step. Of course, the determination of neutralizing capacity of confirmed anti-drug antibody positive samples was also performed.

Here are the results of our immunogenicity assessment. Five patients, all of them in the

Enbrel group, showed confirmed anti-drug antibody positive samples up to week 12. That's a rate of 1.9 percent, which falls in line with the published data in the literature. All anti-drug antibodies were non-neutralizing, transient, and low in titer, and occurred in the initial 4 weeks of treatment. No additional anti-drug antibody positive results were observed up to week 30.

Let me conclude. The efficacy of GP2015 is equivalent to the efficacy of Enbrel. GP2015 is comparable to Enbrel with respect to pharmacokinetic and safety parameters. No immunogenicity concerns exist for GP2015 versus Enbrel. Switching back and forth between GP2015 and Enbrel has no effect on efficacy, safety, and immunogenicity.

We have demonstrated similarity between GP2015 and Enbrel at all levels of our presentation today. That includes the analytical, non-clinical, pharmacokinetic, and clinical data. With this, I would like to thank you for your attention, and I would like to hand over to Professor Kay who will

put our data into clinical perspective. Thank you very much.

Applicant Presentation - Jonathan Kay

DR. KAY: Thank you very much, Malte.

Good morning. I'm Jonathan Kay, professor of medicine and the Timothy S. and Elaine L. Peterson chair in rheumatology at the University of Massachusetts Medical School. I'm here today as a paid consultant for Sandoz, but I have no financial interest in the outcome of this meeting.

As both a practicing rheumatologist and a clinical researcher, I've followed the development of biosimilars for inflammatory diseases very closely over the past six years, and have published a number of papers on this topic in peer reviewed journals. Today, I'd like to share my thoughts on the use of biosimilars, in particular GP2015, in clinical practice.

As Dr. Woodcock stated yesterday, and Dr. McCamish mentioned earlier, the introduction of TNF inhibitors has revolutionized the treatment of inflammatory diseases. Over nearly two decades,

the efficacy and safety of TNF inhibition has been well established. Each of the five marketed TNF inhibitors has been demonstrated to be safe and effective. However, their high cost has limited access to these biologic agents for some patients.

Tiered formularies often require high co-payments of patients, and time consuming and labor intensive prior authorization processes of healthcare providers and their office staff. So, how can the availability of biosimilars improve access to treatment, and what would improved access really mean?

We can look at this question both at the level of the individual patient and at that of society as a whole. First, the availability of lower priced biosimilars should decrease the cost of treating patients. This should make these biologic agents more readily available to patients for whom the bio-originator has been inaccessible because of cost or limited market availability.

At the societal level, once effective biosimilars are available at a lower cost to treat

many more patients, we should expect to see a reduction in the disability, morbidity, and mortality associated with inflammatory diseases.

As an example of how the availability of biosimilars can increase access to treatment, I'd like to share with you some recently published data about the first approved biosimilar monoclonal antibody. CT-P13 is a biosimilar, infliximab, that was first approved in South Korea in July 2012 and, upon the recommendation of this committee, was recently approved by the FDA in April 2016.

Dan Solomon's group found that 15 months after its approval in South Korea, the biosimilar accounted for 19 percent of all insurance claims for infliximab. And, had the bio-originator not reduced its price by 30 percent as soon as the biosimilar became available, the biosimilar's market share might have been even greater.

But, did this introduction of a lower priced biosimilar actually increase access? The authors found that the use of infliximab, combining both that of the bio-originator and the biosimilar,

increased. Over the same time period the use of adalimumab increased less than it had before, and that of etanercept actually decreased.

So, although these weren't dramatic changes, the overall market for infliximab expanded, and there was a shift from use of higher to lower priced TNF inhibitors. I recognize that these data come from a country other than the United States, but these are the best data published to date that reflect market changes following the introduction of a biosimilar to treat inflammatory diseases.

Now, let's look at GP2015 and how the clinical data that we've seen add to the totality of the evidence supporting extrapolation. As you know, data from a clinical trial of a biosimilar in one disease can support approval for other indications, especially when the mechanism of action of the reference product is the same for each of the diseases. Certainly, we know that rheumatoid arthritis, plaque psoriasis, and the other inflammatory diseases being discussed today all respond to TNF inhibition.

The choice of plaque psoriasis as the disease in which to conduct the clinical trial of GP2015 was a good one. Psoriasis is a prototypic inflammatory disease that, when treated with a TNF inhibitor, does not employ concomitant methotrexate.

The PASI directly and objectively measures the extent of disease on the target organ, and does not include a subjective patient assessment. It is sensitive to detecting change over time, thus it should be able to detect even subtle differences in clinical response to a biosimilar compared to its reference product.

The analytical data demonstrating high similarity of GP2015 to Enbrel, and the confirmatory clinical data in plaque psoriasis shown today, justify extrapolation to rheumatoid arthritis and the other proposed indications. These data add to the totality of the evidence that GP2015 is essentially the same molecule as the bio-originator, Enbrel. Thus, since they've been shown to be essentially the same, we can rely on

our accumulated clinical experience with Enbrel across indications to guide our use of GP2015 in these same indications.

So, how would I use GP2015 in my practice? I would have no reservations about initiating patients naïve to TNF inhibition on a lower cost biosimilar. I also would strongly consider transitioning patients currently doing well on Enbrel to a lower cost biosimilar to conserve resources. And, I would feel comfortable treating my patients with GP2015 in each of the indications for which Enbrel is approved.

The use of biosimilars in clinical practice represents a paradigm shift in the treatment of patients with rheumatologic and other inflammatory diseases. With the approval of GP2015, we will have an important opportunity to increase access to safe and effective therapies for our patients with inflammatory arthritis, spondyloarthropathies, and psoriasis in the United States.

Thank you for your attention. Now, I'd like to invite Dr. McCamish back to the podium to

conclude the Sandoz presentation.

Applicant Presentation - Mark McCamish

DR. McCAMISH: Thank you, Dr. Kay.

So we've attempted to share with you our experience and learnings, and our program over an eight-year period to develop a biosimilar to Enbrel. We've shared with you the data that includes the totality of evidence that GP2015 is essentially the same as Enbrel. That included the analytical, the non-clinical, clinical pharmacology, as well as the confirmatory clinical trial, designed again to pick up any differences if they were to exist as a sensitive model of capping off the totality of evidence.

We conclude that the modern technology and analytics does allow for creation and full characterization of biosimilars. We shared with you some of that data. GP2015 has demonstrated both analytically and clinically to be highly similar to the reference product, as required by statute.

This high similarity supports extrapolation

to all indications as the reference product, and we shared with you some of our learnings around extrapolation and how the totality of evidence can be used to justify this.

Biologic drugs are really critically important therapeutic agents. A biosimilar to Enbrel would provide competition and increase access to patients. The approval of GP2015 will expand options available to healthcare providers and patients. And overall what we've attempted to do is provide data that would reassure a treating clinician that using GP2015 is like using another batch of Enbrel for their patients.

So with that, Dr. Solomon, I conclude the sponsor presentation. Thank you.

Clarifying Questions to Applicant

DR. SOLOMON: Thank you very much. I'd like to open it up now for clarifying questions. Dr. Oliver, start.

DR. OLIVER: Alyce Oliver. Do you have data on immunogenicity for treatment period 2?

DR. McCAMISH: We do have data on

immunogenicity for treatment period 2. Dr. Peters shared that with you. Essentially, there were no additional immunogenicity after that. You can see these are the patients that developed transient immunogenicity -- slide up -- in 302 up to week 30.

You can see this happened in the first 4 weeks of exposure, and these were 5 patients that had transient immunogenicity that was present. But then, again, low levels of immunogenicity, transient. You can see by the green dots, they did not become consistently immunogenic, or positive. And during the entire period of the treatment period 2, there was no additional immunogenicity that was seen with switching or without switching.

DR. SOLOMON: Dr. Horonjeff?

DR. HORONJEFF: Hi there. Jennifer Horonjeff. First of all, it was a very impressive presentation, and certainly from the scientific side. I just want to make a note, though, during the last presentation from Dr. Kay in talking about the advantages of using plaque psoriasis for the disease that you were experimenting on here, that

it was noted that the advantage was using the PASI because it didn't have subjective patient data. And it was framed in sort of a negative context that having that patient data would have given us different results that maybe have been unfavorable.

So just urging the sponsor to not see patient input as being a negative source of information.

DR. McCAMISH: No. I appreciate that comment. I think it's valuable. And what we were trying to do is use the approach of differentiating between our product and the reference product in the best way we can. We did include quality-of-life measures that did provide patient-supported information on this to show that there was no difference between our product and GP2015. But this is a very important point.

I would, however, just as a point in terms of clarification, like for Dr. Leonardi to come up and talk about PASI, because this is an important component and psoriasis being a key issue. And this is not to ignore the patient at all, but to

talk about the science of what we were attempting to do here.

DR. LEONARDI: Thank you, Dr. Solomon and committee. My name is Dr. Craig Leonardi. I'm a dermatologist in St. Louis, Missouri, and my office is one of the large psoriasis research and treatment centers.

When patients are done with trials, I generally try to get them on stable prescribed therapies, and as a consequence over the years, I've got roughly 12[00] to 1300 patients who are on prescribed biologics.

Let me have that slide. Sure, PASI is a measurement we inherited from the Scandinavians. And we can poke fun at it for a variety of reasons, but the fact is, this is the one continuous measurement throughout all of the years that we've been conducting. Essentially, it attempts to capture the essential elements of psoriasis on the skin, how much and how bad.

We can argue about whether or not this does it linearly, whether or not these assumptions are

great, but the fact is that it does a pretty decent job in the population of patients who are called moderate to severe psoriasis.

Let me have the next slide, please. This is some data from one of the recent IL-17 antagonists that was approved about a year and a half ago. And I'll just say, well conducted psoriasis trials have incredibly consistent PASI responses.

You can see, in this trial, the ERASURE trial in the green bar, 81.6 percent in one trial, 77 percent in the FIXTURE trial. So nice repeatability. In a placebo arm, we see a nice low placebo response. That's usually important in pivotal trials, not so much in the work we're talking about today.

Let me see the next slide. This is ixekizumab, a drug that was just approved, and spectacular concordance across three large phase 3 trials, 89, 90, and 87 percent. So this is a metric that can have a lot of repeatability across a wide variety of patients in trials by experiences.

Then I think we have one more. This is from the pivotal Enbrel trials way back in the day, around 2003 this research was done. And you can see that there are three lines, three graphs here. The first one is a placebo crossover at the bottom. Patients were on placebo up to 12 weeks, and then crossed over onto active therapy. And you can see an inflection, change, reflecting a response to therapy.

At the top line, though, is an interesting curve. And what you're looking at is the step-down dosing of etanercept. That's where patients started off at 50 milligrams twice a week, or a 100 milligrams a week. And then at week 12, they stepped down to 50 milligrams a week, and you can see the inflection changes. This is a metric that is also sensitive to subtle changes in the way that the dosing occurs.

Now, one of the key issues always in the back of our mind is are we doing anything that makes a difference in patients' lives. And right here, you see an attempt to link PASI, various PASI

improvement bins going across horizontally, to DLQI, dermatology life quality index. You can see quite convincingly that there is a relationship, and that with increased improvement in PASI, even up to 100 percent, you see a marked change in DLQI score. And I have just one more for you.

This is again from the ixekizumab trial, and this is looking at itch. Itch is really insidious for these patients, as you all know. But you can see that with every step of the way, PASI 50 to 75, 75 to 90, 90 to 100, or even 100, there is a statistically significant improvement in itch classification. These are important elements in PASI. I'm saying this to tell you that even though it's an imperfect measure, that you can rely on these results with confidence.

I guess the last slide might be the most interesting one, is my thoughts on this matter. So what makes psoriasis a preferred indication? I think I'm going to tell my rheumatology colleagues, you're going to see more and more of biosimilar trials flow into this space with a psoriasis trial.

It's a well understood and shared mechanism of action that treats psoriasis, and it's common with RA, and ankylosing spondylitis, and JIA, and psoriatic arthritis. The psoriasis patients are typically younger and healthier by about 10 years, and that means they have fewer comorbid diseases, fewer concomitant medicines, and less noise as a consequence of all of that.

The disease is on display. It's easy to assess. There's no invasive testing required. Yeah, even a dermatologist can do this assessment.

(Laughter.)

DR. LEONARDI: In dermatology, biologics are accepted as monotherapy. That could be an important thing because again, whenever you bring methotrexate, azathioprine, prednisone into the mix, there's a lot of noise. It's safety noise. It's noise that interferes with immunogenicity data and efficacy interpretations.

Next slide. Let's see. No, stay right here. There are well established primary endpoints, PASI, and usually some form of

investigator global assessment or physicians global assessment. Psoriasis has the largest treatment effect size in the class, and this allows for detection of small differences in efficacy.

If you're a busy pharmaceutical company, the skin responses are fast. You don't have to wait a year to get these answers, you're getting them in 12 to 16 weeks, and you can make adjustments on the fly. Thank you very much.

DR. HORONJEFF: Can I say just in follow up, that I appreciate walking through the PASI, but since you said that you do have the quality of life data, I would have just been interested to see that presented here for the study that we're looking at now; especially using the public hearing to try to get more patient buy-in as we've heard for the past two -- or yesterday and the one back in February, that clearly we need to be able to explain to the public that this is not something to be feared. So, thank you.

DR. McCAMISH: Sure. Thank you. And I'd like Dr. Peters to share with you the

quality-of-life data.

DR. PETERS: We applied three different quality-of-life instruments, the DLQI, which is a 10-item general Dermatology Disability Index Questionnaire. We applied the EQ-5D, which is a generic instrument to assess patients health status. And for patients who were diagnosed with psoriatic arthritis only, we administered the HAQ-DI test to assess the physical function and activity limitation.

Here's the summary of the results. You can see at the upper left side of the slide, the results for the DLQI. And we compared the results for patients treated with GP2015 and those who received Enbrel, and you can see that the red and the blue curves are superimposable, indicating a highly similar treatment effect.

At the right side, you see the EQ-5D results at week 12. And again, the results were highly similar for patients treated with GP2015 and Enbrel. At the left bottom of the slide, you see the HAQ-DI results.

These were assessed only in patients who were diagnosed with psoriatic arthritis. Remember, 20 percent in both treatment cohorts had psoriatic arthritis. And again, you can see that the treatment effect in patients treated with GP2015 and Enbrel was comparable.

DR. SOLOMON: Dr. Becker, next.

DR. BECKER: Hi, Mara Becker. I had a question about your formulation. I did not see a lyophilized powder as an option. And being a pediatrician, we use much smaller doses than 25 milligrams at a time. I was curious how you thought to address that, or if your pre-filled syringe would be able to be marked in such a way that we would be able to use smaller doses.

DR. McCAMISH: Yes, thanks for the question. And we have a vial under development that we'll use and introduce as part of the interchangeability component. For that, you'd need all dosage forms for that use, and in the meantime use the pre-filled syringe as it would normally be used.

DR. SOLOMON: Dr. Scher?

DR. SCHER: Jose Scher here. I'd just like to go back to Dr. Leonardi's presentation. I'm having trouble with the outcome, the primary outcome of this study, right, PASI 75 of 75 percent on Enbrel.

You showed your seminal study with an outcome of 49 percent when you showed a picture; that's the parent company, Novartis, doing a head-to-head secukinumab versus Enbrel. In that study, the PASI 75 was 45 or 44 percent.

The question is, how do you assess the dramatic difference in the overall efficacy?

DR. McCAMISH: I'd be happy to have Dr. Leonardi address that question.

DR. LEONARDI: By the way, I didn't disclose conflicts of interest. I have contact with many companies. If there's a theme in there, they're all developing the new drugs for psoriasis. I have no financial interest in the outcomes of this meeting at all.

Let me have the first slide. The difference between the pivotal trials and this trial, in my

opinion, the biggest difference that could account for the relatively high PASI response is lack of a placebo arm. I think that's the important issue here.

Placebo arms really help ground the investigators and makes them think about everything. Their assessments get tighter and more accurate whenever there's a placebo arm.

However, we've seen high numbers in the past. If there's a theme here, the trials I'm going to tell you a little bit about are open-label in the sense that there is no placebo arm and that the dose of etanercept is understood.

The first one is this PRISTINE trial. So, what you can see here, this is a trial of "real-world use" of etanercept in a moderate to severe population. After week 12, these patients were on 50 milligrams a week of Enbrel. And they were allowed to use potent topical steroids after week 12, although I think only about 20 percent of them did. But you can see that this number got pretty high, and similar to what was seen in the

EGALITY or the GP2015 studies.

So this is an example of a study that is not placebo-controlled, with similar results. Not happening as fast as what happened with GP2015, but nonetheless, results in the same neighborhood.

There's another study that I'll show you, and this is another real-world etanercept or Enbrel use study, and this is PRESTA. And this is essentially a study with patients who have significant psoriatic arthritis, as well as significant psoriasis. So not the type of psoriasis that is typically found in the rheumatology studies, but the moderate to severe disease, 10 percent body surface area, PASI of 10, PJ of 3.

Again, the dose was understood from the get-go. There was no placebo arm. And you can see that the numbers, you're looking at PASI 75 on the left -- I'm sorry, the mean decrease, mean reduction in PASI is very similar as that was seen with, again, the GP2015 study.

So if I had to put all this together, I

would say that -- next slide -- thank you. There was no placebo control, and in my mind that accounts for the biggest reason that there is a jump in efficacy that was seen. There was a slightly different body weight in the Sandoz trials compared to the Enbrel trials, and that will count for some change in PASI. There's a weight-based effect always in PASI.

The response was, beyond the 12 or 16 weeks was comparable to other published studies. The higher response rates that we see on the most recent etanercept or Enbrel studies are consistent with this as well. The bottom line is that this was a comparison, a comparison of etanercept versus GP2015, and that whatever was going on in the study was consistent, and the results were very similar, as we saw. Thank you.

DR. SCHER: Can I follow up on that?

DR. SOLOMON: Yes.

DR. SCHER: If you can go back two slides on the real-world --

DR. LEONARDI: Yes, we can go everywhere.

DR. SCHER: Yes. Is that twice a week Enbrel that --

DR. LEONARDI: It was twice a week for the first 12 weeks, and then once a week after that.

DR. SCHER: I see, so it's a different criteria compared to the GP2015.

DR. LEONARDI: Yes, this is a dosing that was done throughout the etanercept development programs, right.

DR. SCHER: Okay. Were there any differences in the inclusion criteria, UV light therapy, or other treatments that were --

DR. LEONARDI: To the very best of my knowledge, the answer is no.

DR. SCHER: Thank you.

DR. SOLOMON: Thanks. Dr. Reimold?

DR. REIMOLD: Thank you. Andreas Reimold. I have actually four questions, two from the analytic realm and two with the more clinical. Let's start with the more clinical. On slide CL-30, there is a reference to multiple or repeated switch of GP2015 versus Enbrel. Can we clarify

that? Is it really more than one switch back and forth repeatedly or just one switch?

DR. McCAMISH: Thank you. The slide is depicted here. And for the treatment period 2, so after week 12, we then re-randomized patients as outlined here. And there were three switches that each patient experienced that were randomized to the switch group.

There was a unequal allocation because we wanted to have more experience of continuous treatment, but we did want to probe the issue of switching.

So you can see that in the intermediate lines of the slide, you can see that 100 patients, about 100 patients, in the continuous -- in those that experienced GP2015 were then switched to Enbrel. Those same patients 6 weeks later were switched back to GP2015. Those same patients 6 weeks later were switched back to Enbrel. And the opposite switching strategy for those that were on Enbrel first.

DR. REIMOLD: Okay. Fine. That's a new

finding that was tolerated well.

Also, then in the PK studies, that was slide CP-14, you moved quickly past the different weight categories. Was there any kind of effect of weight in the end that was a secondary endpoint?

DR. McCAMISH: Yes, that was indeed intriguing. So there were the weight categories that we wanted to look at. FDA actually asked us to look at those weight categories. If we can maybe pull up the PK from that. Slide, please.

We could show that there was really -- slide up. This is a PK looking at those. There was no difference in people treated with the pre-filled syringe or the auto injector in each and any of the weight categories of interest. You can see the medium and high weight categories, PK was about the same. There was greater exposure in the lower weight category, as you can see from this.

There's a corollary to that, if we can bring up slide EF-61, please. So a corollary to this, in the clinical trial, the 302 clinical trial, because we also looked at the impact of weight, because

this was a stratification factor. So here you can see that there was an impact on weight and its efficacy here. And you can see almost a 20 percent difference in the primary endpoint whether you were in the higher weight category quartiles here or the lower weight quartile.

Again, this points that there is an impact here that we found. It's important to stratify for them so you have equal allocation. But also it does point back to the sensitivity of psoriasis because we can pick up a difference in terms of a dose that would happen with a higher weight, lower weight individual.

DR. REIMOLD: We have time for my others? Then for the more analytic things, I wanted to clarify, it was mentioned that GP2015 is derived from a CHO cell line. And is that a transfection that your company did and derived at anew? Did you get the original line from the inventor from many years ago?

(Laughter.)

DR. REIMOLD: Was the original product also

made for a CHO cell line?

DR. McCAMISH: Yes. The original product was also made from a CHO line. We did not steal the original line from the originator.

(Laughter.)

DR. McCAMISH: Although I was at Amgen at the time. But no, we developed it. Novartis is a producer of biologics, and so there are cell lines that we use routinely in Novartis, as a company, that we're very familiar with.

We utilized an existing cell line that we have used in the past and were more familiar with, and that cell line was adapted based on the variability of the criteria that we were looking at to make the biosimilar.

DR. SOLOMON: Dr. Ye. Maybe if we can focus on clarifying around some of the analytics, I think that would be most productive. So, Dr. Ye?

DR. YE: Yes, actually I do have a few questions about the analytical part, particularly on slides CA-20 to 24, which are in regards to this misfolded species that seems to have an impact on

the efficacy of the drug.

My question is that given that since that the materials, from the materials that I read, this is only a small fraction of the proteins that has this incorrectly disulfide bonded variants, how could that account for such big variations in the bioactivities from the assay? Particularly when you do the rescue experiments with the redox systems, it seems like there's really a huge variation from the bioactivity from 20 percent to 100 percent.

DR. McCAMISH: The question then is, looking at this variant, and working out the equivalence of the parameter and how we look at that, and then how is this reflected. It seems like when you look at T7, there's a bigger contribution to the binding capacity. Is that the question?

DR. YE: Yes.

DR. McCAMISH: Okay. Thank you. In the slide that you mentioned, again, let me point out that we were looking at the variability of the originator GP2015, very stable over time in terms

of its event, but we're trying to understand the trend down with the originator. And I'll ask Dr. Schiestl to come up and address that regarding the T7 component there and how we quantified it.

DR. SCHIESTL: Yes. Martin Schiestl, Sandoz. If we can have the slide with the structural functional relationship.

So I assume you're referring to this slide, so the question was, I think I understood it correctly, so how the small number in the T7, this relative amount, contribute to such a large difference in TNF neutralizing activity.

The point is T7 is only one of four of those incorrect disulfide bond variants. The number you see here is a relative number, which is a measure for the misfolded portion of those variants overall, but it's just methodological reason.

For example, where you see T7, the relative amount between and 7 and 8, so this has about around 70 percent overall of those misfolded variants.

DR. YE: But what is absolute about the

misfolded variants in these different products? What is the variations of -- what is the proportion of the total misfolded variants in the products?

DR. SCHIESTL: The total portion, so we can only estimate it. It's around 10, somewhat over 10 percent in the Enbrel. But this is a measure, which we were able to establish to measure this misfolding very precisely so that we can compare batches to each other, or also changes in the batches to each other.

DR. YE: But then how do you expand that even if you have this 10 percent misfolded proteins that are completely inactive that actually lead to more than 30, 40 percent of the changes in the activities in slides, let's say CA-20?

DR. SCHIESTL: Come back to slide CA-20.

DR. YE: So the variability is that for the Enbrel seems to range from 120 percent to 80 percent. So that's like 30 percent differences there, and you only have like 10 percent of the products you think are misfolded or inactive.

Do you think that's the reason to explain

these variabilities here? I think there seems to be a disconnection here.

DR. SCHIESTL: As I mentioned, we couldn't quantify the absolute amount very precisely. This is due to technical reasons. What we can quantify is this T7 variant, and we know that this also is a measure for the misfolded variants overall.

DR. YE: Have you compared the overall spectrum of the misfolded species between your products and Enbrel's to show that they are also quite similar in terms of the --

DR. SCHIESTL: We found the same misfolded variants in our manufacturing process development and also in Enbrel. So this is totally -- we found exactly the same structures.

DR. SOLOMON: Dr. Bergfeld?

DR. BERGFELD: Actually that was my question about the disulfide bonds. Thank you.

DR. SOLOMON: All right. Dr. Brittain?

DR. BRITTAIN: Yes, I have a quick question on the clinical trials. So the primary analysis is per protocol and the secondary is intent to treat.

I would have flipped those. I worry about per-protocol analyses because of potential for bias. But I just want to confirm that when you did the secondary analysis, that the results were essentially the same.

DR. McCAMISH: Yes, and it's a good question. When we're looking at biosimilarity and equivalence trial, it's more sensitive to look at the per protocol because what you're actually asking is will patients treated with the two drugs have any difference. So we used the per protocol, although one would generally use the intent to treat. But we confirmed that both intent to treat and per protocol yielded the same result. And on the secondary endpoints as well, they rebuild the same result there.

Let me have the slide, please. So here you can see on the main analysis per-protocol set, on the FAS, which is the full-analysis set intent to treat, you can see the primary endpoint evaluation, PASI 75, and then you can see the secondary endpoints evaluated, and there are

essentially very little difference between those evaluations.

DR. BRITTAIN: Just to follow up just quickly -- that's fine -- I think more people who do non-inferiority trials, it used to be that they wanted to do per protocol to primary, but now the trend has been to do an intent to treat as primary.

DR. McCAMISH: Thank you.

DR. SOLOMON: Okay. We're going to do three or four more questions. And then we're running a little over, but I think this is productive. Dr. Jonas?

DR. JONAS: Beth Jonas. I appreciate the opportunity to actually look at multiple switches because I think that's one of the things we've struggled with on this committee about what would happen switching back and forth, so thank you for that.

Our biggest issue is always safety and immunogenicity, so can you comment on the serious adverse events that were reported comparing the pooled continued and the pooled switching?

DR. McCAMISH: Sure. I'd like to have Dr. Peters address that, please. So this is pooled switching, pooled continuous --

DR. JONAS: Yes.

DR. McCAMISH: -- adverse events?

DR. PETERS: Overall, in our study, we observed 16 serious adverse events: 7 in treatment period 1; 3 in the continuous phase of treatment period 2; and 6 in the patients who underwent switching between GP2015 and Enbrel in treatment period 2. With respect to your question, this slide displays the details. You can see the two columns of patients who have received continued treatment with either GP2015 or Enbrel, or patients who underwent switched treatment between GP2015 and Enbrel.

So the details are listed. The infections and infestations are diverticulitis, pneumonia, tonsillitis. And then there were a couple of singular events that occurred in the patients who underwent switched, including an umbilical hernia, cholelithiasis, one patient who had a psoriatic

arthropathy and psoriasis, and a patient with sarcoidosis. So overall, we consider these to be not clinically meaningful, and these are single events in multiple different system organ classes.

DR. SOLOMON: I'm going to cut it off. I'm sorry. Dr. Curtis?

DR. CURTIS: Sean Curtis. Just regarding your human PK studies, just confirming, you do not have a study that directly compared the two Enbrels, is that correct, within the same study?

DR. McCAMISH: The PK study was done concurrently and across --

DR. CURTIS: Right. But not head-to-head, correct, in the same study.

DR. McCAMISH: Correct.

DR. CURTIS: Okay.

DR. SOLOMON: Dr. Siegel?

DR. SIEGEL: Thanks. I have one analytical and a short clinical question. For the analytical, just go back to the misfolded protein one more time. I appreciate the redox experiment to try to simulate refolding, which might occur in vivo. I'm

just wondering if there was any more physiological experiment that was done with the analytical capabilities that you have, such as injecting into a mouse model or something like that, to look at refolding in any other circumstances other than the redox buffer.

DR. McCAMISH: Thank you for the question. There was no studies reinjecting into animal models or others. What we tried to do is, again, dealing with the issue of the Enbrel reference product variability to show that in a redox you could reverse that back. But no in vivo animal model.

DR. SIEGEL: Just on the clinical side, I have to ask this as a rheumatologist, but in the trial, the psoriasis trial, was joint count, tender swollen joint count, any other measures of the arthritis in the 52 patients who had psoriatic arthritis collected, or do you have any other information on that?

DR. McCAMISH: There was not ACR20 or active provision of information regarding the arthritic component. All we provided was the QoL information

to relate.

DR. SOLOMON: Dr. Reimold for a brief one? Do you have any --

DR. REIMOLD: Just one.

DR. SOLOMON: Okay. Just one?

DR. REIMOLD: Yes. Andreas Reimold. So this is still on the analytics. Slide CA-30 dealt with impurities. I wanted to hear some more on the significance of the galactosylation or the aggregation products. There seemed to be, at least at the scales presented, some slight differences between your product and the comparators. So any speculation on the clinical significance of that or the different manufacturing processes and how that makes these products potentially more different? Thank you.

DR. McCAMISH: Thanks. Again, we're using the most modern technologies for this, and so fairly well controlled, and the aggregation is lower, as you can see. That's the hope, is that you try to control these. On the alpha galactosylation, again, within the variability of

the reference product over time, as we've shown as well.

Again, when we've looked at this, not only from the evaluation from the literature, but also in the clinical evaluation, the product binding, other types of things, there's not an impact on PK nor on the clinical effect that we've shown in a relatively sensitive trial.

DR. SOLOMON: I think, Dr. Hancock, you had one question, and then we're going to close.

DR. HANCOCK: Yes, so I had an analytical question or two. If I could talk about the map, slide CA-14, and then we'll jump to CA-27. GP2015 is a complex molecule, so I had a couple of questions about the map. For example, roughly how many peptides did you separate in the map?

DR. McCAMISH: Okay. Dr. Schiestl, do you want to address that?

DR. SCHIESTL: Martin Schiestl, Sandoz. Yes, so there's a typical number of peaks as seen, you see, so this is a typical number in the peptide maps we have also observed. But as I mentioned, we

used four different enzymes, so we created overlapping fragments to cover the whole sequence.

DR. HANCOCK: Yes. Everybody may not be aware, but to get a 100 percent sequence covered is a tricky job for that molecule, so you used multiple enzymes.

DR. SCHIESTL: Right.

DR. HANCOCK: Okay. And were you able to identify internal clipping by the use of these multiple enzymes? Did you see it? Was it different between the two products?

DR. SCHIESTL: Yes, we see -- so a clipped variance. This is an impurity, which is present in the product and we determined those also in the peptide maps.

DR. HANCOCK: Right. So you characterized them through the peptide map?

DR. SCHIESTL: Yes, right. So we did MSM as experiments to really determine the exact sequence of each of those peptides.

DR. HANCOCK: Good. Then if we could jump, following on the map, to CA-29, to look at the

glycose. I'm just wondering how you determine the O-glycans.

DR. SCHIESTL: The O-glycans we determined with multi-task spectrometry. So we did permethylation, the O-glycosylation, and then we analyzed [indiscernible].

DR. HANCOCK: Okay. Then did you characterize the N-glycosylation of the peptide level, or do you again cleave and do permethylation?

DR. SCHIESTL: We analyzed the N-glycans by also with the peptide map still to assign the glycosylation sites. Then we did a de-glycosylation of the N-glycans, and then we used a separation with HILIC chromatography. By this we quantified them and also identified the exact structures of the N-glycans.

DR. HANCOCK: Did you observe partial occupancy at any of the glycosylation sites?

DR. SCHIESTL: The occupancy was very high. And many O-glycans, not all of them, were occupied on the sites, but in general they were pretty high.

DR. HANCOCK: Okay. So the occupancy was high and similar between the two products?

DR. SCHIESTL: Yes.

DR. HANCOCK: Okay. My last question, I don't run over too far, but did you look at free sulfhydryl content in the two products and also follow a stability program? Because the concept of disulfide shuffling is complicated. So do you see free sulfhydryls at all?

DR. SCHIESTL: The free sulfides?

DR. HANCOCK: Yes. SH group, free SH groups.

DR. SCHIESTL: Yes, we quantified them with [indiscernible] and also followed up also on stability. And they were also comparable.

DR. HANCOCK: And they increased over time, in stability?

DR. SCHIESTL: No, they don't increase over time.

DR. HANCOCK: Well, that's reassuring.

(Laughter.)

DR. HANCOCK: Okay, thank you.

DR. SOLOMON: Okay. Well, we're going to draw this to a close. I'm sorry we went over. And I'm sorry we didn't get to every question, but I think it was a robust conversation. We're going to cut our break to 10 minutes, so be back here at 10:40. And Moon Hee has assured me that the FDA can reduce their presentation to make up time.

(Laughter.)

(Whereupon, at 10:30 a.m., a recess was taken.)

DR. SOLOMON: Okay. We're now going to proceed with the FDA presentations. Dr. Adams?

FDA Presentation - Peter Adams

DR. ADAMS: Good morning. My name is Peter Adams. I am a product quality reviewer in the Office of Biotechnology Products. I will present an overview of the product quality section of the BLA submission.

This presentation will cover the structure, mechanism of action, GP2015 manufacturing, the analytical studies that were undertaken to support a demonstration of biosimilarity, and I will

provide an overview of the analytical similarity data.

GP2015 was developed as a biosimilar product to etanercept. The reference product is US-licensed Enbrel. Etanercept is an Fc fusion protein consisting of the extra-cellular domain of the tumor necrosis factor receptor 2 and an Fc region derived from the IgG1 antibody.

It is a glycoprotein with 3 N-linked glycans, 1 on the Fc region, and 2 on the receptor. It also has approximately 10 O-linked glycans, which are also located on the receptor. It is a dimer with 13 intrachain disulfide bonds, 11 in the receptor, and 2 in the Fc region, to give a total of 26, and 3 interchain disulfide bonds in the Fc hinge region.

TNF is a proinflammatory master cytokine that plays a role in the immune system and inflammatory responses. It is functional as a trimer and is synthesized and presented on the cell surface as a membrane-bound form that can be cleaved by metalloenzymes to yield soluble TNF.

TNF alpha is produced by activated immune cells, such as macrophages, dendritic cells, T-cells, along with adipocytes and fibroblasts. As a master cytokine, it elicits a diverse range of responses that are dependent upon cell type.

The proposed mechanism of action is that etanercept binds to and neutralized TNF alpha and the related molecule TNF beta, also known as lymphotoxin alpha. The biological responses to TNF alpha are mediated by two receptors, TNF-R1 and R2. TNF-R1 is expressed on most cells while the expression of TNF-R2 is limited to hematopoietic and endothelial cells.

Both membrane-bound and soluble forms of both receptors and TNF are present in circulation. Although etanercept binds both soluble and membrane-bound forms of TNF, the major interaction for etanercept is with soluble TNF and blocks it from binding to the membrane-bound receptors.

Based on published literature, reverse signaling, which is mediated by the membrane-bound form of TNF, is unlikely to play a role in

etanercept's mechanism of action. Similarly, etanercept has an Fc region. Evidence suggests that antibody-dependent cell cytotoxicity, or ADCC, and complement dependent cytotoxicity, or CDC, are not part of the mechanism of action.

GP2015 drug substance is produced in mammalian cell culture and purified using standard purification procedures. The manufacturing process was demonstrated to remove process related impurities such as host cell proteins, host cell DNA, and other process related impurities to levels that are consistent with industry standards for biotechnology products.

Multiple lots of GP2015 drug substance have been manufactured at the same scale since 2011. Minor changes in the drug substance manufacturing process were introduced during development and comparability of the GP2015 drug substance was demonstrated between the processes.

In addition, critical quality attributes, such as potency and glycosylation, were assessed to ensure consistency in the manufacture of GP2015.

No major issues were identified during the inspection of the drug substance manufacturing facility in March of 2016.

GP2015 drug product is manufactured as a 50 milligram per mL solution for injection. The container closure is a pre-filled syringe. The formulation of GP2015 differs from US-licensed Enbrel and consists of a citrate buffer along with sodium citrate, chloride sucrose, and lysine. The proposed expiration date is supported by data from stability studies.

I'll now discuss the analytic similarity studies. To evaluate analytical similarity, GP2015 was compared to the reference product, which is US-licensed Enbrel. In addition, pairwise comparisons between US-licensed Enbrel and EU-approved Enbrel, GP2015 and EU-approved Enbrel were carried out to establish the analytical portion of the scientific bridge between the three products. An analytical bridge is necessary to link the EU-approved Enbrel that was used in non-clinical and clinical studies to the

US-licensed Enbrel and GP2015.

For the analytical similarity exercise, a battery of analytical methods was used to assess quality attributes. Broadly, the methods assessed primary and high order structure, high molecule weight species and fragments, charge variants, hydrophobic variants, and N- and O-linked glycans.

Potency was assessed using a TNF alpha reported gene assay, TNF binding by surface plasmon resonance, and an apoptosis inhibition assay. TNF beta was also assessed using a reported gene assay. Antibody effective function and binding to the Fc gamma receptors, including FcRn, as well as binding to the C1Q complement, were also assessed.

Quality attributes that were classified as highly critical included the primary amino acid sequence, high order structure, potency assessed using the TNF reporter gene assay, and TNF binding.

I'll now discuss the analytical similarity data. The lots used in the analytical similarity exercise included 15 lots of GP2015 drug product. Some of these were used in clinical studies.

Drug substance lots were also analyzed but not included in the statistical analysis to avoid duplication with the drug product lots, which have been manufactured from those drug substance lots. Thirty-four lots of U.S. Enbrel and 50 lots of EU Enbrel were analyzed. It should be noted that not all lots were tested with each analytical method.

The primary sequence of US-licensed Enbrel and GP2015 were assessed using peptide mapping in combination with mass spectrometry, and shown to have identical amino acid sequences. The analytical similarity of the tertiary structures was demonstrated using three separate approaches.

First, the TNFR2 region of GP2015 and U.S. Enbrel were co-crystalized with TNF and their structures were determined using x-ray crystallography. The resulting models, shown on the right, are superimposable, and they are structurally equivalent.

Secondly, 1D-NMR was used to compare the 3-dimensional structure of GP2015 and U.S. Enbrel. Although 1D-NMR cannot be used to determine the

structure of large complex proteins, the spectra can be compared and similar NMR spectra demonstrate the two products have similar 3-dimensional structures.

Overlaid traces are shown at the bottom of the slide with GP2015 in blue and US-licensed Enbrel in red. Again, no significant differences are evident.

Thirdly, hydrogen-deuterium exchange was used to compare GP2015 and US-licensed Enbrel. The primary sequence and heat map for GP2015 and US-licensed Enbrel are shown on the right. The underlying principle of this method is that the backbone amide hydrogens can exchange with deuterium at measurable rates when a protein is incubated with heavy water.

The rate of exchange for the process is highly dependent on the local structural environment. For example, amide hydrogens in a disordered region exchange faster than ordered and structured regions.

The heat map displays the exchange rate at

each position, and the intensity of the color increases when the exchange rate is high. Analysis of the data showed that similar patterns and differences existed between the two molecules at less than 1 dalton. Therefore, high order structure similarity was demonstrated using three different approaches.

Disulfide bonds play a significant role in folding and maintaining the tertiary structure of protein. This schematic shows the amino acid sequence for the TNFR2 region. The individual cysteines, along with the disulfide bonds, are shown in yellow.

Etanercept has a total of 13 intrachain and 3 interchain disulfide bonds. The disulfide bonds were identified using non-reducing peptide mapping and confirmed using data from the crystal structure. In addition, etanercept contains misfolded protein, which will now be a focus of my discussion.

Reverse phase chromatography was used to analyze GP2015 in Enbrel. A representative

chromatogram is shown here. It consists of a main peak followed by a post peak. The major component of the post peak is etanercept, which has wrongly bridged to disulfide variants, abbreviated in the slides as WBV.

A comparison of the GP2015 lots with U.S. and EU Enbrel lots was undertaken using reverse phase chromatography. GP2015 has significantly lower amounts compared to the U.S. and the EU Enbrel lots.

The misfolded component can be separated using either reverse phase chromatography or hydrophobic interaction chromatography. Based on the data submitted by Sandoz using the reverse phase chromatography, it was shown that U.S. and EU Enbrel contain 10 to 18 percent of the post peak, while GP2015 contains 9 to 12 percent.

The ribbon diagram shown on the right shows the binding interaction between the TNF receptor domain, shown here in blue, and the TNF, shown here in green. The disulfide bond, shown in the circle, is one of the correct disulfide bonds that is in

close proximity to the TNF binding site.

All wrongly bridged disulfide variants were identified in GP2015 and U.S. Enbrel, and they are shown on the left. The wrongly bridge variants shown in the red box is the non-reduced peptide terms T7. The majority of the wrongly bridged disulfide variants, including the T7 peptide, are also located in the circled area, and potentially could affect the bioactivity of etanercept.

Sandoz used the T7 peptide as a surrogate to quantify the levels of misfolded etanercept that were present in GP2015, US-licensed Enbrel, and EU-approved Enbrel. The T7 peptide is quantified relative to an internal peptide following protolytic digestion, an analysis using reverse phase chromatography in combination with UV detection.

Sandoz showed that there is an inverse relationship between the T7 peptide levels and potency using data from the TNF reporter gene assay, as shown in the graph below. The T7 peptides are on the X-axis and the TNF bioactivity

on the Y-axis.

This plot includes lots from GP2015 process intermediates as well as GP2015 drug substance and drug product lots, and U.S. and EU Enbrel lots. High levels of T7 peptide present in a sample correlate with lower bioactivity. These data establish a structure function relationship between the levels of misfolded protein and potency.

Based on these results, in conversations with Sandoz, the FDA requested that Sandoz investigate if the wrongly bridged component can refold and form with the correct disulfide bonds.

The rationale for this request was based on the growing body of literature about allosteric disulfide bonds. Most disulfide bonds are structural and are important for the correct folding of a protein and maintaining structural integrity.

Other disulfide bonds are allosteric, which can control the function of a protein when they're reduced or oxidized. A number of examples of allosteric disulfide bonds have been identified,

including members of the tumor necrosis factor receptor superfamily. Two well characterized examples containing allosteric disulfide bonds IgG2 and IgG4 antibodies.

In the case of IgG2, covalent dimers are formed, as shown here, where there are intermolecular linkages between the two IgG2 molecules. In addition, there are examples of disulfide shuffling, which leads to the generation of three different disulfide isomers for different IgG2 molecules.

Another example is Fab exchange in IgG4. In this case the Fab-arm exchange occurs between half molecules of different IgG4 antibodies to create a biospecific antibody.

Given the examples of proteins that have allosteric disulfide bonds, which are able to refold in vivo, Sandoz was asked to determine if refolding of etanercept occurs after exposure to reducing conditions that are reported to mimic in vivo conditions, and if potency could be restored after this treatment using the TNF

reported gene assay.

This table shows the data for the T7 peptide levels present in the GP2015 process intermediates drug substance and drug product lots, along with the results from the potency assay that was conducted on the samples before and after treatment with reducing conditions.

The control data is shown in the second and third columns, and the fourth and fifth columns are the same lots following exposure to reducing conditions.

The GP2015 processing intermediates shown here boxed in red have reduced potency and high levels of T7 peptide. Following incubation under redox conditions, the levels of T7 peptide are reduced, and there's an increase in potency. Similarly, exposure of U.S. and EU Enbrel to redox conditions results in reduced levels of T7 peptide and increased potency.

The data provided show that wrongly bridged variants can refold in vitro using experimental system that mimics physiological conditions. The

samples before and after redox treatment shown in green and orange were added to the structure function correlation data shown in an earlier slide.

Again, the T7 peptide is shown on the X-axis and the bioactivity on the Y-axis. These data show that linear relationship between the T7 peptide levels, and potency was maintained after redox treatment and allowed Sandoz to develop a computed potency model where the potency results were adjusted based on the assumption of correct refolding.

Based on the demonstrated structure/function relationship between wrongly bridged variants and potency, and the relevance of the experimental system to physiological conditions, it is likely that similar changes in etanercept folding inactivity occur upon administration to patients. Therefore, the agency accepts that the computed potency model is the most relevant model to assess etanercept potency using the TNF reported gene assay.

The following methods were used to measure biological activity were assessed by the agency using two statistical approaches: TNF alpha binding and the TNF alpha neutralization using the reported gene assay, including data from the computed potency model, were assessed by statistical equivalence. TNF neutralization by apoptosis with TNF beta reported gene assay, ADCC, were assessed using quality ranges.

The number of lots used for methods assessed by statistical equivalence is shown here. The analysis of TNF neutralization, computed potency data was limited by the number of lots which the level of the T7 peptide present had been determined. Dr. Meiyu Shen will now present the statistical equivalence analysis of the critical poly attributes.

FDA Presentation - Meiyu Shen

DR. SHEN: Good morning. My name is Meiyu Shen, the CMC statistical reviewer from Office of Biostatistics. I am presenting the statistical equivalence analysis for bioactivity.

For this submission, the review team focused on two quality attributes that assessed the primary mechanism of action, which is subject to the equivalence test, why is TNF alpha binding and the other is the in vitro TNF alpha reported gene assay for determining bioactivity potency. We also analyzed that the computed TNF alpha RGA data was statistically equivalent analysis.

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 larger 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 of the confidence interval falls within the equivalence margin defined in red, plus or minus 1.5 sigma C. Here sigma C is estimated from the comparator product measured by the applicant.

This slide presents the data graph for TNF alpha binding. The Y-axis represents TNF alpha binding. The data spreads of GP2015 US-licensed

Enbrel and the EU-approved Enbrel are similar; so are the means of three product. TNF alpha binding data are subject to rigorous equivalence testing.

This table here presents equivalence test results for TNF alpha binding. The first column the pair for comparison, second is the amount of lot for the pair. The third column is the mean difference between the test and the comparator. Fourth is 90 confidence interval. Next is the equivalence margin. The last column is the conclusion of the equivalence test.

As indicated in the table and graphs, the 90 percent confidence interval for each of the three pairs falls within corresponding equivalence margin. Hence, all three pairwise comparisons passed equivalence test.

Now let us look at the data graph for TNF alpha RGA. The Y-axis represents TNF alpha RGA percent. There are 31 lots of US-licensed Enbrel, 19 lots of GP2015, and 43 EU-approved Enbrel. The spread of three product are not similar to each other as shown in the graph. The mean of GP2015

is about 10 percent larger than that of US-licensed Enbrel.

Note that all observation of GP2015 falls within the minimum and the maximum US-licensed Enbrel, and also within the minimum and the maximum of EU-approved Enbrel.

The table on the top of this slide presents the equivalence test results for TNF alpha RGA. This table is very similar to the table we just discussed for TNF alpha binding. As indicated in the table and the graphs, 90 percent confidence interval for the first pair is not fully contained in the equivalence margin, plus or minus 10.28. So TNF alpha RGA follows equivalence test between GP2015 and US-licensed Enbrel.

As discussed by Dr. Adams, an active correlation between wrongly-bridged variants present at T7 and the TNF alpha RGA exist. Based on the applicant's data, US-licensed Enbrel and the EU-approved Enbrel has about 10 to 18 percent wrongly-bridged disulfide bonds.

On the other hand, GP2015 has about 9 to

12 percent. To adjust the difference in percent of T7 between Enbrel and GP2015 a mathematical model is developed to convert the TNF alpha RGA into the computed TNF alpha RGA.

Based on the demonstrated structural/function relationship between wrongly-bridged variant and the potency and the relevance of experimental system to physiological conditions, it is likely that similar changes in etanercept in folding and activity occur upon administration to patients. Therefore, the agency accepts that computed potency model is the most relevant method to assess potency use the TNF alpha reported gene assay.

The applicant adjusted TNF alpha RGA by T7 level and they computed TNF alpha RGA for 11 lot values of EU-approved Enbrel, 9 lot values of GP2015, and 13 lot values of US-licensed Enbrel. This graph presented the computed TNF alpha RGA for these lots. The spread of computed TNF alpha RGA of GP2015 is the smallest among three products.

As shown in the table and graphs, the

90 percent confidence interval for each of three pairs falls within the corresponding equivalence margin. Hence, all three pairwise comparisons regarding computed TNF alpha RGA passed equivalence testing.

Based on our independent analysis of the applicant data, we conclude that all 3-way comparisons for both TNF alpha binding and the computed TNF alpha RGA pass equivalence testing. Hence, statistical equivalence testing results of pair activity support that GP2015 is highly similar to U.S. Enbrel and support the analytical bridge between three products.

Next, Dr. Adams will continue his presentation on quality range analysis.

FDA Presentation - Peter Adams

DR. ADAMS: I'll now continue with the presentation. The following data were assessed using quality range. The apoptosis inhibition assay was used as an orthogonal method to assess TNF alpha neutralization. Data from the assay show that GP2015 is within the quality ranges that were

established by US-licensed Enbrel. Similarly, for the TNF beta reported gene assay, GP2015 was within the quality range established by US-licensed Enbrel.

Currently, currently the approved TNF antagonist, other than etanercept, include three intact monoclonal antibodies: infliximab, adalimumab, golimumab, and the antibody fragment certolizumab, a PEGylated Fab, which does not have an Fc region.

All of the TNF antagonists are effective in treating RA. Because GP2015 has an Fc region, the agency expects that the Fc effect on function will be assessed as part of the analytical similarity exercise.

Bioassays, which assess effect of function, include ADCC and CDC. Several published represents demonstrate that etanercept is not as effective at inducing ADCC or CDC compared to the intact antibodies. This may be due to the fact that etanercept binds only one molecule, soluble membrane TNF, whereas the intact antibodies bind

multiple molecules.

Sandoz assessed both ADCC and CDC, and they showed that CDC was similar among GP2015 and U.S. Enbrel and EU Enbrel. Initial data provided by Sandoz showed differences in the ADCC activity among GP2015, U.S. and EU Enbrel. This is due to differences in afucosylated glycans in the Fc portion of the molecule.

GP2015 has lower levels of afucosylated glycans compared to Enbrel. There was a non-structure function relationship between afucosylated Fc glycans and enhanced affinity for the Fc gamma RIIIa receptor that results in enhanced ADCC activity. Products with lower levels of afucosylated glycans will have lower ADCC activity. GP2015 has lower levels of afucosylated Fc glycans bind to the gamma RIIIa receptor and ADCC activity.

Subsequently, Sandoz provided data comparing ADCC activity of GP2015, U.S. and EU Enbrel, two intact monoclonal antibody TNF antagonists, and a control monoclonal antibody whose primary mechanism

of action is via the Fc effective function. The ADCC assay shown in this slide uses a natural killer cell line and targets cells which overexpress membrane TNF.

Based on literature reports, ADCC is not thought to play a role in the mechanism of action of Enbrel, and the data submitted by Sandoz are consistent with these reports. As could be seen, although GP2015 has lower activity than Enbrel, and the ADCC activity GP2015 is lower than that of the anti-TNF antibodies, all are much lower than the control antibody.

Additional data were provided using more physiologically relevant system using primary monocytes that have been stimulated with LPS to express membrane-bound TNF. ADCC levels of GP2015, U.S. and EU Enbrel were compared with alemtuzumab, or Lemtrada, which target CD52. Clearly alemtuzumab is more effective in inducing ADCC compared to GP2015 or Enbrel in this system as well.

These data support that etanercept is not as

effective at inducing ADCC compared to the anti-TNF antibodies or other monoclonal antibodies whose primary mechanism of action is through Fc effect to function.

Based on the analysis of all the analytical data, including the statistical analyses, we conclude that for individual quality attributes listed here, including primary structure, tertiary structure, potency, charge size variants, and most glycoforms, binding assays, and stability profiles -- but the data support the demonstration that GP2015 is highly similar to US-licensed Enbrel.

Even though no data are presented today regarding the levels of aggregates, which can be a risk for inducing anti-drug antibodies in patients, both GP2015 and U.S. Enbrel have levels of aggregates typical for therapeutic proteins, although GP2015 has slightly lower levels.

For hydrophobic variants, data were provided which showed that the misfolded protein is likely minimized by refolding in vivo. Based on the

totality of the analytical data, we conclude that the differences observed for hydrophobic variants, afucosylated Fc glycans, and ADCC do not preclude a demonstration that GP2015 is highly similar to the US-licensed Enbrel.

To summarize, an extensive analytical study was undertaken in order to assess analytical similarity. This included functional and bioactivity assays, physiochemical assays, and an assessment of higher order structure. A comparison of US-licensed reference product with GP2015 and EU Enbrel established the analytical portion of the scientific bridge.

Therefore, based on the totality of the evidence, the analytical data support the conclusion that GP2015 is highly similar to the US-licensed reference product. This concludes my presentation.

FDA Presentation - Yunzhao Ren

DR. REN: Good morning. My name is Yunzhoa Ren, the clinical pharmacology reviewer of GP2015 program. First, I will give a brief overview of

the clinical pharmacology program of GP2015.

There are two goals of the clinical pharmacology program. The first is to evaluate the pharmacokinetic similarity between GP2015 and US-licensed Enbrel. And the second is to assess the PK element of the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel.

In total, the applicant conducted three related PK studies, one cross-study comparison and trough serum concentration assessment in a comparative clinical study to support the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel.

In brief, our assessments show that the PK similarity was demonstrated between GP2015 and US-licensed Enbrel, and PK bridge was established between GP2015, US-licensed Enbrel, and EU-approved Enbrel.

I would like to introduce this triangle from regulatory point of view. Again, because a non-U.S. reference product was used in clinical comparative study 302, we required the applicant to

provide a scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel to justify the relevance of the comparative data generated by EU-approved product in study 302.

As the first step to provide the PK element of the scientific bridge between three products, the applicant conducted predefined two head-to-head studies and one cross-study comparison.

Study 102 was to compare the PK similarity between GP2015 and US-licensed Enbrel. Study 101 was to construct the PK bridge between GP2015 and EU-approved Enbrel. And report 105 was to construct the PK bridge between EU-approved Enbrel and US-licensed Enbrel in a cross-study fashion. In a later slide, I will explain why this approach is acceptable from a clinical pharmacology point of view.

However, during this first step, study 101 did not meet the prespecified criterion, which the lower boundary of 90 percent confidence interval of AUC ratios were off by 2 percent. Therefore, upon EMA's request, another study, study 104, was

conducted three years later to construct the PK bridge between GP2015 and EU-approved Enbrel.

Following, let me introduce the study design of the head-to-head studies 101 and 102, and the cross-study comparison report 105 as a whole. The study design of studies 101 and 102 was identical. Both of them were randomized, double-blind, two-week crossover, single dose studies in healthy males and females. In addition, the two studies shared the identical inclusion/exclusion criteria, clinical unit, bioanalytical method, and the same batch of GP2015.

According to the time line, two studies have 2 months overlap in the same clinical unit. All these head-to-head characteristics made the predefined cross-study comparison report 105 more like a parallel group comparison.

Results from study 102 show that the boundaries of 90 confidence interval of Cmax and AUC ratios were all within the prespecified PK similarity margin indicating that PK similarity was demonstrated between GP2015 and US-licensed Enbrel.

However, study 101 did not meet the prespecified criterion as the lower boundaries of 90 confidence interval of AUC ratios between GP2015 and EU-approved Enbrel were off by 2 percent. The applicant attributed this to the operator's effect. Here, operator is the person who administered the subcutaneous injection. For some subjects in this study, different operators administered different product during different periods.

Results from cross-study comparisons show that PK bridge was established between US-licensed Enbrel and EU-approved Enbrel as the boundaries of 90 percent confidence interval of Cmax and AUC ratios were all within the prespecified criterion.

Because study 101 did not meet the prespecified criterion, the applicant conducted study 104 three years later to help construct the missing bridge between GP2015 and EU-approved Enbrel. The study design was similar to that of study 101 except the following differences.

First, only male subjects were enrolled in study 104 to reduce the PK variability. Second,

the same operator was assigned for each individual subject during both study periods to eliminate the operator's effect. Third, the batches of GP2015 and EU-approved Enbrel were different between two studies. And finally, the bioanalytical methods were different between study 101 and 104, though both of them are validated methods.

The results show that PK bridge was established between GP2015 and EU-approved Enbrel, and the boundaries of 90 percent confidence interval of Cmax and AUC ratios were all within the prespecified criteria.

In addition, PK at a steady state was compared between GP2015 and EU-approved Enbrel in comparative clinical study 302. Pre-dose serum concentrations were collected from 147 patients at day 1 and at week 2, 4, 8, and 12. To be noted, the patients are following a twice-a-week dosing regimen.

The steady state appeared reached from week 2 for both products. The geometric mean of trough serum concentration was comparable at each

time point between two products from week 2 to week 12.

In summary, the PK similarity has been demonstrated between GP2015 and the US-licensed Enbrel. PK data also support a scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel to justify the relevance of comparative data generated using EU-approved Enbrel from study 302. This slide concludes my presentation, and now I would turn the podium to Dr. Fritsch.

FDA Presentation - Kathleen Fritsch

DR. FRITSCH: Good morning. My name is Kathleen Fritsch, and I am the biostatistics reviewer for this application. I will be presenting the results for study 302, the comparative clinical study in subjects with moderate to severe psoriasis.

Study 302 had three parts. The first part evaluated the similarity of GP2015 and EU-approved Enbrel in 531 subjects with moderate to severe psoriasis. The primary endpoint was PASI 75, which is at least a 75 percent reduction from baseline in

the PASI score. And the secondary endpoints were the percent change in PASI and response on the investigator's global assessment.

Subjects with at least 50 percent improvement in PASI at week 12 continued on to the second treatment period where subjects were randomized to either continue the original assigned treatment or switch treatments three times at 6-week intervals. At week 30, subjects continued the same treatment they were on at the previous interval through week 52.

The primary endpoint was PASI 75 at week 12. The statistical analysis plan proposed different analysis methods for this endpoint than the original protocol did. The protocol stated that the primary endpoint would be analyzed with exact confidence intervals for binomial endpoints.

The statistical analysis plan modified this proposal to specify that the confidence intervals would be based on estimates from a logistic regression analysis adjusted for the stratification factors of body weight and prior systemic therapy

for psoriasis.

The protocol specified 95 percent confidence intervals, but FDA has generally recommended using 90 percent confidence intervals in comparative clinical studies, which corresponds to a type 1 error rate of 5 percent. So this presentation will focus on the 90 percent intervals.

The prespecified similarity margin was plus or minus 18 percent. The primary analysis population was the per-protocol set and the analysis based on the full-analysis set was supportive. Missing data in the full-analysis set was handled using non-responder imputation.

The key analysis issue that arose in the review of the study was the handling of the classification of subjects based on their prior systemic therapies for psoriasis. Prior therapy either none, any prior systemic therapy except TNF alpha inhibitors, or prior use of TNF alpha inhibitors was a stratification factor and part of the analysis model.

The guidance provided to the investigators

on how to appropriately classify the subjects according to this was vague, leading to subjects whose stratification classification did not match other data on the case report forms. Therefore, the applicant attempted to reclassify subjects based on the data from the CRFs.

However, between the initial database lock, which was conducted after week 12, and the second database lock, after week 30, the applicant changed their viewpoint on whether certain therapies, such as phototherapy or analgesics for psoriasis pain, should be considered systemic therapies for psoriasis.

The prior therapy classification was important to the analysis because the applicant's final analysis plan included the prior therapy classification as a factor in the model. The applicant submitted an analysis based on both versions of the prior therapy classification into their BLA.

In study 302, approximately 4 percent of the subjects discontinued during the first 12 weeks of

the study. Most common reasons for discontinuation were adverse events and subject decision.

For the primary endpoint of PASI 75 at week 12, the response rate on the GP2015 arm was about 1 to 2 percent lower than on the EU-approved Enbrel arm in both full-analysis population and the per-protocol population.

This table presents exact confidence intervals, which is the analysis method originally specified in the protocol, and does not rely on how subjects were classified with regard to prior therapies. The 90 percent confidence intervals range from about minus 9 percent to plus 6 percent, and for both populations fall within the prespecified margin of 18 percent.

For comparison, this table presents the PASI 75 results using the logistic regression model adjusted for prior therapy and weight as the applicant specified in the statistical analysis plan. This table presents all three ways that the applicant classified subjects with regard to the prior therapies: the information used in the

stratification; the first actual therapy reclassification; and the second actual therapy reclassification, and these analyses used the full-analysis set.

The way in which the prior therapy classification is defined has only a very minor impact on the results, with estimates and confidence bound shifting by only a couple of tenths of a percent. The results of all three covariate adjusted analyses are very similar to the exact confidence intervals showed on the previous slide with the covariate adjusted analysis having slightly narrower confidence intervals. The results in the per-protocol population are similar.

Thus, the conclusions are the same whether the unadjusted or adjusted confidence intervals are used, and also for all definitions of prior therapy classification.

The results for the secondary endpoints of percent improvement in PASI and achieving response of clear or almost clear on the IGA at week 12 are similar to those for the primary endpoint. For

simplicity, I have presented only the week 12 results for the percent improvement in PASI endpoint rather than the results averaged across weeks 2, 4, 8, and 12, which were the protocol specified analyses. For these two endpoints, GP2015 had slightly better outcomes that EU-approved Enbrel.

To interpret a study like study 302 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 towards similarity, and that the specified margin was appropriate.

We looked at the proposed margin in two ways. First, we looked at the percentage of the treatment effect from historical studies that was preserved, which would be relevant to the lower bound. This was the approach used by the applicant to justify the margin. Second, we looked at the

relationship between the proposed margins and sample size with respect to study power.

To assess assay sensitivity, we compared the inclusion criteria and results of study 302 to the published results of placebo-controlled studies of Enbrel. The inclusion criteria in study 302 were comparable to the two phase 3 Enbrel studies, denoted as Leonardi and Papp.

The PASI 75 response rate in study 302 was higher than what was observed in the published studies. However, this high response rate does not represent a loss of efficacy relative to the published studies, and the assay sensitivity assumption appears reasonable.

Ideally, we could just select an appropriate margin that represents broad agreement of what magnitude of differences are not clinically meaningful. However, in practice, there will usually be tensions between reasonable sample sizes and a preference for narrow margins. In the end, we would like to have a margin that is both clinically meaningful as well as practically

feasible.

The applicant used the estimated treatment effect differences from the two published studies, which are each approximately 45 percent, to justify the proposed margin. Using percent preservation of effect, the applicant's proposed margin of 18 percent retains approximately 60 percent of the treatment effect of Enbrel relative to placebo, as represented in the two published studies.

The idea behind preserving a substantial percentage of the treatment effect relative to placebo in non-inferiority studies 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. Therefore, we also evaluated the relationship between the proposed margin and study power using the study design characteristics of the protocol, which included a planned sample size of 546 subjects, and expected a PASI 75 response rate of 49 percent on both treatment arms.

From this plot, we can see that under the design characteristics used to plan the study, if there's truly no difference in response between the two treatments, that the study would have at least 90 percent power, represented by the gray bar, for margins of about 15 percent or larger.

FDA concurred with the applicant's proposed margin of plus or minus 18 percent at the design stage, and we note that study 302 would meet similarity criteria for any bounds of magnitude of about 10 percent or larger.

In summary, for study 302, the estimated treatment difference for PASI 75 in the full-analysis population was minus 1.1 percent with an exact 90 percent confidence interval of minus 8.3 percent up to plus 6 percent. The study met its agreed upon prespecified similarity criteria of 18 percent.

The results were also consistent across study populations, the handling of prior therapy classification, and analysis methods. The secondary endpoints had outcomes consistent with

the primary endpoint. Thus, study 302 supports a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

FDA Presentation – Rachel Glaser

DR. GLASER: Good morning. My name is Rachel Glaser. I will be discussing the safety and immunogenicity results from the clinical program for GP2015, as well as the considerations for extrapolation. I would like to acknowledge that the review of this application was a collaborative effort among multiple disciplines and subject matter experts, including our dermatology colleagues.

We acknowledge the study design of the clinical study in patients with psoriasis includes multiple switching periods. However, the BPCI Act does not encompass the concept of switching or alternating between the proposed product and the reference product for biosimilar products.

This concept is a part of the statutory definition of interchangeability. As such, the data to support a demonstration of biosimilarity

that is the focus of the FDA review includes treatment period 1 in subjects who undergo a single transition from the reference product to GP2015.

While these are additional data that Sandoz has presented involving multiple switches, that data is not expected as a part of demonstrating biosimilarity. However, because the data was provided by Sandoz, FDA did review the pooled safety and immunogenicity data from the multiple switches.

The bulk of the safety data is derived from clinical studies using EU-approved Enbrel as a comparator. As previously discussed, the applicant has established a scientific bridge to justify the relevance of the safety data generated using EU-approved Enbrel in the GP2015 program.

The safety population in the clinical program comprised over 700 individuals, including healthy subjects and patients with plaque psoriasis. Overall, the safety database is adequate to provide a reasonable comparative safety and immunogenicity assessment. The safety analysis

did not identify any new safety signals compared to the known safety profile of Enbrel.

The types and incidences of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation were similar. The most common treatment-emergent adverse events were infections, and the most common infections were pharyngitis and nasopharyngitis.

A single death occurred in the development program in a patient who received EU-approved Enbrel and experienced cardiopulmonary failure. There were no cases of anaphylaxis reported in the development program.

There was a low incidence of anti-drug antibodies, or ADA, in both the GP2015 and EU-approved Enbrel treatment groups. The ADA incidence did not increase following a single transition from EU-approved Enbrel to GP2015.

This table provides an overview of the safety profile in the core control studies. As described by Dr. Fritsch, in study 302, patients

were randomized to GP2015 or EU-approved Enbrel. At week 12, those patients with a PASI 50 or greater response were re-randomized to continue their originally assigned treatment or to undergo switching between the two products.

Those that switched from EU-approved Enbrel to GP2015 at the start of treatment period 2 are designated switched to Enbrel, while those who switched from GP2015 to EU-approved Enbrel at the start of treatment period 2 are designated switched GP2015.

In each study, the overall incidences of treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation, and adverse events of special interest, were similar between GP2015 and the comparator products.

Serious adverse events were rare and did not cluster into any treatment group. As mentioned, there was one death due to cardiopulmonary failure in a patient with diabetes receiving EU-approved Enbrel. There were no other deaths in the development program. In the infections and

infestation system organ class, there were events of appendicitis, pneumonia, diverticulitis, and tonsillitis. These events were distributed across the different treatment groups. One patient in the EU-approved Enbrel group developed drug-induced liver injury.

In the GP2015 treatment group, there was one event of malignancy, a report of malignant melanoma in situ that was excised prior to the start of study treatment with GP2015, however the results were available only after initiation of study drug. There were no serious adverse events reported in the healthy subject studies.

In the context of the known adverse event profile of US-licensed Enbrel, potential and identified risk, defined by preferred terms encompassing all of the special warnings and precautions listed in the labeling for Enbrel, were considered adverse events of special interest. Adverse events of special interest were not defined for the single dose healthy subject studies.

This table provides a summary of the adverse

events of special interest observed in the comparative clinical study in psoriasis. Overall, adverse events of special interest were rare. In the neoplasm system organ class, there was one event of malignant melanoma in situ, as previously discussed, excised prior to the start of study treatment with GP2015. Other events in this SOC were not malignant in nature.

In the infections and infestations SOC, the groups were generally similar with regard to incidence of treatment-emergent adverse events at the preferred term level. There was one case of facial swelling in the EU-approved Enbrel group in treatment period 1, and there were two reports of urticaria, one event in the continued Enbrel group, and one in the switched GP2015 group in treatment period 2. There were no reports of anaphylaxis. Comparison of GP2015 and EU-approved Enbrel showed no notable differences between the treatment groups with respect to adverse events of special interest.

Immunogenicity is an important part of the safety analysis of any therapeutic protein product

or a biologic. Generally, immunogenicity assessment of a proposed biosimilar product is an expected component of 351(k) licensing applications.

Anti-drug antibodies mediate immune reactions that are frequently observed with biologics and can impact PK, efficacy, and safety, such as hypersensitivity reactions and anaphylaxis. While anti-drug antibodies against Enbrel have not been correlated with reduced clinical efficacy or adverse events, this is a theoretical risk.

Therefore, in the GP2015 development program, immunogenicity of GP2015 was prospectively assessed in the studies in patients with plaque psoriasis and healthy subjects. Assessment of anti-drug antibody incidence and multiple time points in clinical study populations reflects the proposed chronic administration of GP2015.

In the control study 302, the rates of immunogenicity assessed as the proportion of ADA positive patients at all time points, were low. Using a sensitive and drug-tolerant assay, no

patients receiving GP2015 had detectable ADA, while 5 patients receiving EU-approved Enbrel had ADA.

The anti-drug antibodies were non-neutralizing and occurred within the first 4 weeks of treatment, and subsequently resolved. No additional ADA were detected up to week 30, and there was no increase in ADA after the transition at week 12.

In conclusion, with respect to immunogenicity, similar immunogenicity was observed between GP2015 and EU-approved Enbrel in psoriasis patients. As previously noted, an analytical bridge, including analysis of product quality attributes that could potentially impact immunogenicity, has been established between GP2015, EU-approved Enbrel, and US-licensed Enbrel. Therefore, the data from the immunogenicity studies adds to the totality of evidence to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

In summary, safety outcomes, including immunogenicity, were similar between patients

treated with GP2015 or comparator products. No new safety signals were identified in the GP2015 clinical program compared to the known safety profile of Enbrel. The safety and immunogenicity results add to the totality of evidence to support the demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

In the next few minutes, I will provide an overview of the scientific justification provided by the applicant to support that there are no clinically meaningful differences across the indication sought for licensure.

Sandoz is seeking licensure of GP2015 for the same indications for which U.S. Enbrel is licensed. The clinical program, however, provides clinical efficacy and safety data, primarily from clinical studies in patients with 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 plaque psoriasis. This concept has previously been introduced as extrapolation.

To better illustrate this, I will compare and contrast the standalone drug development versus the biosimilar development program.

The goal of standalone development programs for innovator biological products is to demonstrate that the product is safe and effective. Drug development starts with preclinical research, moves to phase 1, then 2, and culminates in phase 3 pivotal trials to demonstrate safety and efficacy. 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 proposed

biosimilar, which represents a different paradigm in drug development, which we would like the committee to consider.

In the demonstration of biosimilarity, an applicant may also include extrapolation of data with appropriate scientific justification, which should address issues like potential differences in mechanism of action, pharmacokinetics, and biodistribution, immunogenicity, and safety for each indication.

Further, the FDA has also determined that differences between indications do not necessarily preclude extrapolation, but any differences need to be appropriately addressed. In this context, to support the extrapolation of data on biosimilarity across indications, the applicant provided a comprehensive data package to address these scientific considerations.

First, the applicant provided data to support the demonstration that GP2015 is highly similar to US-licensed Enbrel 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 demonstration that no clinically meaningful differences exist between GP2015 and US-licensed Enbrel based on similar clinical pharmacokinetics, similar efficacy, safety, and immunogenicity in plaque psoriasis, using the approved dosing regimen.

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 for licensure.

Next, I will summarize the scientific considerations for extrapolation of data specific to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis.

The primary mechanism of action of Enbrel is through inhibiting binding of soluble TNF alpha to self-surface receptors, thus inhibiting signal transduction and adhesion molecule expression.

The scientific literature indicates that this mechanism of action is the primary mechanism of action in psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis.

The data provided by the applicant showed similar TNF binding and potency to neutralize TNF alpha, supporting the demonstrating of analytical similarity pertinent to this mechanism of action. Further, based on the totality of the data demonstrating analytical high similarity, PK similarity and no clinically meaningful differences in psoriasis between GP2015 and EU-approved Enbrel, similar PK safety and immunogenicity profiles are expected between GP2015 and US-licensed Enbrel in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis.

Therefore, based on the above considerations, the agency believes it is reasonable to extrapolate data to support that there are no clinically meaningful differences for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis between GP2015 and US-licensed Enbrel.

In summary, the totality of the data submitted by the applicant supports a demonstration that GP2015 is highly similar to US-licensed Enbrel, and there are no clinically meaningful differences between GP2015 and US-licensed Enbrel. The data submitted in the BLA support licensure of GP2015 for the indications for which U.S. Enbrel is licensed, and for which Sandoz is seeking licensure for GP2015.

On behalf of the FDA presenters, I wish to acknowledge our colleagues from multiple divisions and review disciplines 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 the FDA

DR. SOLOMON: Okay. It's now open for clarifying questions. Dr. Mager?

DR. MAGER: Thank you. Just two questions. The first, the briefing documents mention the mathematical model for the correction of the T7 percent. Was that anything more than simple regression?

DR. ADAMS: No. That's just regression.

DR. MAGER: Okay. I just wanted to clarify how that was related. Also, I wanted to just ask about the differences between study 101 and 104. I think many of the differences that were highlighted, the selection of males only, the same operator, et cetera, really did go towards the intra-subject variability and reduced it almost in half. But I don't think those things would necessarily explain the double, almost double exposure that was observed.

So that leads me to maybe the assay that was

used. Could we have some information about what the differences in the assays were and which assay was used for 302?

DR. NIKOLOV: I think we'll give the opportunity to the sponsor to answer maybe this question, since they're most familiar with the data.

DR. REN: You want me to go first?

DR. POETZL: My name is Johann Poetzl, clinical bioanalytics, Sandoz. So there was a certain period of time between the 101, 102 and the 103, 104 study. And what happened in this time period is that the reference material expired, which was used in 101 and 102, and therefore the reference material has to be renewed. The reference material is used for the generation of the calibration curve. So all samples which are quantified in the clinical study are quantified against this calibration curve.

We were aware of that, and therefore we decide to do a full validation of the assay set up used for 103 and 104 study before we start the

analysis. And this validation was successful according to the guidelines from FDA and EMA on bioanalytical assay validation.

Therefore, within each the studies, the correctness and validity of the results is ensured. And as we used the identical assay in 101 and 102, a cross comparison can be done, but the 103 and 104 a different assay setup was used. And this is the reason why numerical differences occurred between 101, 102, and 104 study.

I have another slide. Can you go to my slide, page 16? Okay, here. There were near two-fold numerical differences of the PK parameters, especially the exposure between study 101 and study 104. That is likely due to the change of bioanalytical method, which is summarized in this slide.

Here, I want to emphasize, both methods were validated, ELISA assays, and we agree upon that. However, you can see here, one of the key reagents, the detection antibodies were different between two methods. Study 101 used a goat anti-human

polyclonal antibody, and study 104 used rat and human monoclonal antibody. So those two detection antibodies were from the third party, not generated by the applicant.

In addition to that, the dilution factor of PK samples, the range of the calibration curve, and the lower limit of quantitation [indiscernible] were all very different between those two methods. And it's well known that in the ELISA field, it's quite common to have different results if key reagent changed, such as a detection antibody. Therefore, we consider the results from study 101 and 104 -- I mean, from 104, acceptable.

DR. MAGER: Okay.

DR. SOLOMON: Dr. Margolis?

DR. MARGOLIS: Sure, thank you. So one of the issues that was difficult I think for this committee yesterday was extrapolating from one disease to another, which is all part of this process. And my colleague from Philadelphia, Dr. Waldman, used the straw man concept. And I'd like to sort of evoke a similar kind of thing.

As Dr. Leonardi mentioned, psoriasis is a common disease. It's fairly prevalent. It's recurrent. It's easy to conduct -- or easier perhaps to conduct the studies because of the length of the study and the availability of using PASI scores and visual readouts.

I guess my question is, is of the TNF agents that are available, that have been approved, the biologics, of which there are several, and they affect different pathways, how many of them approved for psoriasis have also been approved to treat rheumatoid arthritis? And of those that haven't, was it because they tried and failed?

DR. NIKOLOV: I can only speak to the publicly available information. But to my knowledge, TNF inhibitors act in both rheumatoid arthritis or rheumatic diseases and psoriasis.

DR. MARGOLIS: So all the agents that have been approved for psoriasis have also been approved for rheumatoid arthritis in this class?

DR. NIKOLOV: Right. So maybe certolizumab was not approved, but whether they were studied,

I'm not sure whether I can provide this information.

DR. MARGOLIS: Thank you.

DR. SOLOMON: Dr. Becker?

DR. BECKER: Actually my questions were all addressed by Mr. Mager's question.

DR. SOLOMON: Dr. Miller?

DR. MILLER: Don Miller. It's been emphasized that the primary mechanism of action for etanercept is binding of TNF alpha, but it also binds TNF beta. I'm just wondering if that mechanism is relevant, and is it more relevant for one disease condition than for another?

DR. KOZLOWSKI: We feel that TNF alpha is the primary mechanism, but I think in any case there was data to show that there's inhibition of both TNF alpha and TNF beta. So even if it turned out that TNF beta was some part of this, that was covered in the functional analysis.

DR. ADAMS: Two points. One is that the antibodies don't bind lymphotoxin alpha or TNF beta.

DR. SOLOMON: Dr. Bilker, and then Dr. Waldman.

DR. BILKER: I just wanted to ask a question about the number of lots of the different products. The number of lots for U.S. Enbrel and for EU Enbrel and for GP2015 vary substantially across the different analyses for the analytical outcomes, sometimes being a third of the total batches that were used overall. And large enough sample size is important, especially when trying to show equivalence or non-equivalence.

So I'm just wondering why were all the batches not considered for all the analytical outcomes?

DR. SOLOMON: Does the applicant have a response?

DR. McCAMISH: Mark McCamish. When we set up all the analytics, it's orthogonal in nature, but over time, each lot is not exposed to each one of the analyses. So it's a convenience component of what we're doing at that particular time, and it's very difficult to have all of the 84 lots used

in all of the analytics.

DR. SOLOMON: Dr. Waldman?

DR. WALDMAN: Scott Waldman. Two small clarifying questions, one on PK, one on analytics. The comparison of EU and GP in 101 apparently failed because of operator issues. And I guess my question there is, was the operator issue only for the GP compound and not for the EU compound? Because that study was used as a cross comparator back to, I think, 102 for EU/U.S. comparisons.

So my question, is the operator issue that sort of fouled that study only specific for the GP compound? You guys get the question?

DR. NIKOLOV: Yes, and I think we'll give the opportunity to the applicant to comment since they provided these analyses.

DR. McCAMISH: As this was blinded, it was not only operator for G15, it was for both.

DR. WALDMAN: It was for both?

DR. McCAMISH: Yes.

DR. WALDMAN: But it didn't affect the comparison to the U.S. compound; it only affected

the comparison to the GP compound?

DR. McCAMISH: It added variability to the evaluation, correct, on both.

DR. WALDMAN: Okay. So the second part of the PK question is, the 104 study, males only, does that impact generalizability in terms of the biosimilarity comparison between EU, PK comparison between EU and GP?

DR. McCAMISH: A good question. In this sense, what we're trying to do is ask the question if the molecules are different. So what you really want to do is narrow the variability to evaluate that. So in each instance it actually is better to narrow the variability to address the question of similarity.

DR. WALDMAN: But it leaves open the question of whether male/female differences will increase the variability and change that comparison.

DR. McCAMISH: Right. And in terms of the male/female variability, it does add to the overall variability slightly, but there's not a lot of data

showing that difference between genders that it has involved.

DR. WALDMAN: Okay. The analytic question goes back to mispaired cysteines, essentially disulfides. Presumably, the misformed disulfides impact the ability of the molecule to bind its target, TNF, and that's why a computation was performed to correct in the RGA comparison.

My question has to do with, if that's true for the RGA comparison, why wasn't that generalized to the binding assay comparison, as well as the apoptosis assay comparison? In other words, if these things are affecting the function, it should affect the function across all the functions, not just one specific function.

So you sort of wonder, if you did the correction for each of the measurements that you did, would that put one of the measurements back in comparability, but take the other two measurements out of comparability? You see what I'm going for here? I'm just curious.

DR. KOZLOWSKI: Steve Kozlowski, FDA.

Sandoz can also comment on this. Different assays may have different sensitivities to this. So all the assays actually were within the range of the reference product. Even the RGA assay, if you look at the points, the biosimilar candidate product were all within that range. But some of our assays we expect this standard of statistics, again not pass/fail, but that's what we have. So that revealed a difference in that assay, and that led to wanting to understand it.

I actually think it's worthwhile going through the misfolded protein a bit because I think there have been a lot of questions about that. And again, I will describe an FDA perception on this. Sandoz is welcome to add their view.

In the data we presented -- and we can go to the slides -- slide 18 in the FDA presentation. This looks at the misfolded protein using reverse-phase chromatography. And you can see, there's around a 10 percent difference, 16-17, 10. Now if you go to slide 32, the difference in potency using this rigorous statistical assay was

around 10 percent. So those numbers are not so out of line.

The T7 peptide may be a more specific and better assay for this, but overall, misfolded protein and the difference in this particular potency assay seemed to match. Again, the point that even though it failed this initially, it was still within the range of the product.

Then the question about refolding. So this is actually a challenge. If you have a product impurity, you want to know does it work or not. And as we don't expect companies making biosimilars to intentionally maintain impurities that happen to have been in the reference product, that doesn't seem like a laudable goal, and we need to really understand what those impurities mean.

So the question about whether this misfolded protein, which in this assay showed a difference in vitro, mattered in vivo. So there are examples of refolding protein. IgG2, the example Peter talked about, does change forms.

In fact one of the initial papers about

that, I think that was one of the ones cited by Sandoz, certainly cited in our evaluation, actually does take patient samples that are purified over time and show, in fact, that this refolding occurs, or this change in folding occurs, and matches that to a particular oxidized and reduced set of thiols that in vitro could mimic that.

So although there's not in vivo data with this, there is the concept that simply the level of thiols that are in plasma can refold products.

The recalculation, we asked Sandoz not only to assume full refolding, but to assume 50 percent refolding, and it still worked. There is a sensitivity analysis to this in case the refolding actually is not as complete in vivo as we would expect.

Furthermore, after they developed the model, we asked them to additionally refold lots and make sure they still fit the model. So there was a certain level of robustness to this.

Again, I think it's really the sum of all those things. It was never outside of the range of

the reference product completely. We expected to meet a particular statistical goal, which I think was useful because it really informed this question, which was important to understand; is this misfolded material to be considered active or not?

Then the judgment of activity, although it didn't have an in vivo component, there are other published examples of where this type of in vitro refolding does match in vivo. The analysis was done assuming this is not 100 percent, and the model at least went through a verification.

DR. SOLOMON: Did you want to add anything?

DR. McCAMISH: Just one. Thanks, Dr. Kozlowski. And I just have this one slide to show, if we can bring this up. And as we've gone through from a sponsor perspective, I just want to point out the information.

If you look at GP2015 on the right-hand side, we're very comfortable it's consistent. We're showing the capability here in terms of a consistent evaluation. And this is one of the

challenges for the sponsor. We have to dig down and understand not only our product, but the reference product.

So a lot of this was understanding the reference product and how we can then bring that back in and show statistical equivalence. Thank you.

DR. SOLOMON: Thank you. Dr. Brittain?

DR. BRITTAIN: I have a really big-picture question, again about the whole biosimilarity enterprise. So the idea, as I understand it, is that because you're demonstrating that at an analytical level, everything is essentially the same, that you then presume that at the clinical level, everything will be essentially the same. And again, the extrapolation is based a lot on that.

In terms of actually testing that premise, would we, outside the FDA, ever know if that premise was failed? I mean, if someone was testing a biosimilar product and everything looked great at the analytical level, but then when they actually

did their clinical trial, it wasn't so good, would we ever know that? I assume you folks would.

DR. KOZLOWSKI: There have been papers written about comparability, where comparability exercises have not gone fully forward for a variety of reasons; they've either failed PK or not. So there is literature on that.

My sense is, as experience is gained with biosimilars, there will be a sense about that, too. And certainly, we're certainly well interested in clinical trials being always available, right. There are expectations for that. So hopefully even failed clinical trials will be notable, and then there will be an ability to learn from those things.

DR. BRITTAIN: But will that be public? If someone does it -- say a failure occurred, and there's a meeting two years from now, and everyone's asking can we count on this equivalence in the analytics meaning equivalence at the clinical level.

DR. KOZLOWSKI: So again, I think this is

evolving. The analytics get better and better. There was an example mentioned yesterday about neutralizing antibodies to an epoetin candidate through one route of administration that was uncovered in the clinical part; root-cause analysis led to potential structural understanding, and that was public, very public.

So my sense is that this will be available. And I actually think it's in the best interest of all the industry participants in this to make it available because it helps all of them.

DR. SOLOMON: I have two questions, one about the analytics. And this is a point that was touched on by the applicant, and then the FDA, this concept of highly critical, how do we grade the different tests and their level of criticality.

It was kind of glossed over, and I'm not sure if this is a conversation that goes on between the applicant and the agency. Can someone from the agency give us a better understanding of that paradigm?

DR. KOZLOWSKI: This concept evolved more in

terms of improving manufacturing changes to really understand what are the most critical attributes, both in controlling lot-to-lot products and dealing with manufacturing changes.

I think these concepts about what attributes are critical have been in the minds of industry and regulators for a long time, but as part of this concept, which was called quality by design, they were really pushing the idea of a more formal way of ranking these attributes. There's actually an ICH document, Q9, that talks about risk assessment in general.

What Sandoz presented was there are a number of areas where you assess risk. Is there a risk to pharmacokinetics? Do you think there's a risk to safety or immunogenicity? Do you think there's a risk to potency? And for any particular attribute based on a variety of factors, literature, experience with related molecules, clinical data if it's available where those variants have had, all that's integrated into a scoring system.

Generally, this is done with a

multidisciplinary team. There's kind of rules about moderating it well because it really does matter how it's done, and they generate a score. And the score may vary. We don't tell industry you have to use this exact scoring system. They generally will propose something that meets those criteria and share with us their results.

The agency generally accepts those assessments, but if an attribute is rated really low that in our experience is high, we may challenge that and say, we would like more data on why our intuition, our past experience with this, differs from your risk assessment.

DR. SOLOMON: That's very helpful. Thank you.

A specific question to Dr. Fritsch about the full sample versus the per protocol. This has been touched on several times by other committee members, but I'm just curious, as a statistician, how do you think about those two? I know that they did line up pretty well, but I'm just curious whether the selection of the primary analysis was

as you might have done it.

DR. FRITSCH: As you noticed, I tended to present the full-analysis population, which reflects my preference for the full-analysis population. And of course I looked at both, and they are consistent.

Generally, I'm concerned that people might be excluded from the per-protocol population for reasons that might be due to treatment. So I think you can argue both ways that people could be -- bias can go either way. So I think the best goal is to try and follow everybody as well as possible, and minimize the missing data, and try to capture the reasons as well as possible.

DR. SOLOMON: Thank you.

Do we have any other clarifying questions? Jose?

DR. SCHER: Jose Scher here. I think I'll follow up on Dr. Solomon's question, and maybe to the agency. I'm not fully reassured with the endpoint efficacy and the explanations that were given.

So let's assume it's true. The question to the agency is, what if the efficacy was 90 percent, the PASI is 75. What's the cutoff where you say this clinically meaningful data is not without procedural uncertainty? In other words, they are clinically equivalent or similar, but in reality this does not reflect historical data.

DR. NIKOLOV: I will ask Dr. Fritsch to address this. But just to clarify your concern, again, this is related to your concern that the effect size in the study was much larger than what was seen in the historical studies, right?

DR. SCHER: Right. And it's related to the point of extrapolation. Right.

DR. FRITSCH: Again, could you rephrase your question one more time?

DR. SCHER: In general, we assume people that are treated with Enbrel, based on pivotal trials by Dr. Leonardi and others, that the PASI 75 response is about 50 percent. The sponsor comes with a dataset showing 70 plus percent, and that does not mitigate, in my opinion, procedural

uncertainty.

So the question to the agency is, say for rheumatoid arthritis, the typical ACR response is 65 percent. Say another sponsor comes in and says it's 95 percent. Would that be still valid in the eyes of the FDA just because they're clinically equivalent in the comparison?

DR. FRITSCH: I think one of the challenges, particularly this -- for this application, we are focusing on PASI 75, which is a dichotomous endpoint. So one thing it can be rather sensitive to, if there are people in that 70 to 80 range, small shifts in percentage could shift a number of people from success to failure, is one possibility.

I do agree with what Dr. Leonardi said this morning, that design of the study does have an impact, that what arms are in the trial can have some impact. Should those arms explain the whole thing? I don't know. The fact that there was no placebo, there was no knowledge that there were people who were not getting any treatment. I don't have a good explanation for why this is different.

The two arms are the --

DR. NIKOLOV: Maybe I can add, and then let Dr. Levin also comment. So you are questioning the constancy assumption for the study. And I think from our perspective, since the effect size is much larger than historical control, historical data, we are not concerned that we may miss a difference if it were to exist.

In other words, if the sample size was small -- if the effect size was smaller, that would be a concern for us. With a larger sample size, we may have better ability to detect differences. But I will let also Dr. Levin comment.

DR. LEVIN: Greg Levin, FDA. So I've been mostly involved in the review of the rheumatoid arthritis programs, where the comparative studies are in that program. And I'll just point out that in the historical studies of TNF inhibitors for rheumatoid arthritis, you see a greater variability in the within-arm response rates, and it's probably because there's more historical studies.

I think there's only two here. You know

it's not psoriasis, it's rheumatoid arthritis, but we do see quite a large variability in the response rates within the active arm across historical studies in rheumatoid arthritis.

You can look to some of the results that were in the briefing document for yesterday's AC, for example, where you see ranges from 50 to 75 percent. I mean, it may be off a little bit, but there is a little bit of a greater range there, which may give you a little more confidence.

But I also agree with the comment that I'd be much more concerned if you were seeing a decrease relative to the historical studies in the within-arm response rates where you were concerned that maybe the study would not have been sensitive to even a difference versus placebo. But other than that, I echo the comments that were made.

DR. SOLOMON: Dr. Brittain?

DR. BRITTAIN: I guess I would say I do share your concern somewhat, that given that the rate did change appreciably, it does raise more question; what would a placebo have done in that

same study?

I think there's less -- I mean, there's always a leap of faith when we're doing anything like this, when we're looking at historic data to understand the treatment effect. But it feels like now we're doing a bigger leap of faith. But I also agree that given the only placebo-controlled trial showed such a dramatic treatment effect -- I think it was like 49 versus 3 or 4 percent, such a dramatic effect -- it's hard to believe there isn't also a dramatic effect that would have been shown in the study had they been able to do a placebo group.

So I'm not too concerned. But I agree, it needs to be considered.

DR. SOLOMON: Okay. I think we've had a robust conversation, and I think we're all ready for a break. So why don't we adjourn for about one hour, so until 1:15, and we'll see you back.

(Whereupon, at 12:13 p.m., a lunch recess was taken.)

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

(1:15 p.m.)

Open Public Hearing

DR. SOLOMON: This is the open public comment session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

I believe speaker number 1 is not here, so we're skipping right to speaker number 2. Will

speaker number 2 step up to the podium and introduce yourself? Please state your name and organization that you represent for the record.

MR. SPIEGEL: Good afternoon. No financial disclosures. My name is Andrew Spiegel, a founding member and steering committee member of the Alliance for Safe Biologic Medicines. I am reading the statement of our chairman, pediatric rheumatologist, Harry Gewanter, who was unable to attend today due to his wife being suddenly hospitalized.

"I believe everyone here has personally experienced or witnessed the dramatic transformation biologics have had in the lives of patients and their families. I started practice prior to the use of methotrexate and have seen us go from crippled children in walkers and wheelchairs, to essentially invisible conditions and considerations of a cure for rheumatic diseases.

"Since every treatment is a unique chemical experiment between an individual patient and a

medicine, I've also witnessed the variability in patient responses to different medications, or even different lots of the same medication. These real-world individual responses to therapies emphasize the critical need for as much clinical data and transparency as possible with all medications, but especially with biologics, both the reference molecules and biosimilars.

"Biosimilars provide opportunities for increased access to more life-saving treatments, more life-saving options, hopefully at reduced cost 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 of the medicines, both at the time of application, as well as throughout the medication'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.

"Producing that level of confidence begins with maintaining and building on the FDA's high approval standards. Formal evaluation starts with solid analytic 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 population 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 the infliximab biosimilar, Inflectra, comparative data was only available for RA and AS.

"Approval was granted for PSO and PSA based on extrapolations since these conditions have similar mechanism of actions to RA and AS, but Health Canada did not approve for the 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 and efficacy of these products in these indications.

"When newly submitted data, biological and observational clinical data, showed no new unexpected safety signals in IBD, Health Canada then allowed an extrapolation based approval for CD and UC indications. We encourage the FDA taking this cautious, comprehensive, and data-driven approach to approvals as well.

"Clear product identification is critical to

approval to ensure safety and confidence to 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, memorable suffixes, such as that used in the FDA's approval of Zarxio.

"Indeed, ASBM surveys show U.S. biologic prescribers prefer suffixes based on manufacturer names over random by a 6 to 1 margin. ASBM survey of 401 U.S. pharmacists also showed 77 percent prefer manufacturer name derived suffixes to random letters.

"Comprehensive data collection of biosimilarity should not end with its approval. Strong post-market surveillance data is also important. Patient/physician confidence in biosimilars is critical to their success. It must be earned and maintained through high approval standards, distinguishable naming, transparent labeling, strongly comprehensive pharmacovigilance,

manufacturer accountability, and open communication. Thank you very much."

DR. SOLOMON: Thank you. Speaker number 3 does not appear to be here. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization that you represent.

DR. CRYER: Good afternoon. For those of you who were not here yesterday, or who were here yesterday, you may get a sense of déjà vu from today's speakers. But my name is still Dennis Cryer. I am the lead physician co-convener of the Biologics Prescribers Collaborative, or BPC. I have no financial disclosures and no conflicts of interest.

I'm here on behalf of physicians who routinely prescribe biologic medicines, and professional organizations with numerous biologic prescribers as members. Our comments today are general. They focus on four key biosimilar policy issues rather than on a specific biosimilar product.

Among these issues, first, each biologic product deserves a distinguishable and also meaningful 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, which was the first licensed, and marketed biosimilar in the U.S.

Second, biosimilar product labeling must include 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 to manage potential adverse events. As such, it is of the 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 it. As ADA finalizes the guidance on biosimilar labeling, we urge the agency to include the product-specific information that physicians overwhelming consider to be important.

Third, the FDA should proceed with thoughtful caution when considering biosimilar applications for indication extrapolation. Biologic medicines are often indicated and used to treat multiple and unrelated disease states. And under the new abbreviated approval process, data presented for certain indications but not for others, the 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 for the reference product that it's 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 and expected toxicities among sensitive patient populations, as well as the mechanisms of action in each condition. Those might include: the target or receptors for each relevant activity or function of the product; the binding, dose response, and pattern of molecular signaling upon engagement of target; the relationships between product structure and target or receptor interactions; and the location and expression of the target. We appreciate the increased focus on these areas and issues over the past two days of meetings.

Fourth and finally, the FDA should provide clear and concise guidance to industry surrounding interchangeability between the biosimilars and their reference products. As more biosimilars that

could be put forward for interchangeability enter the developmental pipeline, it's critical that sponsors be 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 to provide that clarification on this issue at the federal level.

We encourage FDA to consider the implications of these policies as biosimilar products advance onto the market. These policies, if adopted, will determine the 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 which are critical for the safe use of biosimilars and other biologics. Thank you.

DR. SOLOMON: Thank you. Will speaker number 5 step to the podium and introduce yourself? Please state your name and any organization that

you represent.

MR. HODGE: My name is Richard Hodge, and I am a member of the board of the American Autoimmune Related Disease Association. Neither I nor AARDA have any financial conflicts of interest with the subject before this committee.

AARDA, or the American Autoimmune Related Disease Association, is an organization that represents multiple autoimmune diseases and some of the 50 million Americans that suffer from autoimmune diseases, including over 100 established diseases. It's important to note that of those 50 million, almost 75 percent are women.

AARDA is a national not-for-profit organization that's dedicated to raising awareness and addressing the problems of autoimmunity, which is a leading cause of chronic illness and disability in the country. AARDA is also the facilitator of the National Coalition of Autoimmune Patient Groups, a coalition of some 37 of those different patient advocacy and patient assistance groups representing numerous autoimmune diseases.

The development of biologic and biosimilar drugs offer by far the best hope for those suffering with autoimmune diseases. Individuals with autoimmune diseases suffer from significant health challenges, often requiring lengthy evaluations and referral processes involving many different specialists, as well as therapeutic trial and error, in order to diagnose, treat, and manage their medications.

We have witnessed firsthand the impact of biologics are having on improving and extending the lives of autoimmune patients. However, we must continue the strong patient advocacy protections for which the FDA has been noted, and for which many groups here have long advocated.

Autoimmune disease patients have a proven susceptibility to the unintended consequences of inappropriate drug therapies and are highly vulnerable to the ravages of unnecessary changes to their therapies. Autoimmune patients often experience many months, or even years, of searching for an appropriate combination of drugs, including

biologics and biosimilars, appropriate for the individual patient.

AD patients often have a combination of comorbid autoimmune diseases, and different patients with the same condition often respond different to the same therapies. Individuals with autoimmune diseases face these significant health challenges and are often requiring unique combinations of drugs to diagnose, treat, and manage their conditions.

According to an ongoing AARDA survey of autoimmune patients, 95.9 percent had to try more than one medication before they found the one that worked for them. The average time it took to find the right medication was 2.9 years. Over 37 percent said their condition worsened, and 35.8 percent experienced adverse side effects when they were switched to another medication.

According to Dr. Gregory Schlamizi, the leading rheumatologist and cofounder of the Coalition of State Rheumatology Organizations, patients with autoimmune diseases have responses

that are different from other patients.

Autoimmune patients can have specific characteristics, such as blunted antibodies and cellular immune responses that can lead to heightened responses. It cannot be assumed that patients with one lymphocytic HLA marker set will respond to a biologic agent in an identical manner as another with the same lymphocytic marker set.

In the case of biologic therapeutical agents, some patients may develop an antibody response to one biological agent and have a lower response to that agent as a result. These lower responses are caused by antibodies destroying the biologic agent, so the beneficial effect is reduced and the patient having a reaction to the drug.

As we know, by the very nature of their production, biosimilar drugs are not identical to the others or with the innovator biologic. Subtle differences in the biological structure can be expected to be a source of different potential reactions in the same patient. Therefore, one individual, a patient with highly receptive

lymphocytes, may have no reaction to one biological agent, but will have a reaction to another, but not similar identical agents.

This is no more true than in AD patients. There's a considerable body and growing body of evidence that subtleties and the severe adverse consequences can occur from the inappropriate switching of autoimmune disease patient therapies, especially biologics and biosimilars. Our written statement provides a summary of some of the recent research on that. Time will not allow me to go into that at this point.

DR. SOLOMON: Thank you.

MR. HODGE: Thank you.

DR. SOLOMON: Will speaker number 6 step to the podium, introduce yourself? Please state your name and the organization you represent.

MR. SPIEGEL: Good afternoon. My name is Andrew Spiegel. I have no financial disclosures. I come before you in two capacities this afternoon. First, as the executive director of the Global Colon Cancer Association, but I'm also proud to

represent an organization that I cofounded six years ago, the Alliance for Safe Biologic Medicines. ASBM is an organization comprised of patient and physician groups who advocate for patient-centered policies in this arena.

Biologic medicines have helped more than 300 million patients worldwide. These medications have helped triple the life expectancy of the most advanced colon cancer patients, and we expect biosimilars to bring tremendous benefits to the patient community, not only offering new treatment options, but doing so at a reduced cost. We hope this reduced cost translates into increased access for patients.

We are excited to see biosimilars entering the U.S. market and the U.S. healthcare system, but in order to feel comfortable taking biosimilars, the patient community wants to know that they are as safe and as effective as their reference product. 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 with the 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 that the structural, functional, and clinical similarity of the product are similar to that of the innovator.

Extrapolation is an area of concern for the patient community. At a minimum, we feel that approval for each indication should be granted individually rather than an all or nothing approach. We don't suggest that safe extrapolation is not possible. To the contrary, we simply feel that each indication should be approved individually based upon solid data.

This panel should have the flexibility and should not be forced to approve the drug for all or no indications. This is a constraint that is not legally required, nor in the patient's best interest. This is not to suggest that there is a

lack of data for today's product, or yesterday's product, but more common is the overall process. You committee members should have the right and should have the option of approving each indication presented.

Once approved, informative and transparent labeling that lets us make informed treatment choices 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 data in other diseases. We want to know whether or not the product is a biosimilar, and whether it's interchangeable with its reference product. Therefore, informative and transparent labeling is required.

Comprehensive data collection on a biosimilar after approval is of utmost concern. Strong post-market surveillance data improves care and limits risks to patients. Real-world data helps us better understand these medicines and promote more efficient, safer, and personalized

use.

Strong post-market pharmacovigilance will improve care and provide further confidence in biosimilar medications. The FDA really does have a unique opportunity to ensure new drugs on the market remain safe for patients well after approval.

Clear product identification and naming are critical to ensure safety and confidence in biologic medicines. We agree with the FDA's approach in promoting distinguishable names for all biologics, including both innovator and biosimilar drugs. We continue to believe that the benefits of distinct naming will be best realized through meaningful, memorable suffixes. How long would it take you to remember your passwords if they were not memorable or meaningful to you?

For patients to realize the benefits of biosimilars, we need to be confident that our health and safety remains a 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 7 step up to the microphone and introduce yourself? Please state your name and the organization you represent.

MR. CARDENAS: Good afternoon. My name is Jasey Cardenas, senior policy associate at the United Spinal Association. And I'm speaking today on behalf of Larry La Motte 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. While our 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 for new treatments.

PBSA believes that the complexity and

uniqueness of each biologic medicine require that FDA ensures all biologics and biosimilars are thoroughly tested and meet the highest safety standards. We remain concerned that FDA has now approved the first two biosimilars and is now in the final stages of review of two others without putting in place transparent and finalized policies to safeguard patients.

To date, the agency has yet to issue final guidance on a range of issues that will impact patient safety, including interchangeability, naming, labeling, non-medical switching, a robust pharmacovigilance monitoring system, and indication extrapolation. While we are pleased there have been draft guidance issued on naming and labeling, completion of final guidance on all these key patient safety issues should be FDA's top priority in implementing the law.

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. Compared to Neupogen, the two products that are now before the committee are much larger and more complex in structure, will be taken by patients for many years versus months, and will seek to treat a number of widely varying, serious chronic conditions.

We would appreciate the experts on the committee to thoroughly discuss the adequacy of the data presented given the statutory requirements for approval and the confidence patients who will be taking these products for many years can have in their long-term safety.

When stabilized on a biologic, patients are concerned about being switched for non-medical reasons to a non-interchangeable biosimilar. This was the point of substantial debate and discussion at the February 9th advisory committee meeting considering the infliximab biosimilar application.

With the possibility of now three biosimilars on the market for the same indications, our concerns about non-medical switching have grown. Is the FDA seeking evidence on safety of

non-medical switching among the three biosimilars? If so, what is the safety standard the agency is using to measure the safety of multiple switches to, from, and among the biosimilars and their reference products?

In PBSA's meeting in May with Dr. Woodcock and other FDA leaders, we were pleased FDA expressed a willingness to consider our recommendation to require future biosimilar advisory committees to have the ability to vote on single indications if the committee has doubts about extrapolated data for an indication rather than vote against the entire application.

We are disappointed that this step has not been taken, and we will continue to urge its adoption. This would be an important step towards boosting patient and prescriber confidence in biosimilars.

In crafting the biosimilar laws, Congress expressly limited FDA's approval process to assuring no clinically meaningful differences in safety and effectiveness, and that the products are

highly similar to their already approved reference products. Congress explicitly indicated that cost should not be a factor in approval of these new drugs.

We call on FDA to ensure these and future biosimilar advisory committee discussions are focused on matters of safety and efficacy, in determining biosimilarity, and that committee members are advised in advance that their advice and judgment should be based on those matters. There should never be a situation where advisory committee members are voting on approval of new products based on cost and not solely based on safety and efficacy.

Thank you for the opportunity to provide the views of the patients on the biosimilar process today. Thank you very much.

DR. SOLOMON: Thank you. Will speaker number 8 step to the podium and introduce yourself? Please state your name and your organization that you represent.

MR. GINSBERG: I have no disclosures to make

regarding my travel here today. And on behalf of the non-profit Global Healthy Living Foundation, and its arthritis organization, Creaky Joints, I'd like to thank the FDA for its commitment to listening to a diverse set of stakeholders today. We are not scientists or doctors. We are patients.

My name is Seth Ginsberg, cofounder of Creaky Joints and the Global Healthy Living Foundation, and I was diagnosed with spondyloarthritis at the age of 13. See, for patients, biosimilars represent hope as well as fear. Hope for expanded treatment options through a broader formulary, and fear of being switched from a drug that works to one they don't know, and not participating in the promised cost reductions.

Our community is carefully processing these two emotions because biologics transform our lives. Whether it's Mariah from Colorado who was able to finish her master and law degrees because of her medicine, or Cindy from Texas, who took one last road trip with her elderly father before he passed away.

In addition, our community fears biosimilars could represent losing the biologic treatment they've searched years to find and worked tirelessly to gain access to. In the case of Brenda from North Dakota, a decade. I know, I've been to North Dakota. I've met Brenda, and I've celebrated her successes with her. A biosimilar may be essentially equivalent to a scientist or an insurance company, but it's not to the biologic patient whose life has been completely transformed from it.

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 and will track patient reported outcomes. We encourage the FDA to look at ways to formally incorporate PCORI's patient reported outcome data into post-market surveillance activities. It's been built, let's use it.

In order to achieve the promise originally

intended by the BPCIA in 2010, we are addressing patient and physician confidence in our biosimilars. 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.

Although it's a controversial topic among the patient community, we support FDA's position to allow indication extrapolation. We understand that you can't have biosimilars without having extrapolation. It's needed in order to reduce cost and allow biosimilars to reach many more patients.

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 one part of biosimilar success. Use and satisfaction by the patients is where success will ultimately be measured. And Arthritis Power, our organization, and many others stand ready to measure that success.

We'd like to thank the FDA for emphasizing the value of the patient perspective through public meetings, such as this one, as well as yesterday's, and we continue to mobilize our patient community to create a better life for those who will benefit from biosimilars. Thank you very much.

DR. SOLOMON: Thank you. Will speaker number 9 step to the podium and introduce yourself? Please state your name and any organization that you represent for the record.

MS. LEMISKA: Hello. My name is Emily Lemiska, and I am a representative of the U.S. Pain Foundation. I am also a chronic pain patient with a rare spine and spinal cord disorder. I'm reading testimony for Casey Cashman, our executive director, who is unable to be here today. Neither I nor U.S. Pain have any financial conflict.

"Thank you for allowing me the opportunity to further expand on biosimilars and non-medical switching. Today I would like to discuss how substitution and switching intrudes into the physician/patient relationship, and erodes patient health, with significant financial and social costs.

"Switching medications for non-medical reasons can mean unnecessary new side effects, reduced effectiveness, or even relapse. This translates into disease progression, reduced function, and a lower quality of life. For example, switching treatments, even those the FDA deems as equivalent, can cause people with epilepsy to experience breakthrough seizures. For Crohn's disease patients, even voluntary switching is associated with a loss of effectiveness within one year.

"As for higher healthcare costs, rheumatoid arthritis patients, who incurred non-medical switching, experience 42 percent more ER visits and 12 percent more outpatient visits over six months.

Meanwhile, studies also show people with epilepsy who were switched saw more in patient and emergency care than those who did not.

"Generally speaking, non-adherence to treatment regimens contributes direct annual costs of $100 billion to the U.S. healthcare system. Indirect costs exceed $1.5 billion annually in lost patient earnings, and $50 billion in lost productivity.

"But when we talk about patients who are losing the ability to manage their disease because of non-medical switching, please realize the true negative impact is hard to quantify. The potential harm of non-medical switching represents losses like not being able to make your family dinner, missing your child's soccer game, not being able to attend your best friend's birthday party.

"We are here, of course, to discuss switching as it relates to biosimilars specifically. Biosimilars represent an opportunity for patients, but they also represent an opportunity for insurers to save on costs, at

patients' expense. Patients should not be forced to try alternative measures that may be less effective and cause adverse reactions. This is especially true if their existing treatment has proven beneficial.

"Please understand that interchangeable does not mean the best option. It does not mean less risk to the patient's health. It does not necessarily mean less costly. Transparency also needs to be addressed here. Chronic pain requires patients and clinicians work together, sometimes for years, to find the best treatment regimen. Ideally, insurers should not be playing doctor, but at the very least, patients and physicians must be made aware of any changes insurers or pharmacy benefit managers are attempting to make.

"On behalf of chronic pain patients everywhere, we ask that you create restrictions to limit the practice of switching, steal patients from the treatments they rely upon, and the harm quantifiable and unquantifiable that can cause. Thank you for your time and consideration."

DR. SOLOMON: Thank you. Will speaker number 10 step to the podium and introduce yourself? Please state your name and any organization that you represent for the record.

MR. PHILLIPS: Good afternoon. My name is Thair Phillips, and 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 activists. I have nothing to disclose concerning this testimony today.

As I testified yesterday, and at previous advisory committee meetings, RetireSafe looks forward to the promise of increased access offered by biosimilars, but we are still concerned about safety. My statement today will again deal with safety issues that continue to exist within the overall biosimilar approval process.

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. Again, both

the answers and comments from our activists voiced an overwhelming desire for commonsense safeguards when it comes to the naming, labeling, switching, approved indications, and the open communication required for biosimilars.

Our questions about safety always bring a positive result. The percentages were unusually high with most answers in the high 80s, and one in the 90s. I will focus on two of the updated questions.

Over 95 percent of the respondents said that biosimilars should not be substituted if it had not been adequately tested for safety and efficacy, specifically for the disease or condition it was prescribed to treat. This commonsense answer should highlight the need for a change in how the advisory committee votes.

I've testified at every advisory committee meeting on biosimilars. At every meeting, there are some indications that the committee members feel fine with, and some that elicit questions and concerns. The up or down vote hides this valuable

information. The advisory committee needs the option to have an up and down vote on each indication on a biosimilar's application. This issue was our survey respondents' number one concern.

A second question that elicited much interest concerned non-medical switching. Almost 86 percent of the people said that their medicine should not be switched for non-medical reasons. This type of switching has been one of the common themes we've heard from this podium. It is a complicated but very important consideration.

To 86 percent of the mature Americans that answer our survey, changing a medicine that was working seems absurd. Anybody with any commonsense wouldn't do it, yet many stakeholders here today feel that it will, or has already begun to become a reality, with good reason.

You may not see how this type of switching is affected by your decisions or how it is something you have any control over. I think your decisions here, and the decisions of the FDA, do

have an effect on non-medical switching. The requirement for all or nothing voting on indication mask the reservations you have voiced here concerning some indications.

Labeling considerations that don't reflect which indications were tested and which sued extrapolated data, hide critical information. Even FDA's unexplained regression to favoring a non-meaningful suffix in a name hides important manufacturer information.

All of these decisions make it easier for payers and PBMs to create formularies and guidance that promote non-medical switching. They even keep important information from doctors as they evaluate what's best for their patients.

A patient responding to our survey told us, quote, "My RA has not progressed in any damaging manner. In fact, it improved the first few years and then stabilized. I use the biologic Enbrel, and I don't want any change." Close quote.

I wrestled with a decision to use this particular comment for obvious reasons, but the

fact of the matter is, this is an honest response to a serious question. It is also a fact that it's always been RetireSafe's position that non-medical switching is not acceptable, and it doesn't matter whether it is to or from an innovator biologic, a biosimilar, or a small molecule drug.

I am encouraged by your desire to broaden the scope of discussion at these advisory meetings to deal with some of these important issues. The promise of biosimilars won't be realized if we keep blinders on. We can't be afraid of being spooked by something in our peripheral vision. That something may be the very thing that causes us to fail or succeed, and shouldn't be ignored.

Once again, I'll end by saying that Americans trust the FDA. Dr. Woodcock said that the safety would not be sacrificed when it comes to biosimilars. I continue to take her at her word. As a voice for the people you protect, we ask that you work to broaden the discussion, realize the breadth of impact your decisions have, and maybe listen a little more closely to the stakeholders.

To do otherwise would undermine the trust Americans have in the FDA. Thank you.

DR. SOLOMON: Thank you. Will speaker number 11 step to the podium and introduce yourself? Please state your name and any organization you represent for the record.

MR. SPIEGEL: Good afternoon again, Andrew Spiegel. This time I'm reading the comments for Katherine Arntsen, also a member of the Alliance for Safe Biologic Medicines. And I promise this is the last speech I will do today. Katherine did testify yesterday, you may recall. But she had to leave town, and so I will read her comments today.

"I am here as a leader, advocate, and patient who lives with multiple autoimmune diseases, take over 40 drugs a day, and has unique sensitivities to both active and inactive ingredients in drugs. Please understand no one-size-fits-all products exist for complex patients like me. Our immune 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 have the norm and who are labeled outliers by their treating physicians.

Patients like me are so hyper sensitive that even the slightest change in manufacturing, dose, or method of delivery can provoke immunogenicity and disease complication. Sufficient proof of clinical efficacy, safety and 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 a biologic reference product. Therefore, we support a policy requiring rigorous criteria that includes non-clinical 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 timelessness in addressing adverse events.

"We ask you to evaluate this biosimilar through real-world, post-market surveillance to maintain efficacy and patient safety. Pharmacovigilance is essential as these treatments may produce immunogenic responses in patients who may also be hypersensitive to changes in product, methods, or impurities.

"We commend the FDA for addressing immunogenicity in the draft guidance, but ask that final guidance include requirements that biosimilar labels specify which indications were approved based on extrapolation of data rather than clinical testing, pertinent clinical data and adverse events specific to the biosimilar, and a statement declaring whether or not the product has been approved as interchangeable. This information is

necessary for patients and prescribers to make fully informed choice.

"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.

As an individual who was harmed by the egregious payer utilization management practice, step therapy, and am now blind in my right eye, I am extremely concerned that patients who are stable on a biologic will be switched for a non-medical reason 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 plans, 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 that they will apply step-therapy protocol to ensure patients are pushed into the preferred drug, and they expect nominal use of grandfathering, which means that patients currently successfully managing their diseases will be forced to switch therapies to appease cost control measures.

"We cannot emphasize 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, and should only be determined by the treating provider and the patient.

"Biologic medicines are prescribed to individuals with serious life-threatening diseases, and therefore the potential for immune responses and serious adverse effects is heightened

exponentially in these vulnerable patient populations. Thank you for the opportunity to share my perspective and for recognizing the importance of the patient voice during the drug review process."

DR. SOLOMON: Thank you. Will speaker number 12 step to the podium and introduce yourself? Please state your name and any organization that you represent for the record.

MS. BOYLE: Hi. My name is Alison Boyle. I have no financial relationships to disclose. I've had systemic juvenile idiopathic arthritis since I was 5 years old. By looking at me, you probably wouldn't know that I have a disease that three rheumatologists have described as the most vicious they've ever seen.

I walked into this hearing without the help of an assistive device, such as a cane or wheelchair. I work as a healthcare consultant and travel across the country each week for work. I can walk, run, climb, open jars, and take spin classes. When you look at my x-rays, there are no

signs of progressive joint damage. There's one reason I am able to live a full and active life, and that is because of biologic medications.

I grew up during an interesting time for the field of rheumatic disease, as well as medicine in general. Biologic medications were first being approved in the United States. For example, Enbrel was first approved when I was 9 years old in 1998. Before biologic medications, people with juvenile arthritis almost always developed severe joint damage that severely limited the use of their hands and their mobility.

It took a long time to find the right biologic to treat my arthritis. In the times when my arthritis was uncontrolled, I had joint pain and stiffness, swelling, sore throats, nausea, fevers as high as 105 degrees. My disease also has muscle involvement, and my muscles were frequently so weak that I couldn't even walk to the bathroom. This muscle weakness affected my chest muscles, and I was hospitalized several times because my muscles were so weak that I couldn't breathe.

Given the high burden of this disease and the potential for correct biologic medications to prevent this pain and suffering, we should seek to ensure that individuals who need these medications are able to access them.

Unfortunately, biologic medications are currently extremely expensive. This cost often makes procuring these medications prohibitively or debilitatingly expensive. For a person without insurance, a single dose of biologic medication could cost more than $1000. Even with insurance, copayments are often hundreds of dollars.

No parent should be forced to choose between paying bills and paying for their child's medication. And no family should be forced to make these types of tradeoffs simply because their child was born with a disability. Even with the insurance I get through my company, I still hit my out-of-pocket maximum of $2000 quickly every single year. Ask yourself, is that fair?

The approval of biosimilar medications will provide a more affordable alternative for patients

so that they don't have to make these impossible tradeoffs. We already have proof that this will happen. In the United Kingdom, the approval of biosimilar medications has led to increased access to colony-stimulating drugs for cancer patients.

One argument brought up against biosimilar medications is that their approval will stifle innovation because drug manufacturers will have no incentive to create new medications. I believe the choice between access and competition in this instance is a false dichotomy.

First, if drug patents are unlimited and biosimilars are not allowed, then drug companies will have very little competition. Biosimilars introduce additional competitive products into the market. When faced with competition, drug companies will have to produce additional products to stay relevant.

This is especially important for arthritis since there are over 500 different types of rheumatic disease. For example, I have systemic idiopathic arthritis, which causes fevers, rash,

and muscle and organ involvement. This is different from psoriatic arthritis, which causes psoriasis in addition to joint pain or ankylosing spondylitis, which causes degeneration of the back. The more competition there is, the more drug companies will look to provide targeted therapies for different types of rheumatic disease.

Of course, as a patient, it's absolutely critical to me that biologics are safe and effective. Fortunately, the process for creating and testing biosimilars has been extremely stringent. Biologic drugs are made up of large and complex molecules, however in order to create a biosimilar, drug companies analyze the biologic drug in detail and develop a highly similar product.

After this development, drug companies will be required to perform stringent data analysis, and possibly conduct clinical trials to prove that their product is so similar to the original biologic medication that there are no statistically significant differences in ability to treat the

targeted disease.

Of course there is some uncertainty, and one of the previous speakers spoke about how patients have fear about these biologic medications, and that's certainly true. However, that uncertainty exists in the status quo as many of us feel uncertain about the long-term outcomes of the biologic medications we take right now. However, they have the potential to improve the quality of life of individuals so much that increasing access is absolutely paramount.

In addition, I feel it's important to closely monitor outcomes, do post-market surveillance, and track these outcomes closely so that we can understand the impact of these biosimilars on patients.

Juvenile arthritis has historically not gotten a lot of public attention in this country, and few realize the emotional, physical, and financial toll this disease has on families in the United States. It's the number one cause, arthritis is, the number one cause of disability in

the U.S., and more than 300,000 children are affected with a form of the disease.

You have an opportunity to expand access to critical medications for these children and families while ensuring safe implementation of these drugs. Your actions can prevent pain and suffering and financial hardship for families, and will lead to more innovation in this critical area. It is for these reasons that I urge you to approve this biosimilar for Enbrel, and sincerely thank you for considering the patient's perspective.

DR. SOLOMON: Thank you. Will speaker number 13 step to the podium and introduce yourself? Please state your name and any organization that you represent for the record.

MS. SIMMON: Thank you. Hi. 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 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 toward the creation of a regulatory framework that maximizes patient access to these medicines. And we thank this committee in particular for yesterday's and today's meetings, and the opportunity to provide comments.

The Biosimilars Council is a division of GPhA, and it 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 biosimilar products with the intent to compete in the U.S. market.

Education is really our core mission, and we could not agree more with those on this committee who have identified education around biosimilars as an ongoing and critical need. The Council is activity engaged on this front, and we stand ready to work with the agency and other stakeholders as we continue these efforts.

To that end, the Council recognizes that

development, production, and approval of biosimilars 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 biologics 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 FDA 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 product risks undermining the important provider education that is already being done by 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 turning around and requiring a differentiator in the labeling, sends mixed signals to providers responsible for establishing patient familiarity and comfort with these products.

As with our position supporting non-unique naming, we believe that policies that needlessly differentiate between biosimilars and their reference products not only create barriers to

provider and patient confidence and use, but also make the education efforts that we all clearly favor, and many here have spoken about, that much more challenging and confusing for those very audiences.

We encourage the agency to develop regulatory policy that supports education around biosimilars, rather than sow the seeds of confusion. Thank you again for the opportunity to speak today.

DR. SOLOMON: Thank you. Will speaker number 14 step up the podium and introduce yourself? Please state your name and any organization that you represent for the record.

MS. SCHAEFER: First, I want to thank the FDA for giving me this opportunity to speak regarding the challenges with patient access to biologic treatments. My name is Christine Schaefer. I have two potential conflicts of interest. In the past two years, I've been a paid consultant for Eli Lilly and Novartis. For both companies I participated in roundtable discussions

about access issues with other patient care coordinators.

I've been employed by Central Dermatology in St. Louis for 15 years as a biologic coordinator involved with over 1200 patients who receive biologics. The scope of my job includes dealing with prior authorizations, coordinating with appeal letters, teaching patients how to gain and maintain access to biologic therapy, explaining to patients insurance, copayment, deductibles, coinsurance, out-of-pocket max, and specialty pharmacies. Also a big part of my job is solving problems caused when so many companies and people are involved, the nurses, medical assistant, patient care coordinators, and the doctor all involved in this effort.

As we know, biologic drugs are very expensive, and this creates a huge access problem. Not one of our non-insured patients have ever paid for a biologic out of pocket. Only one patient has paid through her portion of Medicare Part D. Good commercial insurance is a necessity. Indigent care

programs exist, but they run out of funding very early on.

Commonly harmed are the many patients who are underinsured. A typical problem is someone who makes too much money to qualify for an indigent assistance, but whose insurance is inadequate.

There are patient assistance programs that are very unique for each drug. They are complicated and confusing. Additional information is always required. This includes W2 forms, pay check stubs, and tax returns. Most patients are unaware of the assistance programs.

Due to HIPAA, we are the ones to introduce the patients to the assistance programs. As a consequence, many patients think our office runs these assistance programs, that we are the ones who approve or deny their assistance. Sometimes we get blamed for problems caused by others, like lack of paperwork being completed, or faxes not being received.

In my meetings with Novartis and Eli Lilly, I have learned that many physician offices choose

to limit their involvement. In my opinion, very few patients can navigate this process without help. Both patient and doctors are forced to deal with step edits that are predetermined sequences of treatments. Usually that means older, cheaper, before newer, more costly. This might include methotrexate before being able to use Humira, Stelara to finally get to Cosentyx or Taltz. The same with the Otezla to Humira to Cosentyx.

Step edits are unique for each insurance carrier, and they can change annually. They also change in midstream. For example, if the patient changes his or her insurance, or changes jobs. This is very frustrating there is no coordination between payers.

Medicare patients have limited income and limited options. Co-pay cards are not allowed. I've been told that Medicare patients are disallowed for this because it can look like an incentive to that biologic, but I'm not an expert in that area.

Senior citizens and the disabled have

severely restricted options, Part B for Medicare, 80-percent of allowed charges are covered. Most Midwest, where they're responsible for the 20-percent. And most Midwest patients cannot afford that. Good commercial coinsurance is almost always required.

Part D is unaffordable for the average Midwest patient. Out-of-pocket expenses will exceed over $7000 a year because that includes the initial coverage, the donut hole, the catastrophic event. These coverage reoccur annually. Bottom line, Medicare coverage is inadequate.

In concluding, psoriasis is a chronic, life ruining disease on full display. There is no question that the biologic drugs have dramatically changed the lives of many psoriatics. Access is limited by cost, complexity, and the unwillingness of offices to properly staff for this activity.

Our first biologic was in 2002. Since then, the process has become increasingly complicated and expensive. I urge the committee to consider any safe strategy that stabilizes cost, increases

access, and allows us to concentrate on patient care. Thank you.

DR. SOLOMON: Thank you. Will speaker number 15 step to the podium and introduce yourself? Please state your name and any organization that you represent for the record.

MR. BANFIELD: Good afternoon. My name is Matt Banfield, and I'm speaking on behalf of the Biosimilars Forum. The Forum appreciates the opportunity to comment at today's FDA public meeting of the Arthritis Advisory Committee. Education of the advisory committee about the science of biosimilars is critical.

The Biosimilars Forum is a non-profit organization whose mission is to advance biosimilars in the United States with the intent of expanding access and availability of biological medicines and improving healthcare. It is comprised of manufacturers and other organizations that work on a consensus basis to develop policy positions to ensure the U.S. has a competitive, safe, and sustainable biosimilar market, providing

more options to patients and physicians.

The Forum's mission includes providing evidence-based information to inform and support public policies that encourage access, awareness, and adoption of biosimilars. The founding members of the Forum represent the majority of companies with the most significant U.S. biosimilars development portfolios. Based on the most recent publicly available data, about 70 percent of the proposed biosimilar products currently advancing with the FDA are sponsored by members of the Forum.

The introduction of biosimilars in the U.S. can help expand access to high-quality treatment options for clinicians and patients, as well as reduce the cost to families, caregivers, payers, and the healthcare system. To fulfill this promise, policy makers and stakeholders must work together.

Members of the Forum recognize that there is a need for a sustained and unbiased biosimilars education and advocacy program in the U.S. That's why since its inception, the Forum has worked

collaboratively with FDA on policy issues, as well as designing mechanisms to educate physicians and the patients about the science behind biosimilars.

In addition, policies that support biosimilar development and use are critical. This includes reimbursing policies that establish separate payment and coding for each biosimilar, as well as an efficient and rigorous regulatory pathway to approval that ensures safe and effective products reach patients as soon as possible. Adequate resources for FDA are also essential.

We anticipate more biosimilars coming to market in 2016 and beyond. We appreciate that FDA has worked hard to implement a new abbreviated licensure pathway, taking steps that include issuing multiple guidances on biosimilars, and we expect more in the coming weeks and months.

The Forum looks forward to a continued collaborative and excellent working relationship with the agency. We encourage the agency to continue to work with industry as this field advances in the days ahead. Thank you.

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 for the record.

MS. McCASLIN: Hi. My name is Tiffany McCaslin, and I am here representing the National Business Group on Health. I have no financial disclosures to make. And for those who were here yesterday, I apologize in advance for the duplicative nature of my comments, as they are consistent.

The National Business Group on Health represents approximately 425 primarily large employers, including 72 of the Fortune 100. These employers voluntary provide group health plan coverage and other health programs to over 55 million Americans who are employees, retirees, as well as 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 medicines, and we believe competition among biosimilars may be able to do the same as biosimilars competing for market share with each other 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 a referenced product, and we believe the FDA has put in place the appropriate patient safeguards to permit data extrapolation to inform biosimilar use.

On this point, we would encourage the agency

to engage in more stakeholder outreach to better communicate to patients and consumers around the safety considerations that are undertaken during biosimilar development. Yesterday and today's hearings have underscored the lack of information available on this point, and we feel it is critically important to close this information gap.

Again, we thank the committee for holding this important meeting today, as well as yesterday's, as well as all of those at FDA, CDER, OND, and other sister agencies. We recognize the significant challenges associated with your work, and appreciate your continued commitment to a clear pathway by which manufacturers may bring biosimilars to market.

Additionally, we thank the sponsor here today, as well as the sponsor yesterday, for your commitment to innovating in the biosimilar space, which we hope will lead to lower prices and increased access to both life-improving and life-saving medicines for patients, payers, public programs, and other consumers. Thank you very

much.

DR. SOLOMON: Thank you. I think I speak on behalf of the committee saying that we appreciate the public comments that were made.

The open public hearing portion of the meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Dr. Nikolov will now present the charge to the committee.

Charge to the Committee - Nikolay Nikolov

DR. NIKOLOV: Thank you, Dr. Solomon.

Good afternoon. As we prepare for the committee discussion and voting this afternoon, I want to provide a brief reminder of the issues, the regulatory framework and underlying decision making for 351(k) marketing applications for proposed biosimilar products and the questions to be discussed and voted upon.

As discussed earlier, 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 products and the reference products 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.

We acknowledge the open public hearing comments, which not surprisingly are very consistent with the sentiments and comments provided yesterday. However, we would like the committee to focus on the data presented and the

questions posed for the discussion and voting.

The issues that we would like the committee to discuss are whether based on the totality of the evidence, the applicant provided adequate data to support the demonstration that GP2015 is highly similar to the US-licensed Enbrel with respect to the primary, secondary, and higher order structures, post translational profile and in vitro functional characteristics, purity stability and potency, including TNF binding and neutralization; also whether the clinical data submitted supports the demonstration that no clinically meaningful differences exist between GP2015 and US-licensed Enbrel; and also whether the applicant provided sufficient scientific justification to support that there are no clinically meaningful differences for the additional indications sought for licensure.

Consistent with these considerations, the first question to the committee is to discuss the adequacy of the analytical data to support a demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor

differences in clinically inactive components.

Then the committee will be asked to discuss the adequacy of the data to support the demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied condition of use, plaque psoriasis.

The last discussion question is whether the applicant provided sufficient scientific justification to support that there are no clinically meaningful differences for the additional indications sought for licensure. These include rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis.

The FDA is also requesting the committee's discussion on concerns with extrapolation to specific indications, and what additional information would be needed to support this extrapolation.

The last question is a voting question on the committee's recommendation, whether based on

the totality of the evidence GP2015 should receive licensure as a biosimilar product to US-licensed Enbrel for the indications for which the U.S. Enbrel is currently licensed and Sandoz is seeking licensure. These includes rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. The voting will be followed up by discussion on the reasons for your vote.

As a reminder, similar to yesterday's approach to the question, that would be one question on all the indications, not separate by indication. With this, I thank you, and I will turn the podium back to Dr. Solomon.

Questions to the Committee and Discussion

DR. SOLOMON: Thank you. So let me read the first discussion question and make sure everybody understands what we're being asked to focus on. First, question number 1 is to please discuss whether the evidence from analytical studies supports a demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding

minor differences in clinically inactive components.

Are there any questions about the question? Any comments about the question before we open it up for discussion?

(No response.)

DR. SOLOMON: Okay. So this is really about the analytics, and I think there were some issues raised this morning around some of the analytics, which we might want to revisit now in this forum, issues around the assays, issues around the disulfide bonds, other issues. Would anyone -- Dr. Siegel?

DR. SIEGEL: I thought we had a good discussion of the disulfide bond issue. There's still some unknowns in terms of I think assays weren't done post administration to find out what happens. But I think I'm satisfied that the analytical to efficacy issues, in vitro efficacy issues, were dealt with.

DR. SOLOMON: Dr. Hancock?

DR. HANCOCK: William Hancock. As we

discussed this morning, this is a very complex molecule. We had a comprehensive analytical program, provide good I think characterization information. I think moving forward, it would be good to have, again, a discriminating quality control program just to make sure that over the years, the product stays within specifications, because it is a very complex molecule.

DR. SOLOMON: Thank you.

DR. KOZLOWSKI: Steve Kozlowski, FDA. So the data that's presented at these meetings are sort of the analytical comparison. There is a whole part of the review of the application about the manufacturing process. There are a separate set of specifications. There's process validation.

So this represents an exercise to show similarity from the material that was manufactured to the reference product, but this is not the sum of the quality control. There is far more that goes on to assure long-term batch to batch that the product is controlled and reproducible.

DR. SOLOMON: Thank you. Dr. Ye?

DR. YE: I want to follow up around disulfide bonding misfolded protein issue we discussed this morning, because I do appreciate that the company's comments on that, the reference product has more misfolded forms, which seems to correlate with the lower efficacy there.

But nonetheless, there is still 10 percent or more or less misfolded products demonstrated by this reverse hydrophilicity chromatography analysis. And the question here is whether a long-term administration of a product into patients with that kind of misfolded protein is going to have any adverse effects in disease situations that has not been tested. Should that be a concern for this committee?

DR. SOLOMON: When you say long-term implications, can you be more explicit?

DR. YE: I would assume this is a chronic disease that will require patients to take the medicines repetitively over months or years. And at the moment, there is really no very good understanding of the impact of misfolded proteins,

in particular when it applies to patients in the extracellular manner and how would that impact patients health.

Just taking, for example, the neurogenic disease area, it has been known that some neurogenic diseases are actually affected because misfolded proteins are secreted and propagated from cell to cells such as the prion disease, et cetera. And a particular case here, apparently it's really not clear what exactly misfolded proteins they have in the products represented; are there going to be any toxic or toxicity effects there or not?

Because we really don't have a very good technology at the moment to really compare the precise misfolded proteins from, say, the reference products to the GP2015, for example, in that regard I think there's a gap there as to if we want to extrapolate the applications into other diseases, I think it should be more cautious with that.

DR. SOLOMON: A follow-up question. The 10 percent misfolding is true also for the reference product. Is there --

DR. YE: The reference product has more than that. It's like 16 something, if I remember correctly.

DR. SOLOMON: Okay. But we do have long-term data on the reference product.

DR. YE: Well the reference product has been used in all those diseases, right. It has been tested for each of the cases. Whereas the company, Sandoz, is trying to extrapolate the application based on testing in one clinical situation, and they want to extrapolate that into other situations where they haven't tested that. They don't have data on that.

DR. KOZLOWSKI: Steve Kozlowski, FDA. So again, as was mentioned by the chair, there is a long history, and you saw many years and many lots that were analyzed by Sandoz showing that in fact there was a misfolded protein similar in many ways, including the analyses like T7 peptides and other ways. So it's not just they share the name misfolded. They're misfolded in similar ways, maybe not exactly the same.

Enbrel has been used in all those indications for many, many years. So I think, again, that you'd have to really say that this misfolding is different in some fundamental way that would in fact only show up in an indication that wasn't studied. And that seems unlikely in the scheme of things.

I understand the point that maybe this is misfolded a little differently than that, even though there is less, and that might be disease specific. But that seems very unlikely to sort of be misfolded in a different way that wasn't detected by all these assays, and then that would only play out in other indications.

DR. SOLOMON: Dr. Aronson? Or Diane, sorry.

MS. ARONSON: It's okay. I appreciated the public testimony and heard some themes that some are outside of our purview: labeling, naming. But one issue that may or may not, I'd like to hear a little bit more from the FDA, is the term "highly similar" in relationship to interchangeability.

I think it was Dr. Christl that mentioned

that the agency would be working on that terminology, and it seems to be a theme. What's the process, or did you say this year, so the end of this year or within a year, or just because it seems so critical?

DR. CHRISTL: Right. In terms of sort of clarifying around the terminology that you just used, highly similar is a part of a definition of biosimilarity, and biosimilarity is a part of the definition for interchangeability. So interchangeability is an additional standard that encompasses biosimilarity and has additional factors that need to be considered, including the concept or the impact of switching or alternating between the products.

Again, interchangeability guidance demonstrating interchangeability is on FDA's guidance agenda for this calendar year. I can't give a timeframe because we have a very complicated, multilevel clearance process. And once it leaves the agency, we don't really have that much control over the review timing of any

guidance that we would issue. But we're certainly very actively working on it as an agency and within HHS. And we know that this is a priority, and we are very determined to get this out. We know how important it is.

DR. SOLOMON: Thank you. There was some discussion this morning between the results on study 101 and 104. I don't know if we want to go back and revisit any of those issues or if people feel like we -- there was a change in the reference material over time, and it created some uncertainties. I don't know if people feel like we've satisfied those questions. Don Mager?

DR. MAGER: Hi. Don Mager. Yes, I think that the comments from the applicant, as well as the FDA, addressed that very nicely. And I think the clinical pharmacokinetic component of this served to bridge both the reference product in both the EU and the U.S. So I feel pretty comfortable with that.

DR. SOLOMON: Okay.

DR. MAGER: I would like just to make a

comment. As I said yesterday, I think a pharmacodynamic biomarker would have been very useful in this case. When you have targeting an endogenous circulating substance, it would pretty much alleviate any concerns one might have with in vitro activity studies if you can show that you've similarly suppressed TNF alpha either through the assay for free, which can be more difficult. But in particular total ligand could be measured and shown very clearly that you have the same activity.

Is it required or essential? Absolutely not. But in this case, it could have been useful to have a pharmacodynamic marker. But otherwise -- and of course, you have the clinical studies that sort of trump that. You have efficacy. You have the adverse events, immunogenicity, all of that has been covered. So I don't consider that an issue in this case. But again, a pharmacodynamic marker would have served to address any uncertainty left with the bioassays.

DR. SOLOMON: Okay. Any other issues,

discussion on this question, the analytical studies?

(No response.)

DR. SOLOMON: If there's no more comments, let me try to summarize. On this specific question, Dr. Siegel commented that the in vitro assays, while not perfect, were satisfactory. Dr. Hancock appreciated the complexity of the molecule and the excellent data that were presented, and stressed the importance of a quality control program. And Dr. Kozlowski reassured the committee that a lot of those data were available but hadn't been presented to the committee.

Dr. Ye talked about the misfolding and wondered about the long-term implications of the misfolding. Dr. Kozlowski talked a little bit about the fact that there's misfolding likely, or we know in the reference product, and that Enbrel has been used for years across all the indications being sought.

Diane Aronson talked about the questions around interchangeability. And Dr. Christl

recognized that sometimes these guidances get out of the realm of the agency, and we're all going to wait patiently before we hear about the interchangeability guidance. And Dr. Mager talked about the importance of pharmacodynamic biomarkers going forward.

Other comments before we move on?

(No response.)

DR. SOLOMON: Okay. Why don't we move to the next question, so question 2. I'm going to read it for the record, make sure everyone understands it.

Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied conditions of use, plaque psoriasis.

Again, here we're really talking about the clinical data that were presented, not necessarily the analytic data. There was some discussion, Dr. Scher and others, about the differences in response rate that were notable. I don't know if

people want to go there, or if people feel like there some -- okay, Dr. Brittain?

DR. BRITTAIN: Yes, in terms of the question, the results for the single clinical trial were good. I thought the switch design was helpful, and the low missing data rate was also appreciated. With respect to the topic you just raised, the fact that the success rate differed from the two historic placebo-controlled trials does add some concern about the interpretation because at some level, we want to know how the placebo group would have done in this study, and you never know. But in this case, because the rates are different in this study than the historic study, we have even more uncertainty.

So it's a little harder to interpret than it would have been, however, and I think this is the important thing, I still feel quite confident that the great majority, or certainly the majority of the treatment benefit has been retained, and perhaps the great majority.

DR. SOLOMON: Dr. Reimold?

DR. REIMOLD: Andreas Reimold. I just wanted to add to that, then. Even if the effectiveness isn't totally as expected, whether it's a little better or even a little worse, we're reassured that the safety is there. And clinically, we can deal with the appropriate level of effectiveness by using or not using the drug.

DR. SOLOMON: Dr. Margolis?

DR. MARGOLIS: I just have a comment, and I should have mentioned this yesterday, too. I still don't understand why the question says US-licensed Enbrel when it was bridged to the European. Why can't there just be transparency and say that the study compared EU, or EMA that was bridged to the US-licensed Enbrel? And that would have been true yesterday as well. I mean, it's sort of a misrepresentation, and certainly if this were in a journal, it would get changed.

DR. NIKOLOV: I will try to clarify this. This was certainly intentional and not in error. I think the statute requires that the biosimilar is biosimilar to a referenced product, which means no

clinically meaningful differences to the reference product. I think this statement is predicated on the fact that there is already an analytical and PK bridge between the EU and U.S. product, so we can rely on the data generated by the EU product to make this conclusion.

DR. MARGOLIS: But it's still not transparent, and you could still say as bridged to the U.S. product. It's just misleading, right? And for somebody who wasn't at this meeting, or somebody who didn't see all the results, all they see is this discussion, they're going to assume -- just like yesterday, it's not any different. They're going to assume that it was the U.S. product, but it wasn't.

DR. NIKOLOV: We understand this, and this is the reason we emphasized so much the additional data that allowed us to make this bridge. Again, in the interest of transparency, this was an intentional phrasing of the question. And I want to make clear the study was done with the European Union-approved Enbrel. Again, we have sufficient

data to rely on those data to make this conclusion or to ask the committee to comment on that.

DR. SOLOMON: Does the applicant want to make any comments about these issues, because we've been having some comments that they may have some --

(No response.)

DR. SOLOMON: No? Okay. Other comments about this question in hand, the clinically meaningful, no clinically meaningful difference? Do we feel like the clinical data that the committee's been presented gives us confidence and this question?

(No response.)

DR. SOLOMON: Other issues. Okay. Well, if there are none, I'm going to summarize. But I don't mean to close the conversation. If people have any other comments, feel free.

So just to summarize. Dr. Brittain commented on the low missing data rate as being a very -- a marker of a high integrity study. There was a high response rate, which is concerning, but

we've discussed this issue, similar response rates in both arms. And I think we've heard comment on that.

Dr. Reimold focused us on the safety and the equal safety is reassuring, and the immunogenicity as well. Dr. Margolis asked the question about why it's phrased this way. I think we heard from Dr. Nikolov that that's part of the agency's purview to focus on US-licensed products. So that's what we're heard.

Other comments on the clinical differences before we move on?

(No response.)

DR. SOLOMON: Okay. We'll go to question 3. Please discuss whether the totality of the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel for the following additional indications for which US-licensed Enbrel is licensed: rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis. 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. Dr. Waldman?

DR. WALDMAN: Let me try a straw man.

(Laughter.)

DR. WALDMAN: These molecules are highly similar analytically. They perform highly similarly in clinical trials. The molecules have the same mechanism of action. They bind TNF alpha the same. And all of these indications are TNF alpha mediated. The mechanism of action is the same; they're all TNF alpha mediated.

So given the substantial data that we've heard, the highly similar nature of the molecules analytically and their clinical performance, it seems to me, based on the similarity, the identical mechanism of action, that extrapolation would be reasonable.

(Laughter.)

DR. WALDMAN: I just want to see if you kill this one also.

(Laughter.)

DR. SOLOMON: Thank you. I think the straw man might survive. Dr. Miller?

DR. MILLER: I will agree with you this time.

(Laughter.)

DR. MILLER: Don Miller. I want to thank the FDA for educating us about the extrapolation really being between products, not two different indications so much. You have really convinced me. And for the public people here, I want to say I'm totally confident in the extrapolation to all the indications.

DR. SOLOMON: Dr. Becker?

DR. BECKER: Mara Becker. Being that I'm one of the representatives of the smaller sized patient population, let me say for the record I hope you reconsider maybe marking up those 25 milligram vials so we can use them until you're done creating the formulation that allows us to use smaller doses.

That being said, I completely agree with

Dr. Miller that the reality is that the data presented today, it's convincing that this application is similar enough to etanercept that I would feel comfortable using it in the children that I treat. However, at this time, I cannot because there are plenty of kids less than 20 kilos that we might need to use this on.

So with an indication for JIA down to the age of two, you're limiting some patient accessibility with the current formulations.

DR. NIKOLOV: This is Nikolay Nikolov. If I can respond to this. Actually, FDA requires that sponsors, not only of biosimilars but of biological products, develop age-appropriate formulations or presentations. In the case if they are not submitted in the original application, the FDA still requires that these are developed. So that's under the authority of the PREA, which is Pediatric Research Equity Act.

DR. BECKER: Thank you.

DR. SOLOMON: Dr. Horonjeff, and then Dr. Spiegel.

DR. HORONJEFF: Just in terms of the packaging, I do want to state that I appreciate that the sponsor talked about how you involve patients in your design and development. So I think that's really wonderful, and I look to see that in the formulations for the pediatric version.

DR. SOLOMON: Dr. Siegel?

DR. SIEGEL: I agree with your straw man today as well. I think the situation from a TNF biology point of view is very different than yesterday, where we had to have a mechanism of action that was not tested. The Fc-dependent mechanism of action here, we're not really having to deal with that. So I feel more comfortable, even though I'm on the receiving end as a rheumatologist, thinking about approving indications for which they weren't tested, unlike yesterday with the GI situation.

I want to thank the FDA. And also, particularly, I thought the slide from the sponsor about extrapolating based on the molecule not the clinical indication, helps. Certainly all

indications -- all drugs that work for psoriasis don't work for RA, but in the TNF sphere they do. Just I thought some of the comments were a little imprecise. And I want to clarify that there are certainly lots of biologics that work in psoriasis that are less effective. But in the TNF area, I would agree.

DR. SOLOMON: Dr. Mager?

DR. MAGER: Yes, I am also very happy to agree today, this time, to the straw man. But I would go one step further, and I think that it goes even beyond when you have a clear mechanism of action. I think there are going to be compounds brought forward in the future that may not necessarily have the clear mechanism, or maybe not completely understood. But when you have something that's highly similar in exposure, highly similar in molecular properties, and also have no clinically meaningful differences, then I think then extrapolation is scientifically sound, as has been put forward by the FDA.

DR. SOLOMON: Good. Well, I would concur

with what's been said. I think the straw man seems to have survived.

(Laughter.)

DR. SOLOMON: And I think that the presentation by the applicant in light of the presentation yesterday was very helpful to kind of hear your thoughts about the differences and how to contextualize what we heard today. And I think that the FDA has done a really excellent job educating the panel about what the questions at hand are. So I appreciate that.

Other comments before I summarize?

(No response.)

DR. SOLOMON: So again, Dr. Waldman put forth a straw man, which was agreed upon widely. I think Dr. Becker's comment about age-appropriate delivery systems is important, and Dr. Nikolov assured us that that's an FDA mandate.

Dr. Horonjeff appreciated the patient focus of the data. And Dr. Siegel made some important clarifying comments about the mechanism and why TNF is important here in the extrapolation to other

conditions.

Other comments before we move on? We could move on to the voting question.

The question that we'll vote on today, question 4, does the totality of the evidence support licensure of GP2015 as a biosimilar to US-licensed Enbrel for the following indications for which US-licensed Enbrel is currently licensed, and for which Sandoz is seeking licensure -- that's actually a tongue twister I think -- RA, JIA, AS, psoriatic arthritis, and psoriasis? Please explain the reason for your vote.

Let me read what I have to read here. We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing, and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote, or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the

vote will be locked in. The vote will then be displayed on the screen. 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.

If there are no questions or comments, we'll now begin the voting process. And please press the button on your microphone that corresponds to your vote. And you'll have approximately 20 seconds to vote.

(Pause.)

DR. SOLOMON: Everyone has now voted three times.

(Laughter.)

DR. SOLOMON: The vote is now complete. Now that the vote is complete -- oh, sorry.

DR. CHOI: For the record, we have 20 yes, zero no, zero abstentions.

DR. SOLOMON: Now that the vote is complete, we will go around the table and have everyone who

voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

Why don't we start with Dr. Siegel?

DR. SIEGEL: Sure. I voted yes. I thought it was a very well presented, clearly presented case, both by the sponsor and the FDA. And I hope the marketplace will validate the hope of the sponsor that this will increase access and decrease price.

DR. YE: My name is Yihong Ye, and I vote yes. And although I initially had some concern about the presence of the misfolded species in the GP2015, given the robust data of the efficacy and also the demonstration of mechanism, I think I agree with Steve that it's less likely that this -- and also the misfolded species being present in the reference product, and this probably is going to be safe to put in patients with the disease.

DR. SHILOACH: Joseph Shiloach. I vote yes. It was a convincing case. Thanks.

DR. BERGFELD: Wilma Bergfeld. I voted yes. I was very impressed with the completeness of the presentation and the responses of FDA and the sponsor. So thank you.

DR. ROBINSON: June Robinson. I voted yes.

DR. MARGOLIS: David Margolis. I voted yes. But to be consistent with my comments from yesterday, I would still encourage post-marketing studies to demonstrate that extrapolation was correct and the overall safety of the products long term.

MS. ARONSON: Diane Aronson. I voted yes. I thought that the analytical evaluation showed that the biosimilar was highly similar. The clinical data showed no meaningful differences, and extrapolation was indicated.

DR. HORONJEFF: Jenn Horonjeff, and I voted yes as well. I thought today was a much easier decision for me to think about the extrapolation to this group of diseases that we're evaluating. And I will just note before we go that my feeling as a consumer is that we've been sitting around here for

the past two days as scientists talking about this, but when we leave here and go back into the real world, the clinicians among us work less like scientists sometimes and more like artists with their patients and their treatment.

My concern being that if the physicians are trying to work with their patient while painting their Mona Lisa, that the payers may not understand what we're thinking here, and may take away their paint set and give them a box of crayons instead. So I look forward to the FDA working to put out a position statement about how we deal with biosimilars so not only I can feel comfortable as a consumer, but the public as well.

DR. OLIVER: Alyce Oliver. I voted yes. I thought the data package by the sponsor and the FDA was very complete.

DR. MILLER: Don Miller. I voted yes. I also thank Sandoz for a very strong package.

DR. BECKER: Mara Becker. I voted yes. I don't have anything to add.

DR. SOLOMON: Dan Solomon. I voted yes. I

think the non-medical switching is a major concern of clinicians and policy makers that we have to have some greater clarification from the agency. If there is some statement to be made, make it soon. I think the post-marketing surveillance issues are going to be critical to understand the validity of the extrapolation.

DR. JONAS: Beth Jonas. I voted yes. I agree that today was a little bit easier than yesterday with respect to extrapolation, but I think we've all learned a lot about this process, so it's been very valuable. And I think Sandoz did an excellent job of educating us also about how to think about these issues, so that was very helpful. And I do think that we need to be very careful going forward in how we look at these drugs, and also how we assess how they do in the market after the approval process.

DR. REIMOLD: Andreas Reimold. I voted yes as well. I thought that it was convincingly shown that the GP2015 is a biosimilar for Enbrel. I think that the label -- going along with the

interchangeable issue, that the label should clearly state that this is a biosimilar, not an interchangeable drug.

DR. SCHER: Jose Scher. I voted yes. I think the analytical data is extremely robust. The clinical data, I voiced my concerns. Just a comment to the FDA for the record. Maybe the way to mitigate uncertainty is to have a placebo arm on these studies. Also for the record, perhaps to have a proportion of the patients participating in these studies to be U.S. patients may help as well with the design. But other than that, I think the sponsor did a good job as well as the FDA.

DR. BILKER: Warren Bilker. I voted yes. I thought that we were presented with very strong evidence of biosimilarity of GP2015. But I, too, would like to strongly encourage active post-marketing surveillance for all of the extrapolated indications.

DR. HANCOCK: William Hancock. I voted yes on the strength of the package. I also appreciated the strategy that set up the whole study, and I

thought the FDA made some very helpful guidance.

DR. BRITTAIN: Erica Brittain. I voted yes, like everybody else. The results in the single clinical trial were reassuring. I'm always going to be uncomfortable with the extrapolating to the indications without clinical data, but this seemed to be the best-case scenario.

I do want to raise a possibility. You know, there's nothing unethical about doing a randomized trial in these other indications later. I don't know who would ever do it, but it could be done.

DR. WALDMAN: Scott Waldman. I voted yes on the robustness of the data package put together by the sponsor. They're to be congratulated. And the clarifying discussion by the FDA, the discussion was wonderful. Thank you very much.

DR. MAGER: Don Mager. I voted yes, also based on the strong packet that was submitted. I'd like to commend the applicant both for their insights, in addition to what's already been mentioned, the insights into the misfolded protein component, but also the unique study design. I

thought that was a real strength of the application. And I again thank the FDA for a very careful and thoughtful review and for their discussion.

DR. SOLOMON: Before we adjourn, are there any further comments from the FDA?

DR. NIKOLOV: Again, this is Nikolay Nikolov. I would really like to thank the committee for again an excellent discussion. I feel that we focused more on the data today compared to yesterday because I guess the educational component of what we tried to convey was well absorbed by the committee, even yesterday.

So we certainly appreciate the comments, and we took notes, and we'll take these into consideration, both from the committee and from the open public hearing speakers.

I would like to thank my team, or our team, for the hard work that they put to prepare for this advisory committee in reviewing these products. Certainly thank the sponsor for a very elegant presentation of not very easy to describe issues.

And certainly, again, commend our advisory committee staff who made these two advisory committees work as smooth as they did. With this, appreciate you being here and hope to see you again.

DR. KOZLOWSKI: One additional comment. All of you are experts in your fields, so as you've been educated about this, it may be useful to think about how you can explain this to your colleagues. Because it takes some thinking about, about changing this. And I think, you know some of you for two days have been learning about this. Slides will be posted. I think you're free to think about how to share this with your colleagues.

Adjournment

DR. SOLOMON: Good. We adjourn. Thank you.

(Whereupon, at 3:09 p.m., the meeting was adjourned.)