FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE (AAC)

Tuesday, February 9, 2016

8:00 a.m. to 5:13 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Stephanie Begansky, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ARTHRITIS ADVISORY COMMITTEE MEMBERS (Voting)

Mara L. Becker, MD, MSCE

Associate Professor of Pediatrics

University of Missouri-Kansas City

Director, Division of Pediatric Rheumatology

Children's Mercy Kansas City

Kansas City, Missouri

Liron Caplan, MD, PhD

(Acting Chairperson)

Associate Professor of Medicine

University of Colorado

Aurora, Colorado

Jeffrey Curtis, MD, MS, MPH

William J. Koopman Endowed Professor in
Rheumatology and Immunology
University of Alabama at Birmingham (UAB)
Division of Clinical Immunology & Rheumatology
Director, UAB Arthritis Clinical Intervention
Program
Co-Director, UAB Center for Education and
Research on Therapeutics (CERTS)
Co-Director, UAB PharmacoEpidemiology and
Economic Research (PEER) Group
Birmingham, Alabama

Jennifer Horonjeff, PhD

(Consumer Representative)
Research Fellow & Patient Advocate
Center for Immune Disease with Onset in Childhood
Division of Rheumatology
Department of Medicine
New York, New York

Beth L. Jonas, MD

Director, Rheumatology Fellowship Training Program

University of North Carolina School of Medicine

Chapel Hill, North Carolina

Donald R. Miller, PharmD, FASHP

Professor of Pharmacy Practice

North Dakota State University

College of Health Professions

Fargo, North Dakota

Veena K. Ranganath, MD, MS

Associate Clinical Professor

Division of Rheumatology

David Geffen School of Medicine at UCLA

Los Angeles, California

Eric J. Tchetgen Tchetgen, BS, PhD

(via phone)

Professor of Biostatistics and Epidemiologic Methods

Harvard TH Chan School of Public Health

Departments of Biostatistics and Epidemiology

Boston, Massachusetts

Therese M. Wolpaw, MD, MHPE

Vice Dean for Educational Affairs

The Pennsylvania State University

College of Medicine

Hershey, Pennsylvania

TEMPORARY MEMBERS (Voting)

Diane Aronson

(Patient Representative)

Naples, Florida

Wilma Bergfeld, MD, FAAD

Professor of Dermatology and Pathology

Senior Dermatologist & Emeritus Director

Dermatopathology

Director, Dermatopathology Fellowship

Departments Of Dermatology and Pathology

Cleveland Clinic

Cleveland, Ohio

Erica Brittain, PhD

Deputy Branch Chief and Mathematical Statistician

Biostatistics Research Branch

National Institute of Allergy and Infectious

Diseases (NIAID), National Institutes of Health

(NIH)

Bethesda, Maryland

Steve Cramer, PhD

William Weightman Walker Professor

Department of Chemical and Biological Engineering

Rensselaer Polytechnic Institute

Troy, New York

Linda Feagins, MD

Associate Professor

Internal Medicine Division of Digestive and

Liver Diseases

University of Texas – Southwestern Medical Center

Director of Inflammatory Bowel Disease Clinic

Veteran Affairs North Texas Health Care System

Dallas, Texas

Ivan Fuss, MD

Staff Clinician

Mucosal Immunity Section

Laboratory of Host Defenses

Division of Intramural Research

NIAID, NIH

Bethesda, Maryland

Jogarao Gobburu, PhD, MBA, FCP

Professor

School of Pharmacy

University of Maryland

Baltimore, Maryland

Eric O. Long, PhD

Chief, Molecular and Cellular Immunology Section

Laboratory of Immunogenetics

Division of Intramural Research

NIAID, NIH

Bethesda, Maryland

Donald E. Mager, PharmD, PhD

Associate Professor of Pharmaceutical Sciences

School of Pharmacy and Pharmaceutical Sciences

University at Buffalo

State University of New York

Buffalo, New York

Mary E. Maloney, MD

(via phone)

Chief, Division of Dermatology

Professor of Medicine

University of Massachusetts Medical School

Worchester, Massachusetts

Antonio R. Moreira, PhD
Vice Provost for Academic Affairs
Professor of Chemical, Biochemical and
Environmental Engineering
University of Maryland, Baltimore County
Baltimore, Maryland

John E. Schiel, PhD
Research Chemist
Bioanalytical Science Group
Biomolecular Measurement Division
Material Measurement Laboratory
National Institute of Standards and Technology
Gaithersburg, Maryland

Tor A. Shwayder, MD, LRAM, FAAP, FAAD
Director of Pediatric Dermatology
Department of Dermatology
Henry Ford Hospital
Detroit, Michigan

Richard M. Siegel, MD, PhD

Chief, Immunoregulation Section

Autoimmunity Branch

Clinical Director, Intramural Research Program

National Institute of Arthritis and

Musculoskeletal and Skin Diseases, NIH

Bethesda, Maryland

Steven Solga, MD

Solga Gastroenterology

Chief, Gastroenterology

St. Luke's University Hospital

Bethlehem, Pennsylvania

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Sean P. Curtis, MD

(Acting Industry Representative)

Head, Global Scientific Affairs

Merck Research Laboratories

Merck and Co, Inc

FDA PARTICIPANTS (Non-Voting)

Leah Christl, PhD
Associate Director
Therapeutic Biologics
Therapeutic Biologics and Biosimilars Staff
Office of New Drugs (OND)
CDER, FDA

Badrul Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of Drug Evaluation II (ODE-II)
OND, CDER, FDA

Nikolay Nikolov, MD
Clinical Team Leader
DPARP, ODE-II, OND, CDER, FDA

Steven Kozlowski, MD

Director

Office of Biotechnology Products (OBP)

Office of Pharmaceutical Quality (OPQ)

CDER, FDA

Kurt Brorson, PhD

Product Quality Team Leader

Division of Biotechnology Research and Review 2

OBP, OPQ, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. CAPLAN: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other device if you've not already done so. I'd like to identify the FDA press contact, Eric Pahon. If you are present, please stand. Waving hand there to the left.

My name is Liron Caplan, and I am the acting chairperson of the Arthritis Advisory Committee, and I'll be chairing this meeting. I will now call the Arthritis Advisory Committee meeting to order.

We'll start by going around the table and introducing ourselves. Let's start down on my right with Sean --

DR. CURTIS: Hi. Good morning. My name is Sean Curtis. I'm the industry rep. I work at Merck Research Labs.

DR. BECKER: Hi. I'm Mara Becker. I'm a pediatric rheumatologist at Children's Mercy

Hospital in Kansas City.

DR. SOLGA: My name is Steve Solga. I'm a gastroenterologist in solo, independent private practice.

DR. FUSS: Ivan Fuss, at the National Institutes of Health, specialty is gastroenterology and immunology.

DR. CRAMER: Good morning. I'm Steve Cramer from RPI, specialist in downstream bioprocessing.

DR. SCHIEL: Good morning. I'm John Schiel, from NIST. I'm a specialist in analytical characterization of therapeutic proteins.

DR. SHWAYDER: Tor Shwayder, pediatric dermatologist, Henry Ford Hospital in Detroit.

DR. BERGFELD: Wilma Bergfeld, Cleveland Clinic, dermatologist and dermatopathologist.

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

DR. HORONJEFF: Jennifer Horonjeff. I'm the consumer representative, and I am also a researcher at Columbia University Medical Center.

DR. JONAS: Good morning. I'm Beth Jonas

from the University of North Carolina at Chapel Hill, and I'm an adult rheumatologist.

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

DR. RANGANATH: I'm Veena Ranganath. I am a faculty at UCLA.

DR. CAPLAN: I'm Liron Caplan. I'm at the University of Colorado and the Denver VA.

LCDR BEGANSKY: Stephanie Begansky. I'm the designated federal officer for today's meeting.

DR. WOLPAW: I'm Terry Wolpaw. I'm an adult rheumatologist at Penn State Hershey Medical Center.

DR. CURTIS: I'm Jeff Curtis. I'm an adult rheumatologist and pharmacoepidemiologist at the University of Alabama at Birmingham.

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

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

DR. LONG: Eric Long. I'm a scientist at the National Institute of Allergy and Infectious Diseases.

DR. MOREIRA: Good morning. I'm Antonio Moreira, University of Maryland, Baltimore County, and I'm a specialist in bioprocessing.

DR. MAGER: Good morning. My name is Donald Mager. I'm an associate professor in the Department of Pharmaceutical Sciences at the University of Buffalo.

DR. BRORSON: Kurt Brorson, quality team leader for this product, CDER, Office of Biotechnology Products.

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

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

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

DR. CHRISTL: Good morning. Leah Christl,

associate director for therapeutic biologics in OND, CDER.

DR. CAPLAN: We also have a number of folks who are unable to be here in person, on the phone. Do we have Eric?

DR. TCHETGEN TCHETGEN: Yes, Eric Tchetgen Tchetgen. I'm professor of biostatistics and epidemiology at Harvard.

DR. CAPLAN: Mary?

DR. MALONEY: Good morning. Mary Maloney, University of Massachusetts. I'm a dermatologist.

DR. CAPLAN: We also have two folks that are running late -- okay, one person who is running late, and that is Richard Siegel, gastroenterology and immunology.

Dr. Gobburu, could you introduce yourself please?

DR. GOBBURU: Yes. Jogarao Gobburu, professor, University of Maryland.

DR. CAPLAN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of

opinions, some of which are quite strongly held. Our goal is that today's meeting will be fair and an open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings.

However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Lieutenant Commander

Stephanie Begansky who will read the conflict of interest statement.

Conflict of Interest Statement

LCDR BEGANSKY: Thank you. 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 founds at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with Federal ethics and conflict of

interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the 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 125544 for CT-P13, a proposed biosimilar to Janssen Biotech's Remicade, infliximab, submitted by Celltrion. The proposed

indications for this product are:

(1) reducing signs and symptoms of inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy;

(2) reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease;

(3) reducing signs and symptoms and inducing and maintaining clinical trial remission in pediatric patients, 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy;

(4) reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;

(5) reducing signs and symptoms and inducing and maintaining clinical trial remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had inadequate response to conventional therapy;

(6) in combination with methotrexate, reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active rheumatoid arthritis;

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

(8) reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function in patients with psoriatic arthritis; and

(9) treatment of adult patients with chronic severe plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

This is a particular matters meeting during

which specific matters related to Celltrion's BLA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

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

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

personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

DR. CAPLAN: I'd like to now invite Janet Woodcock to deliver the FDA's opening remarks.

FDA Opening Remarks – Janet Woodcock

DR. WOODCOCK: Thank you very much. I thank the audience and particularly the members of our advisory committee for attending this meeting with the inclement weather. We really appreciate it. This is such an important milestone.

This is the second application under the biosimilar pathway to be discussed at an advisory committee meeting, and it's the first application to be discussed for a proposed biosimilar for monoclonal antibody, this one being a TNF inhibitor.

TNF inhibitors have revolutionized treatment for a number of autoimmune diseases, as we heard the indications read out by our advisory committee chair/consultant. They've really become a major part of the therapeutic armamentarium. For example, 9 of 11 new molecular entities that have been approved for rheumatoid arthritis since 1998 are biologics.

These molecules are therapeutically important, but they're also very complex. Therefore, proposed biosimilars are evaluated very carefully by the FDA to ensure they are highly similar to the reference product and that there are no clinically meaningful differences, as will be discussed in the presentations today to this advisory committee.

These evaluations are based on an extensive set of data on the structural and functional characteristics of the molecules, and this provides a high degree of confidence that biosimilar and a reference product would be expected to have similar efficacy and safety. The evaluation that FDA is

supposed to do is to evaluate this whole data set to make a finding of biosimilarity or not.

This really requires a multidisciplinary approach to evaluate this, and I think that's reflected by our advisory committee members today. Not only do we have multiple medical specialties represented, but we also have experts in protein structure and many of the other immunology and some of the other characteristics that we must evaluate as part of our evaluation of the totality of the evidence for biosimilarity for any given application.

The biosimilar pathway is really an important mechanism to get additional versions of these important treatments on the market and improve access for patients who need them. On the other hand, you are helping us today forge this new pathway because we only are just on the first steps of it.

I thank you again for attending and look forward to the scientific advice of the committee. Thank you.

DR. CAPLAN: Thank you, Dr. Woodcock.

I'd like to now invite Leah Christl to give us an overview of the 351(k) regulatory pathway.

FDA Opening Remarks – Leah Christl

DR. CHRISTL: Sorry. We're having little technical difficulties here. But we'll go ahead and get started while, hopefully, we can sort that out.

Good morning. My name is Leah Christl. I'm the associate director for therapeutic biologics in the Office of New Drugs. And before we begin speaking about the proposed product that will be the subject of today's advisory committee meeting, we wanted to take this time and give an overview, not only for the advisory committee members but also for the audience here listening, about the Biologics Price Competition and Innovation Act, the biosimilars pathway.

I'll spend some time giving you an overview of the pathway, talk to you about some definitions, familiarize you with some terminology, and then talk about the FDA's scientific approach that

they've articulated in various guidance documents about the development and approval of biosimilars, and touch on some specific development concepts that will help to guide the discussion and thinking today.

To begin with, the Biologics Price Competition and Innovation Act of 2009 was passed in March of 2010 as a part of the Affordable Care Act. What it did is it created an abbreviated licensure pathway for biological products that are shown to be biosimilar to or interchangeable with an FDA licensed reference product. And we'll talk a little bit about each of those key terms.

What do we mean by an abbreviated licensure pathway? What this means is that a biological product that's demonstrated to be highly similar to an FDA licensed reference product may rely for licensure on, among other things, publicly available information about the FDA's previous determination that the reference product is safe, pure, and potent.

This licensure pathway permits the

biosimilar product to be licensed based on less than a full complement of preclinical and clinical information. You couple that with, again, being able to rely for licensure on what's publicly available about FDA's previous finding that the reference product is safe, pure, and potent. And that's where we get this concept of an abbreviated licensure pathway.

What does it mean to be biosimilar? Biosimilar or biosimilarity is defined in the BPCI Act to mean that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the proposed product and the reference product in terms of the safety, purity, and potency of the product. Both of these essentially prongs of biosimilarity need to be met.

Again, the product needs to be highly similar and it has to be demonstrated to have no clinically meaningful differences. So there can't be one but not the other. Again, both of these of

prongs needs to be met in order for a product to be licensed as a biosimilar.

What do we mean by reference product? Reference product is defined in the Act to mean that it is the single biological product licensed under 351(a) of the Public Health Service Act against which a proposed biosimilar or interchangeable product is evaluated in an application submitted under 351(k).

You may hear some reference to 351(a) BLAs, 351(k) BLAs. This is the statutory pathway, but what it means is an application that's submitted under 351(a) of the PHS Act is a standalone application that contains all the information and data necessary to demonstrate the proposed product is safe, pure, and potent for those requested conditions of use or indications.

In contrast, an application that's submitted under 351(k) of the Public Health Service Act needs to demonstrate that the proposed product is biosimilar to the reference product, and for licensure, that proposed biosimilar product relies

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

At the end of the day, whether you're under the 351(a) pathway or the 351(k) pathway, FDA won't approve the product if it can't determine that the product is safe, pure, and potent for the requested and then subsequently labeled conditions of use.

The differences in the data package that underlines that finding for a 351(a), that's a standalone application that contains all the information that's specific to that product, whereas the 351(k) has a combination of comparative data, product-specific information, that allows the product to rely on what's previously known about the reference product.

As I said, the Act's created an abbreviated licensure pathway for products that are biosimilar to or interchangeable with a reference product. Interchangeability is defined in the Act to mean

that the biological product is biosimilar to the reference product, so it needs to meet those standards 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 proposed interchangeable product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

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

Just to remind folks, the product that we will be speaking about today, CT-P13, is a proposed biosimilar product, not a proposed interchangeable product. But we did want to share the definition of interchangeability in terms of a background of

the Act. But again, we're talking about biosimilarity today for this proposed product.

The Act describes, in general, requirements about the expectations of the information that would be included in a 351(k) BLA. That includes information and data demonstrating that the proposed product is biosimilar to the reference product. It utilizes the same mechanism or mechanisms of action for the proposed conditions of use as the reference product but only to the extent that those are known for the reference product.

It has the same conditions of use proposed in labeling that have been previously approved for the reference product. What that means is a biosimilar product cannot have novel conditions of use or novel indications. The conditions of use have to be what has been previously approved for reference product.

It has the same route of administration, dosage form, and strength as the reference product, and that the product is manufactured, processed, packed, and held in a facility that meets FDA

standards for a biological product. And that is no different than for a 351(a) product in terms of those standards around manufacturing.

The types of data that a sponsor would be expected to submit in a 351(k) application are also outlined in the Act. These would include analytical studies demonstrating that the proposed product is highly similar to the reference product, again, notwithstanding minor differences in clinically inactively components; animal studies including the assessment of toxicity in a clinical study or studies, which can 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 proposed biosimilar product.

The Act does state that FDA may determine at its discretion that one of these data elements described above is unnecessary for a 351(k)

application.

While the PHS defines reference product, for a 351(k) application, as the single biosimilar product licensed under 351(a) against which the biosimilar product is evaluated, FDA has taken a scientific position and has articulated this in various guidance documents that data from animal studies and certain clinical studies comparing the proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a U.S. reference product.

But the sponsor needs to provide adequate data or information to scientifically justify the relevance of those comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product. And you'll hear more about these concepts in the product-specific presentation today, so this is an important concept to keep in mind.

The type of bridging data that would be expected as a scientific matter would include direct physical chemical comparison of all three

products, so again, direct pair-wise comparisons of the proposed biosimilar to the US-licensed reference product, the proposed biosimilar to the non-US-licensed comparator product, and the US-licensed reference product compared to the non-US-licensed comparator product.

This would also likely include 3-way bridging PK and/or PD studies if PD is relevant for the particular molecule. Again, it would be all three pair-wise comparisons. All the pair-wise comparisons for either the analytical or the PK and PD, if it's relevant, comparisons need to meet the prespecified acceptance criteria for both analytical and PK or PD similarity.

A sponsor should justify the extent of the comparative data needed to establish a bridge to the US-licensed reference product and that may depend on certain product-specific factors regarding complexity and what may be publicly known about the U.S. reference product and the non-US-licensed comparator and any connection if it's the same sponsor, the same license holder, if

there's publicly available information about the site of manufacturing, things like that. These are all product-specific discussions, as well as program-specific discussions as a sponsor moves forward in their development program.

Now, we'll talk a little bit about the approach to development of biosimilars. We found the best way to do this is to highlight some key development concepts. The first concept is that the goals of a standalone development program and the goals of a biosimilar program are different.

A standalone development program -- again, this is under 351(a) of the PHS Act. The goal is to establish safety and efficacy of the new product. It would be traditional drug development that most folks are used to; the analytical or the chemistry manufacturing control since the information would be generated for that product throughout the development of the product, all the way from early development of inception of the idea all the way through submitting the license application and including in to the post-approval

phase.

Non-clinical development would also occur. This would be a full toxicology package, including reproductive and toxicology studies, any dermal toxicity studies -- again, it's that full toxicology package -- clinically pharmacology data, looking at phase 1, phase 2, dose ranging, dose finding studies, trying to determine the appropriate clinical dose to bring into what would then be those phase 3 studies.

Typically, there would be an expectation of two adequate and well controlled clinical studies, phase 3 clinical studies to demonstrate safety and efficacy for each of the proposed conditions of use for that product.

On the other hand, for a 351(k) program for a proposed biosimilar, the goal is to demonstrate biosimilarity or interchangeability. It is not to independently establish the safety and effectiveness of the biosimilar product. The reference product did that.

The goal of the biosimilar development

pathway, again, is to demonstrate biosimilarity, so there's a different approach that occurs here. You have the same types of pieces in terms of data elements but how they're used is different. The analytical similarity data is this comparative data, and we'll talk more about this, and that's the foundation of the biosimilar program.

Then you consider non-clinical studies, any animal studies that may be relevant and tell you something about similarity or safety of the product, then look at clinical pharmacology studies, and then make a determination of what additional clinical studies are needed to support biosimilarity.

Within that type of concept, the next key development concept is step-wise evidence development. This is what FDA has outlined in various guidance documents and how it is that we approach data development to support to biosimilarity. It's a step-wise approach with evaluation of residual uncertainty at each step, and then there's the totality of the evidence in

terms of evaluating similarity.

Applying the step-wise approach to data generation and this evaluation of residual uncertainty includes the concepts of what differences have been observed, again, beginning with the analytical similarity assessment; what differences do you see in an analytical level between the products and what's the potential impact of those differences based on what you know about mechanism of action, PK, toxicology, clinically performance? Then based on assessing that residual uncertainty and the potential impact, what are the study or studies that will best address that residual uncertainty?

For a biosimilar development program, there's no one pivotal study that demonstrates biosimilarity. Folks are used to that phase 3 pivotal clinical efficacy study in a standalone development. We don't have that here. It's a totality of the evidence that demonstrates biosimilarity, and it's all the data and all the studies that build on that to ultimately

demonstrate biosimilarity.

There's no one-size-fits-all assessment. There are product-specific considerations and program-specific considerations that need to be taken into account in terms of looking at the evaluation of residual uncertainty.

The third key concept, again as I had mentioned, is that the analytical similarity data is the foundation of a biosimilar development program. What this requires is extensive structural and functional characterization of both the reference product and the proposed biosimilar, and that's really the starting point in this building block and foundation of a biosimilar development program.

What this means is that there needs to be a comparative assessment of the attributes of the products on an analytical level, structural and functional characterization, looking at a number of things, including amino acid sequence and any modification, various heterogeneity such as size, aggregate, charge, looking at glycosylation

profiles, bioactivity, differences in impurities between the products if there could be a different safety profile, if a molecule is known to have multiply biological activities.

Where feasible, each of those biological activities should be demonstrated to be highly similar between the proposed biosimilar product and the reference product.

This requires that a sponsor understand the molecule, the function of that molecule, and identify what the critical quality attributes are for that molecule.

To do this analytical similarity assessment, what the sponsor would need to do is adequately characterize the reference product quality characteristics and the product variability, and really understand the variability of that reference product; what other quality characteristics look like?

Then they create a manufacturing process for their proposed product in a manner that's designed to produce a product with minimal or no differences

in those product quality characteristics compared to the reference product.

Sponsor needs to identify and evaluate the potential impact if any difference is observed, and again, in that context of evaluating residual uncertainty, determine what studies will address that residual uncertainty.

There's a real need to understand the relationship between the quality attributes and the clinical safety and efficacy profile, and this aids in the ability to determine residual uncertainty about biosimilarity and essentially predict expected clinical similarity from the quality data.

Also, as a scientific matter, FDA has looked at a statistical analysis of analytical similarity as part of the demonstration of supporting the demonstration that the products are highly similar in an analytical level. There are statistical analyses of the analytical similarity data that are conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product.

With this type of an approach, quality attributes are ranked based on criticality with regard to their potential impact on activity, PK/PD, safety, immunogenicity, and other product-specific factors.

The data are then analyzed by various testing methodologies, and these could include equivalence testing for certain highly critical attributes, quality range testing, mean plus-minus X standard deviations for other highly critical or lower criticality attributes, and then raw and graphical comparison for other attributes with either very low criticality or attributes that are not amenable to the aforementioned other testing methodologies.

Again, this isn't a pass/fail type of system. This is something that we look at to add rigor to the analytical similarity assessment and support the demonstration that the products are highly similar. This is a part of that analytical similarity assessment.

In thinking about animal data, again, that

was one of the elements that's outlined in the BPCI Act regarding data that could be expected in a 351(k) application. Animal toxicity data are certainly useful when there's uncertainties that remain about the safety of the proposed product prior to initiating clinical studies.

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

Again, a lot of the look around the animal data is more towards evaluating the safety of the product before initiating clinical studies. There are times that a comparison of PK or PD, if relevant in a relevant animal model, may also be useful from not only a safety perspective but also, in that case, a similarity perspective.

Moving on through the step-wise evidence development, the next key concept is thinking about

the role of clinical studies in a biosimilar development program. We talked about the analytical similarity data being the foundation and then considering the value of animal studies in a specific development program.

Now we're looking at that upper part of the pyramid of those clinical studies, including clinical pharmacology studies and additional clinical studies, which could include safety and efficacy evaluation and then also immunogenicity testing.

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

The types of clinical data that would be expected, as a scientific matter, FDA has stated in guidance that it expects that there be an adequate clinical PK, PD if it's relevant, comparison between the proposed biosimilar product and the

reference product.

Also, as a scientific matter, at least one clinical study that includes the comparison of the immunogenicity of the proposed and reference product will also be expected.

Again, 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, any animal testing, human PK and PD, and the clinical immunogenicity assessment.

When we talk about comparative human PK and PD data for a biosimilar program, PK and/or PD data is generally considered the most sensitive clinical study or assay in which to assess for differences between the products, should they exist.

Again, we're looking at a comparative assessment, not determining a dose ranging or a dose finding. We know the clinical dose. Again,

this is intended to be a biosimilar.

What we're looking at are differences between the products should that exist. PK and/or PD can be the most sensitive clinical study or assay to detect those differences should they exist. Again, you're looking for product differences in a comparative manner.

For PK, sponsors needs to demonstrate PK similarity in an adequately sensitive population to detect any differences should they exist. This may be a healthy volunteer population; it could also be a patient population, again, depending on product-specific factors regarding safety, immunogenicity, and also sensitivity in terms of response.

PD, similar PD using PD measures that reflect the mechanism of action of the product or reflecting the biological effect of the drug, can also be useful in this setting, again, to look for differences should they exist.

PK and PD similarity data supports a demonstration of biosimilarity with the assumption

that similar exposure and pharmacodynamic response, if applicable, will provide similar efficacy and safety; in other words, an exposure response relationship exists for that product.

When thinking about if additional clinical studies are needed and thinking about whether or not there needs to be a comparative clinical study, if there does need to be a comparative clinical study, if there's a PK assessment but there's no good PD marker and it's a very complex molecule and there may be some residual uncertainty about whether or not there are clinically meaningful differences between the products, you would look to a comparative clinical study within a biosimilar development program.

But that comparative clinical study, again, it's not designed to demonstrate the safety and efficacy of the product. It should be designed to investigate whether there's clinically meaningful differences in safety and efficacy between the proposed product and the reference product.

There are considerations when thinking about

the design of the study such as population, endpoint, sample size, study duration. And again, these all need to be adequately sensitive to detect differences should they exist.

Typically, for a biosimilar development program, an equivalence design would be used. Again, it's no clinically meaningful differences. You're going to be wanting to make sure it's essentially no better, no worse, within a certain range. But there are other designs that may be justified, depending on product-specific and program-specific considerations.

Also, within a comparative clinical study, there would be an expectation that there would be an assessment of safety and immunogenicity. FDA, as a scientific matter, expects that any clinical study include an assessment of safety and immunogenicity.

Another key concept is extrapolation. 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 clinical data intended to demonstrate biosimilarity in one condition of use to other conditions of use for which licensure is sought.

This is really a key concept in the concept of an abbreviated development program, but it's not a given. Scientific justification for extrapolating data is necessary as part of a biosimilar development program.

FDA has outlined in guidance a number of factors that should be considered by the sponsor, as well as the agency, when considering what would provide adequate scientific justification for extrapolating clinical data from one condition of use to other conditions of use for biosimilarity.

These include, for example, the mechanism of action in each condition of use for which licensure is sought; the PK and biodistribution of the product in different patient populations; the immunogenicity of the product in different patient populations; differences in expected toxicities in each condition of use and the patient population.

It is important to note the differences between these conditions do not necessarily preclude extrapolation. What it means is that those factors need to be addressed through data and information.

For example, if there is some difference in the mechanism of action for each condition of use, it's not necessarily that there needs to be additional clinical data if structural and functional, looking at binding assays and other assessments of that molecule, can go towards addressing the residual uncertainty that there might be around that.

It's incumbent on the sponsor to provide this adequate scientific justification addressing these factors. But it is important to note that any differences in these factors, again, don't necessarily preclude extrapolation. It just means that a sponsor needs to ensure that the totality of the evidence, including the scientific justification for extrapolation, supports the approach and supports a demonstration of

biosimilarity in each of the conditions of use that are requested for licensure.

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

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

With that, I am happy to take any clarifying questions the committee with may have.

Clarifying Questions

DR. CAPLAN: Thank you for those remarks. Are there any clarifying questions for Dr. Christl? Please remember to state your name for the record before you speak.

(No response.)

I guess in the absence for questions, I have one, and that is around the issue of interchangeability.

Recognizing that the application before us today is not one that is applying for this, could you give an example of the difference between interchangeability and biosimilarity in terms of what kinds of studies you'd be looking at for that?

DR. CHRISTL: Well, the agency has not issued guidance on interchangeability as yet. It's something that is on our guidance agenda for this year, and it's something that the agency is working on.

But there are differences again in the statutory requirements to demonstrate. It includes the potential to look at the evaluation of switching or alternating in a clinical setting. That would be one type of thing in a given program, depending on the product, that is additional data that a sponsor may need to provide in an application.

DR. CAPLAN: Thank you.

DR. SHWAYDER: Tor Shwayder. I have a nonmedical question. How do they get around the laws of copyright and patents? If they're just reverse engineering a molecule, making another molecule, why isn't Remicade suing them? Are they off patent now?

DR. CHRISTL: That, I cannot answer for you. Yes, there are some very complicated patent exchange or patent provisions in the BPCI Act that a biosimilar applicant and the reference product or the patent holder would need to engage in sharing information and making assessments regarding patent infringement.

What FDA looks at in terms of being able to accept an application for a product or license a biosimilar interchangeable product has to do with exclusivity.

A reference product could be granted 12 years of exclusivity from the date of first licensure of the product. And the Act states that FDA could accept an application for a proposed biosimilar to that reference product four years

into that 12-year period, and then ultimately approve the product once that 12-year period had expired. But the patent exchange process is something that occurs between the biosimilar applicant and the reference product or the patent holder.

DR. CAPLAN: Thank you very much for those remarks. I would now like to invite Dr. Nikolov to provide some additional introductory remarks on behalf of the FDA.

FDA Introductory Remarks - Nikolay Nikolov

DR. NIKOLOV: Good morning, everyone. The fact there were not too many questions to Dr. Christl, I'll take it as a good sign. Otherwise, we'll have to explain ourselves again and again, but we're happy to take any questions later on.

I would like to welcome you to the Arthritis Advisory Committee meeting for the 351(k) biologics license application for the CT-P13, a proposed biosimilar to US-licensed, Remicade. My name is Nikolay Nikolov. I'm clinical team leader in the

Division of Pulmonary Allergy and Rheumatology Products. I'm also an adult rheumatologist.

Before I begin, I would like to thank the members of the Arthritis Advisory Committee for taking the time off your busy schedules to come and share your expert opinion even in this dicey weather. I would also like to acknowledge the attendance in the room, which is indicative of the importance of this meeting to the community.

In the next five minutes or so, I will provide an overview of the CT-P13 development program in the context of the abbreviated licensure pathway that Dr. Leah Christl just described.

The applicant, Celltrion, has submitted a biologics license application under Section 351(k) of the Public Health Service Act for CT-P13, a proposed biosimilar to US-licensed Remicade, which is the reference product for Celltrion's application.

The BLA for Remicade was initially licensed by FDA in 1998. CT-P13 is being developed for the same indications for which US-licensed Remicade is

licensed as listed on this slide.

Of note, the FDA previously scheduled an advisory committee meeting for March 17, 2015 to discuss this application, but postponed the meeting due to information requests pending with Celltrion. These requests have been adequately addressed by the applicant.

To support this application, Celltrion provided extensive analytical data intended to support a demonstration that CT-P13 and US-licensed Remicade are highly similar and a demonstration that CT-P13 can be manufactured in a well controlled and consistent manner, leading to a product that is sufficient to meet required regulatory standards for product quality.

To support the demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade, Celltrion provided data intended to demonstrate: 1) similarity in exposure in healthy subjects and in patients with ankylosing spondylitis; 2) similarity in efficacy and safety in patients with rheumatoid arthritis and

ankylosing spondylitis; and 3) similarity in immunogenicity between CT-P13 and Remicade in patients with rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and healthy subjects, as well as in patients who underwent a transition from Remicade to CT-P13.

The next two slides summarize the clinical development program for CT-P13 and key design aspects of the clinical studies supporting this application.

The first three studies from this table, which will be discussed in detail later in the FDA presentations, constitute the core clinical studies that provide the data on similarity in exposure, efficacy, safety, and immunogenicity between CT-P13 and Remicade comparator products.

The last three studies in this table were reviewed as supportive and will not be discussed in much detail by the FDA.

This table summarizes the two main open label extension studies in rheumatoid arthritis and ankylosing spondylitis. These studies provided

safety and immunogenicity data in the setting of patients undergoing a single transition from Remicade to CT-P13.

This information is important to ensure that if approved as a biosimilar, CT-P13 could be administered safely to patients who may have been previously exposed to Remicade.

The second table summarizes the clinical program in inflammatory bowel disease indications, which is currently ongoing and will only be discussed by the FDA to the extent limited to the assessment of immunogenicity in this patient population.

As discussed by Dr. Leah Christl, in addition, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product to the reference product; in this case, US-licensed Remicade.

As noted in the previous slides, for the most part, the CT-P13 clinical development program used a non-US-licensed comparator, specifically European Union approved Remicade or EU Remicade.

The FDA has determined that in situations like this, the applicant must 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, the applicant provided extensive analytical bridging data that directly compared all three products and conducted a clinical study to demonstrate a 3-way similarity in exposure or pharmacokinetic profile parameters between the three products.

The agency has also determined that it may be appropriate for a biosimilar product to be licensed for one or more additional indication for which the reference product is licensed based on data from clinical study, or studies, performed in only one indication such as rheumatoid arthritis in the CT-P13 program. This concept is known as extrapolation.

Consistent with the principles outlined in

the FDA guidance documents and previously discussed by Dr. Christl, the applicant provided an extensive data package to justify the proposed extrapolation of clinical data from studies in the rheumatoid arthritis and ankylosing spondylitis to the indications eligible for licensure.

Later this afternoon, we will be asking the Arthritis Advisory Committee members' thoughts on the following questions: 1) whether CT-P13 is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; 2) whether clinically meaningful differences exist between CT-P13 and US-licensed Remicade in the studied indications of rheumatoid arthritis and ankylosing spondylitis; and 3) whether extrapolation of biosimilarity to the remaining indications for which U.S. Remicade is licensed is sufficiently justified.

Following this discussion, the committee will be asked to vote on one question, and the question is, Does the committee agree that based on the totality of the evidence, CT-P13 should receive

licensure as a biosimilar product to US-licensed Remicade for each of the indications for which U.S. Remicade is currently licensed and CT-P13 is eligible for licensure? These are listed in the parentheses.

After that, we will ask the committee to explain the reasons for their vote. And if you voted no, we would ask you to explain whether this is applicable to a specific indication, or to all, or some, and why.

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

With this, I'd like to thank you for your attention, and I will turn back the podium to Dr. Caplan.

Clarifying Questions

DR. CAPLAN: Thank you, Dr. Nikolov. We do have a question that was posed by Dr. Maloney on the telephone, I think originally for Dr. Christl. Dr. Maloney, could you ask your question?

(No response.)

Dr. Maloney? If you're on mute, could you unmute your phone, and then ask your question?

(No response.)

Okay. We'll come back. All right. The chair recognizes Dr. Fuss?

DR. FUSS: On the presentation from Dr. Nikolov, you mentioned that the Celltrion product was developed for the possible uses in adult and pediatric Crohn's disease and ulcerative colitis.

On the vote charge to the committee, it mentions adult UC but not pediatric UC. I just want to clarify that it is only adult UC and not pediatric UC also indication?

DR. NIKOLOV: This is Nikolay Nikolov. Thanks for the question.

I just want to clarify that for the discussion part, we would ask the committee to comment on the extrapolation argument for all the indications, including adult and pediatric ulcerative colitis and adult and pediatric Crohn's disease.

But for the voting question, we would ask you to vote on all but pediatric ulcerative colitis indications because the pediatric ulcerative colitis is protected under orphan exclusivity as an indication. So the agency cannot grant or cannot license CT-P13 for that indication.

DR. CAPLAN: Thank you. The chair recognizes Dr. Solga.

DR. SOLGA: I have a question for either of the first two presenters. I'm wondering more about the historical background of 351(k).

All of the materials that I was provided simply states it was passed, in the past tense, in March of 2010. Since the FDA was the FDA at least since the '60s, it's all been about standalone safety and efficacy. This is a really very, very

different thing. And I understand our committee is charged with deciding, does this meet 351(k) expectations?

What went into 351(k)? Who were its parents and what were they intending to do? Was this an FDA initiative or is it something that the industry involved in? Did this come out of Capitol Hill? Because the context is all wrapped into that question, I'm interested in learning more about the context.

DR. CHRISTL: Right. The BPCI Act in terms of creating an abbreviated licensure pathway for biological products was new, but the concept of an abbreviated approval pathway for drugs that are approved under the Food, Drug, and Cosmetic Act has been in place for a long time, from Hatch-Waxman.

There are two abbreviated approval pathways; one of them is very familiar. It's the 505(j) pathway or what we think of as ANDAs or generics. There's also another abbreviated approval pathway under the Food, Drug, and Cosmetic Act that is under 505(b)(2) of the Act. It's a different

abbreviated pathway. Generics need to meet certain requirements including being the same active ingredient and be demonstrated to bioequivalent.

This other abbreviated pathway for drugs is a little bit more broad than that. There are some differences that would be very complex to get into. But until the BPCI Act was passed, there was not an abbreviated approval pathway for biological products.

Again, the concept for biologics is new, but the concept of an abbreviated approval pathway for products that are regulated by the FDA is not new at all. In terms of looking at an abbreviated approval pathway for biological products, there was involvement from industry, as well as FDA in the drafting process of the Act.

Certainly, it was a law that was passed by Congress, so there was various input that went into that, but it's not FDA's piece of legislation. FDA does not make legislation or pass laws, so it's Congress that did that. But certainly, FDA, as well as industry were part of the discussions.

DR. CAPLAN: Okay.

DR. KOZLOWSKI: Steve Kozlowski, FDA. I just wanted to add another antecedent because companies that make biologics have made manufacturing changes throughout development, scale-ups, adding new sites.

Since the mid-1990s, the FDA has used analytical data and sometimes some additional clinical data to make decision on those changes. There is an antecedent science to this in terms of using analytics to make judgments about the clinical performance of biological products.

DR. CAPLAN: Thank you. My understanding is we have Dr. Maloney on the phone now.

Dr. Maloney, could you pose your question, please?

DR. MALONEY: Yes, thank you. I wanted to be entirely clear about the safety requirement and understanding of the way that safety data is collected so that we know that the side effects of biosimilars are in fact also similar. I just wish you'd review that one more time.

DR. CHRISTL: I can start, and then maybe ask my clinical colleagues to weigh in as well. Again, what's being looked at in terms of the clinical space is a demonstration that there are no clinically meaningful differences in the safety, purity, and potency of the product.

Safety, purity and potency is language that's used in the Public Health Service Act, but you can think of it in terms of safety and efficacy for lack of a better terminology, and that might be a little bit more accessible.

But a sponsor would need to look at all of their data, the comparative analytical data and any comparative clinical data, which could include PK data, as well as comparative clinical study data, immunogenicity evaluation within those clinical studies, in addition to a possibility of standalone immunogenicity assessments.

But it's looking in that and totality of the evidence of making a determination that essentially the safety profile of that proposed product would be expected to be the same as the reference

product.

Again, there's no one study that would be looked at. It's really looking at the totality of the evidence and looking at residual uncertainty based on any differences that might exist between the molecules.

Within a given development program, the agency will work with the sponsor of looking at any product differences that could exist, making an assessment about are those differences in analytical attributes, characterization of the molecule that could impact either PK, safety, immunogenicity, and then conducting the appropriate assessment, if that is a clinical assessment, to evaluate whether or not those analytical differences actually manifest as any sort of clinical differences.

But again, you have to look at it somewhat in the context of a specific development program and specific uncertainties that you would have about that product. But the expectation is that the totality of that data package would, at the end

of the day, support an assessment that there's no clinically meaningful differences in safety or efficacy of the product.

I would ask my clinical colleagues to add anything.

DR. NIKOLOV: This is Nikolay Nikolov. I will just try to add to what Dr. Christl said.

Generally, clinical safety and immunogenicity would be expected in a proposed biosimilar development program at least in one indication, and then we'll talk later on about the considerations for extrapolation with respect to safety and immunogenicity.

DR. CAPLAN: Thank you.

DR. MALONEY: May I ask a follow-up?

DR. CAPLAN: Yes, go ahead and pose your question. We're running just a little bit behind.

DR. MALONEY: Very quickly, is there any plans to collect safety data after release of the product and be certain that nothing occurs that is unexpected?

DR. CHRISTL: Certainly, any biological

product that is licensed by FDA, whether it's under the 351(a) pathway or 351(k) pathway, that there's an expectation of postmarket surveillance safety monitoring. The biosimilar product would be no different in that space. But there is not an expectation that there would be a different pharmacovigilance or postmarket safety requirement simply because a product is biosimilar.

Again, FDA will not license a product as a biosimilar product if they don't have the data to demonstrate that there's no clinically meaningful differences between the reference product and the proposed biosimilar product.

Again, when FDA licenses that product, it's the expectation that the safety profile would be the same between the products, so a biosimilar won't have something different simply because it's a biosimilar, but it will need to meet the same requirements in terms of postmarket safety surveillance as any approved product would.

DR. CAPLAN: A very brief question now from Dr. Ranganath.

DR. RANGANATH: Through this application process, are you allowed to submit for a biosimilar product based upon an FDA-approved biosimilar product?

DR. CHRISTL: Are you asking if a proposed biosimilar product could compare itself to another biosimilar product?

DR. RANGANATH: Yes.

DR. CHRISTL: No. A proposed biosimilar product needs to demonstrate that it's biosimilar to an FDA-licensed reference product, which is defined as a product that's licensed by FDA under 351(a) of the Public Health Service Act, which would be that standalone product.

DR. CAPLAN: Thank you. That was an interesting question. We now move to the applicant's presentations.

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

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

We will now proceed with Celltrion's presentations delivered by Elizabeth Pollitt. Dr. Pollitt?

Applicant Presentations - Elizabeth Pollitt

DR. POLLITT: Thank you.

Good morning, Mr. Chairman, members of today's advisory committee, and members of FDA. My name is Elizabeth Pollitt. I'm vice president of CMC for regulatory affairs at Celltrion.

We're pleased to be here today to present the BLA data that support our application for CT-P13, a Remicade or infliximab biosimilar, which will be marketed as Inflectra. For today's agenda, I'll introduce the biosimilar pathway in CT-P13. I'll discuss the structural and functional studies to show biosimilarity and describe how we address residual uncertainties. I'll also briefly introduce the nonclinical data.

Then, Dr. Kudrin will review the clinical data including the pharmacology, immunology, efficacy and safety, followed by a summary of the totality of evidence that support biosimilarity. Next, Dr. Lakatos will present the CT-P13 data that support treatment of patients with inflammatory bowel disease, and finally, Dr. Strand will provide a clinical perspective on CT-P13.

We have internal and external responders

with us today to take your questions. All external experts have been compensated for their time. In addition, we have representatives from Pfizer, our U.S. marketing partner.

Let me begin by briefly reviewing how CT-P13 fits the requirements outlined at FDA biosimilarity guidance. Our assessment of biosimilarity and extrapolations follows the FDA pyramid development pathway, and it's how we'll present the data today.

CT-P13 fulfills the statutory requirements and biosimilar guidance in that the single reference product is U.S. Remicade. Analytical data demonstrate the CT-P13 as highly similar to the reference product from a structural and functional standpoint and residual uncertainties have been fully addressed.

Nonclinical studies confirm the pharmacologic and toxicological profiles are similar. Clinical studies assessed comparative pharmacokinetics, pharmacodynamics, immunogenicity, as well as clinical efficacy and safety of CT-P13 and showed similarity of the product. Data support

the safety of a single transition from Remicade to CT-P13.

The mechanism of action of CT-P13 and Remicade are the same to the extent that it's known for Remicade. They act by binding and neutralizing soluble and transmembrane TNF alpha.

The same conditions of use are proposed. The route, form, and strengths are the same, and biosimilarity has been demonstrated in clinically active components, and there were no clinically meaningful differences. The bridging criteria have been fulfilled with analytic and PK data.

It is important to note that we are not seeking an interchangeability designation at this time. In line with FDA guidance, we are seeking extrapolation to all approved Remicade indications. Extrapolation is supported by a common mechanism of action, consistency of PK, and similarity of immunogenicity and safety.

It's important to note that extrapolation is not only from the indication studied with the biosimilar but from the reference product label,

and it's based on biosimilarity. In addition, differences between conditions of use do not necessarily preclude extrapolation.

So let me show you how CT-P13 development follows the FDA guidance. Development of CT-P13 began in 2008, and this was prior to establishment of USA legislation or FDA guidance. Development was carried out under scientific and regulatory guidance from the European Medicines Agency.

Analytical and clinical studies compared CT-P13 against EU Remicade. These studies led to EU approval in 2013 and approvals in more than 60 countries including Canada, Australia, and Japan.

The data package to demonstrate biosimilarity in these study countries include a comparative analytical data, mechanistic studies, non-clinical studies, clinical pharmacology, as well as comparative efficacy and safety. Celltrion fulfilled the requirements for biosimilar review for EU Remicade, and these studies align with the FDA biosimilarity pathway.

The FDA guided us to conduct studies to provide a scientific bridge between CT-P13, EU, and U.S. Remicade, including analytical comparison of the structure and function of the three products. In addition, FDA recommended a 3-way PK study to establish a bridge to a comprehensive EU clinical data package. A cross-immune reactivity study was also conducted.

To put the bridging studies in context, it is worth noting that same clinical studies were used to support licensure of Remicade in both the EU and the U.S.

So what is Remicade? Remicade, or infliximab, is a TNF alpha inhibitor that's been used in the United States for 18 years. The therapeutic effect of infliximab is mediated by TNF alpha blockade. Its structure and function are well understood, and its linear pharmacokinetics are well characterized.

Remicade has an established efficacy and safety profile. It's licensed throughout the world with considerable experience in over 4 million

patients. The U.S. and European clinical guidelines support its use in all labeled indications.

Infliximab is a chimeric immunoglobulin type 1 and there are two main regions of the infliximab molecule: the Fab, TNF alpha binding region, which is responsible for the primary mechanism of action through binding TNF, and the Fc effector region, which influences pharmacokinetics and can bind to molecules and cells involved in innate immunity.

The proposed indications, dosage, and regimen for CT-P13 are identical to Remicade. Remicade is approved in multiple chronic autoimmune disorders characterized by auto-expression of TNF alpha with the dosing and administration as listed here.

Why does this molecule work across these indications with different clinical presentations? The reason infliximab works is because it binds and neutralizes TNF alpha, which is a central mediator of inflammation in all these conditions.

Binding of soluble or transmembrane TNF alpha prevents it from binding to the TNF receptors and driving inflammatory disease. Binding to TNF prevents forward signaling, which depending on the type of cell and the environment of the cell, can result in cell death, cell survival, differentiation, and inflammation.

Binding to transmembrane TNF alpha also induces reverse signaling into the immune cell resulting in activities such as inhibition of cytokine release and induction of apoptosis. Interaction between infliximab and the transmembrane TNF alpha and other immune cells can result in induction of regulatory macrophages, which inhibit T-cell proliferation.

As shown, binding with both soluble and transmembrane TNF alpha play key roles in infliximab efficacy.

I'll now describe the structural and physical chemical similarity studies and explain how residual uncertainties were investigated. To support our BLA, analytic studies were conducted

comparing CT-P13 EU and U.S. Remicade to show similarity of CT-P13 with U.S. Remicade and to provide an analytic bridge between EU and U.S. Remicade. This analytic bridge supports reliance in the comparative clinical trial data accumulated with EU Remicade, which show clinical similarity and that there were no clinically meaningful differences between the products.

As recommended by the FDA, we used a tiered approach to statistically assess similarity. Structural attributes and biological activities were ranked based on potential for clinical impact. Assay sensitivity and the level of attribute present were also considered. Biological assays were given high rank in the structure and physicochemical tests.

Three tiers of statistical analysis were applied. Equivalence tests were based on 1.5 times reference product variation as suggested by FDA. Structure and physical chemical test data and the remaining biological assay data was statistically analyzed using the quality range approach.

Quality range limits were based on three standard deviations of U.S. Remicade data, and results were considered to be highly similar where over 90 percent of the data points are within the quality range of U.S. Remicade. Raw or graphical data were visually compared when statistical analysis was not appropriate.

Let me describe the structural and physicochemical studies and data, which provide the first step and foundation for demonstrating similarity of CT-P13 and Remicade.

Analytical tools enable us to characterize the infliximab molecule and its activities and thus demonstrate that CT-P13 is structurally and functionally highly similar to Remicade.

We examined the quality attributes of all three products using orthogonal analytical methods to analyze the primary structure, which is the linear sequence of amino acids; the higher order structure, which is the three-dimensional form that results from folding of the linear chain; protein content, which could impact efficacy and would

manifest through PK in the clinical studies; purity and impurities, which can include high molecular weight forms or non-effect assembled forms; charge variants, which may be deaminated forms, forms with C-terminal lysine variants or charge glycans; and glycosylation where the glycan structures are added to the amino acid to the molecule as its produced in the cell, which can impact Fc receptor binding.

Knowledge of these structural attributes is important since they contribute to the function and biological activities tested in the next step and theoretically can impact efficacy, safety, and/or immunogenicity.

Based on FDA's concept of using a meaningful fingerprint-like analysis, over 20 orthogonal analytical methods were included in side-by-side analysis to analyze the structural and physicochemical attributes.

Each method measures multiple attributes, and all methods were validated or qualified and shown to be suitable prior to use in similarity studies. These data are generally assessed using

the quality range approach.

Let me show you the conclusions starting with the comparison of EU and U.S. Remicade. Overall, EU and U.S. Remicade were highly similar with two exceptions. Two methods, peptide mapping and IEC-HPLC, showed some C-terminal lysine variant variability. The results were specific glycans by analytic glycan analysis were not corroborated by other methods using a greater number of lots.

Overall, high similarity in structure and physicochemical attributes was demonstrated providing the analytic bridge between EU and U.S. Remicade.

When we reviewed the results for CT-P13 and U.S. Remicade, we found that, overall, CT-P13 and Remicade are highly similar in structure. The primary structure of CT-P13 and U.S. Remicade were confirmed to be identical. The higher order structure was highly similar with comparable folding of the proteins. The strength measured of the protein concentration match that of U.S. Remicade predicting similar PK and efficacy of

CT-P13 and Remicade.

Fewer than 90 percent of lots were within the quality range for some attributes but these have no impact on key biological activities, PK or immunogenicity, as we'll see. In the interest of time, we'll only show you some of the many analyses that support high structural similarity.

Here, the data show peptide mapping by HPLC to analyze the primary structure. These offset overlays, show U.S. Remicade in yellow, CT-P13 in blue, and EU Remicade in gray. You can see a highly similar peak profile without missing or additional peaks. Other test methods provided in the briefing book indicate that the structures of the three products are highly similar.

Here is the analysis of higher order structure using differential scanning calorimetry, which measures the heat required to induce a change in the molecule. The transition temperatures for the CH2, Fab, and CH3 domain are marked with dotted lines. The thermal unfolding profiles and transition temperatures indicate that thermal

stability and confirmation are highly similar for the three products. Thus, higher order structure predicts a similar clinical profile.

We also looked closely at the purity and impurity profiles. SEC-HPLC, shown here, detects monomer high molecular weight forms such as multimers and low molecular weight forms such as non-assembled forms. For all three products, a large monomer peak and small high molecular weight peak were observed.

A slightly higher level of high molecular weight forms was detected in CT-P13 but the levels in all three products were below 1 percent. The size of monomer and high molecular weight forms in the three products was the same as shown by other methods.

We also analyzed sub-visible particles. Although there's variability between the lots of each product, the three products were equivalent in sub-visible particles in the 1 to 10 micron range. The high molecular weight forms did not affect efficacy or immunogenicity as supported by our

clinical studies.

Turning to charge variants, using IEC-HPLC, six charge variant peaks were detected in all three products. Minor differences in the proportion of peaks related to C-terminal lysine heterogeneity and studies demonstrated that C-terminal lysines are rapidly removed in serum both in vitro and in vivo. Thus, charge variants are unlikely to affect biological activity or safety.

With regard to glycosylation, results of oligosaccharide profiling by HPAEC-PAD, a normal phase use PLC, revealed that the types and proportions of uncharged glycans was reasonably conserved between the products.

Other methods confirmed that the site of glycosylation and the types of glycan structures present were the same. High similarity was observed in sialic acid content and in monosaccharide analysis.

As you can see, for certain oligosaccharide structures such as G2F and sialylated SA1 and SA2 forms, there was inherent variability between lots

of U.S. Remicade. As explained in the briefing book, CT-P13 contained lower level of G0 glycans than EU or U.S. Remicade. G0 is an a-fucosylated glycan, a glycan structure without a fucoside group [indiscernible], and is present on endogenous antibodies. The magnitude of the difference was very small as shown in the figure.

G0 content is not related to TNF binding. However, a-fucosylated glycans such as G0, can impact Fc-gamma receptor 3a binding affinity, although this is unlikely to have any impact on biological activity or clinical outcome as we'll see.

Overall, the few differences were very small and need to be considered in the context of the entire 1,328 amino acid molecule, its structure, and its function. A step-wise approach was taken to investigate the potential impact of residual uncertainties, and all were fully characterized. The impact on function and biological activities was evaluated, and these studies, together with clinical data, resolved any residual uncertainty.

Let me turn to our function and biological assays, which provide a key component of the analytic biosimilarity exercise and a powerful tool to investigate residual uncertainties.

The biological activities included in similarity studies relate to the Fab binding region, the effector Fc region, and those requiring both binding of Fab and effector regions shown on this slide.

To support ranking for statistical analysis and extrapolation, we looked at literature reports of the structurally-related and structurally-distinct TNF inhibitors to gain an insight into the relative importance of biological activities across infliximab indications.

The primary mechanism of action of infliximab and other TNF inhibitors is the binding and neutralization of soluble and transmembrane TNF that prevents TNF alpha from binding to its receptors. As shown here on the top row, all TNF inhibitors bind TNF alpha with binding affinity in the peak molar range, and all are effective and

licensed for use in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis or psoriasis.

Binding of transmembrane TNF alpha may also be important in IBD. There were differences between TNF inhibitors in both licensed indications and activities. Blocking of transmembrane TNF alpha macrophages induces apoptosis of T-cells, which is thought to be important in IBD.

Reverse signaling and macrophage inducers lead to cytokine suppression, which is also associated with efficacy in IBD, whereas apoptosis induced by reverse signaling in some cell types may not be critical for efficacy in IBD.

In vitro, complement-dependent cytotoxicity, CDC, and antibody-dependent cell-mediated cytotoxicity, ADCC, have been reported for TNF inhibitors with Fc receptors. Unlike antibodies used to induce cell death in oncology indications, the relative importance of CDC and ADCC in TNF inhibitor efficacy is questionable.

For example, Cimzia does not have the Fc

portion required for CDC or ADCC activity but is effective in and licensed for treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderate-to-severe active disease.

This understanding of the mechanism of action provides the basis for assignment for statistical testing and scientific justification for extrapolation of Remicade indications to CT-P13.

We conducted over 20 tests to examine the functional and biological activities. We sought to examine the reported in vitro activities of TNF inhibitors, including soluble TNF alpha binding and neutralization activities, transmembrane TNF alpha binding affinity, induction of reverse signaling and regulatory macrophage induction, C1q binding and CDC activity, and binding to the Fc receptors; ADCC activity induced by both binding transmembrane TNF alpha and an Fc receptor.

EU Remicade was within the equivalence margin of U.S. Remicade for all six activities directly related to primary mechanism of action and PK, shown in the blue, and high similarity was shown for other activities. Thus, overall, EU and U.S. Remicade are highly similar in function and biological activities.

Looking at CT-P13 and U.S. Remicade, CT-P13 was within the equivalence margin for all six tests of activities and related to mechanism of action. Let me show you some of these data in more detail.

These data were analyzed by equivalence tests. The analyses showed that CT-P13 and EU Remicade were equivalent to U.S. Remicade in binding and neutralization of soluble TNF alpha. The top row shows data from studies of TNF alpha binding affinity. The central column shows the data points for U.S. Remicade in yellow, CT-P13 in blue, and EU Remicade in gray. Equivalence test results are shown in the right-hand column.

The second row shows data from TNF alpha neutralization assays using a TNF sensitive cell

line and shows equivalence in this activity.

We also analyzed neutralization of soluble TNF alpha and inflammatory cytokines in an intestinal cell model. Under cultured conditions, these cells differentiate and polarize to resemble enterocytes lining the small intestine. The data show the products to be equivalent.

These data relate to binding of transmembrane TNF alpha. The top row shows cell-based binding affinity determined by ELISA and shows that products were equivalent in binding to transmembrane TNF alpha.

The next three rows show data on inhibition of cytokine release resulting from reverse signaling. The data and statistical analyses indicate that, overall, the three products are equivalent in this activity.

Binding to neonatal Fc receptor, FcRn, is important in protecting antibodies from lysosomal degradation and can affect PK. Analysis of binding affinity showed CT-P13 and EU Remicade within the equivalence margin of U.S. Remicade, supporting

that the products can be expected to have the same PK profile.

Overall, high similarity of CT-P13 and EU and U.S. Remicade were shown in these most important assays relating to binding to soluble and transmembrane TNF and PK. We assessed other biological activities used in the quality range approach and showed high similarity and induction of apoptosis by reverse signaling, binding to most Fc receptors and C1q, and in CDC activity.

However, using a highly sensitive system, a trend to lower values of binding to Fc-gamma receptor 3a of V and F allotypes was observed. This was associated with the lower level of a-fucosylated glycans.

However, there was no significant difference in binding to Fc-gamma receptor 3a present on NK cells in the presence of serum, and to determine the potential impact of this, we examine ADCC activity, although this activity is of questionable importance in infliximab efficacy.

We used three in vitro models with different

target and effector cells. Despite a small downward shift, even the most highly sensitive model, using Jurkat cells that are engineered to over-express high levels of transmembrane TNF alpha and purified NK effector cells showed statistical high similarity between CT-P13 and Remicade as shown by the overlapping data at all three concentrations.

Using preferable blood mononuclear cells, which are more representative of the range of cell types expected to be present at the site of inflammation in vivo, high similar ADCC activity was detected for all three products.

Importantly, no ADCC activity could be detected using the lipopolysaccharide stimulated monocyte model shown at the bottom. This model is considered to be the most representative of the in vivo ADCC target cells and inflammatory foci in the gut. This has also been reported in publications for other TNF inhibitors. These findings were also confirmed using LPMC NK cells from IBD patients.

Overall, the investigations found that there was no impact on functional or biological activities and the residual uncertainties that arose from structural analyses. The difference in intact IgG did not impact biological activity in vitro.

C-terminal lysines were shown to have no consequence as they're rapidly removed in serum, both in vitro and in vivo, and glycation sites were outside of TNF binding region and didn't impact biological activities.

While G0 content did have an impact on binding affinity to Fc-gamma receptor 3a, our ADCC analyses showed that this minor difference does not impact ADCC and thus isn't likely to have significant clinical impact in any of the licensed indications.

The levels of each attribute present in lots of CT-P13 used in clinical studies are consistent with the lots used in these similarity studies. The clinical data indicate no impact on PK, efficacy, or immunogenicity in RA and AS studies.

Let me turn to extrapolation. As we've shown equivalence between CT-P13 and U.S. Remicade and binding and neutralization of soluble and transmembrane TNF alpha and consequential reverse signaling, high similarity was also observed in ADCC assays.

Clinical studies of a biosimilar are not required in all indications. To support extrapolation to inflammatory bowel disease, a number of assays were included to reflect intestinal cells or simulate GI mucosa, so let me show the rest of these data.

As you can see on the top row, high similarity in apoptosis induced through reverse signaling on binding to transmembrane TNF alpha was detected. Although this assay is considered semi-quantitative, data on suppression of T-cell proliferation by regulatory macrophages show high similarity.

There was also high similarity in the induction of regulatory macrophages by CT-P13 and Remicade in mixed lymphocyte reaction, and we used

these regulatory macrophages in a wound-healing assay.

This experiment used co-culture of a colorectal carcinoma cell line with the induced regulatory macrophages. As can be seen from the pictures, similarity in closure of the colorectal cells was observed for three products.

The percentage closure was calculated and the results are shown in the bar chart show similarity between the products in closure of colorectal cells induced by the regulatory macrophages.

Overall, our assays to support IBD indications showed high similarity of CT-P13 in U.S. Remicade and high similarity of EU and U.S. Remicade, and thus support biosimilarity, the analytical bridge, and some extrapolation of Remicade indications to CT-P13.

In conclusion, our comprehensive structural and physicochemical analyses, as well as the in vitro and ex-vivo analyses of biological activities demonstrated that CT-P13 is highly

similar to Remicade. Residual uncertainties identified in structural and physicochemical studies had no impact on functional and biological activities.

Thus, the statutory requirement for analytic studies that demonstrate biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components has been fulfilled.

Studies also confirmed that EU Remicade is highly similar to U.S. Remicade and thus nonclinical and clinical data obtained with EU Remicade are relevant for U.S. Remicade. Knowledge and studies of activities relevant to the mechanism of action support that extrapolation is appropriate to all indications and these data contribute to the totality of evidence demonstrating biosimilarity of CT-P13 with Remicade, supporting that the products can be expected to perform like Remicade in all indications for which Remicade is licensed.

Moving to the nonclinical studies, which fulfill the statutory requirement for animal

studies, including an assessment of toxicity, inform the next step of the pyramid. Overall, the nonclinical pharmacology, pharmacokinetic, toxicokinetic, and toxicology profile of CT-P13 and EU Remicade was similar in animal studies. No residual uncertainties were identified in nonclinical studies.

Now, I'd like to invite Dr. Kudrin to the podium to discuss the clinical studies, which support that there were no clinically meaningful differences between CT-P13 and Remicade.

Applicant Presentation - Alex Kudrin

DR. KUDRIN: Good morning. I'm Alex Kudrin, vice president of clinical development of Celltrion. As a physician, I treated patients with both rheumatic conditions and inflammatory bowel disease and it led to my interest in enabling patient access to affordable biological medicines and development of biosimilars.

Our clinical program was designed to demonstrate biosimilarity and address residual uncertainties. My presentation will focus on three

clinical studies: two studies in ankylosing spondylitis and rheumatoid arthritis patients randomized to either CT-P13 or EU Remicade for 54 weeks. These studies were designed with input from European Medicines Agency and served for EU approval of CT-P13.

A 3-way PK study in healthy subjects using a single-dose, parallel group design to compare the PK of CT-P13, U.S. Remicade and EU Remicade, this study was designed upon request from FDA and was specifically intended to provide a PK bridge between the formerly completed clinical program against EU to U.S. Remicade and support other 3-way analytical data against the U.S. reference product.

All three studies collected PK, immunogenicity and safety data. RA and AS studies also collected efficacy data with RA study designed as a therapeutic equivalence study against EU Remicade.

First, I will begin with clinical pharmacology, the most discerning method for demonstrating biosimilarity to the reference

product.

The rationale for the study population is supported by the following: healthy subjects served for PK bridging study represent an immunocompetent population; in AS, there is no background immunosuppression, and the 5-milligram is representative both for non-arthritis indications in IBD and psoriasis; RA is accompanied by extensive clinical PK and safety experience and uses potentially more immunogenic dose of 3 milligrams; lastly, similar comorbidities observed in patients with psoriatic arthritis and psoriasis.

Let me turn to our assessment of PK. All three studies collected PK measurements at baseline and periodically during each shown as shown. The PK endpoints employed in these studies were selected in line with FDA expectations for a single-dose or repeat dose studies.

The AS and 3-way PK studies predefined the similarity margin as 80 to 125 percent of Remicade PK based on the ratio of geometric means.

This range is justified given the linear and well characterized Remicade PK across all indications.

Publication supports a broad therapeutic index in terms of impact of study doses of 3, 6, and 10 milligrams. Importantly, there are no prominent drug-drug interactions and comparable safety profile across indications and wide range of plasma concentrations.

Let's now look at the long-term PK data in patients beginning with ankylosing spondylitis. Ankylosing spondylitis study was randomized, double-blind, multicenter, parallel group prospective phase 1 study in patients with active AS based on 1984 New York criteria with history of disease for at least three months prior to screening and who were not receiving background immunosuppressive therapy.

Upon completion of 54-week period for the control study, patients who were treated with Remicade were allowed to transition on CT-P13 and were monitored for efficacy, safety, and immunogenicity up to week 102.

This graph illustrates serum concentrations over time and show highly similar PK profile between CT-P13 and the EU Remicade at the steady state period.

We have also examined PK in RA study. Patients were dosed with 3-milligram on background with methotrexate. Again, we see highly similar PK when compared in CT-P13 and EU Remicade when looking at repeat Cmax and Cmin over 54 weeks.

Moving now to 3-way PK study, this study demonstrated that CT-P13 has a highly similar PK profile when compared into either EU or U.S. Remicade in healthy volunteers with similar Cmax and elimination profile over 56 days following a single dose of 5 milligrams. The inset shows a more detailed PK over the first 72 hours.

We have measured C-reactive protein and ESR in AS and RA studies. This pharmacodynamic marker showed similar pattern of reduction from baseline from treatment initiation through 54 weeks. As an example, on this diagram, the concurrent effect of CT-P13 and Remicade on ESR and DAS28 CRP in RA

study shown illustration is similar PD effect. As a next step, I'll discuss the evaluation of immunogenicity.

We conducted in vitro cross-reactivity experiments using serum from inflammatory bowel disease patients who are positive for EU Remicade anti-infliximab antibodies. This graph illustrates the titer of the antibody binding between SERA of ADA-positive patients with different clinical lots of CT-P13, EU, and U.S. Remicade.

This in vitro experiment demonstrated similarity in presence of immuno-dominant epitopes between CT-P13, U.S., and EU Remicade and showed strong correlation in binding and neutralization titers and pattern.

The immunogenicity profile within AS and RA studies with EU-approved Remicade was similar in patients treated up to 54 weeks. Of note, the RA study employed 3-milligram dose plus methotrexate. In the AS study, a dose of 5 milligrams was used in the absence of background immunosuppression.

Antibody formation increased with time and

became steady after week 30, indicating that it takes repeated administration for the anti-infliximab response to completely unfold. This is similar to antibody formation reported with Remicade in AS and RA patients.

There was a similar and consistent pattern of titer and density and evolution with time. A consistent immunogenicity profile was observed in both extension studies when treating patients up to week 102. Levels did not change significantly from levels reported at week 30.

Patients maintained on CT-P13 and patients transitioned from Remicade to CT-P13 demonstrated antibody rates in line with baseline and published data and long-term treatment with infliximab. Importantly, the immunogenicity profile remains stable following single transition. This data support immunogenicity similarity between CT-P13 and Remicade.

We found the incidence of either infusion-related reactions or anaphylaxis, based on the Sampson criteria 2006, were generally similar

and supportive that any small variation in immunogenicity did not lead to clinical sequela.

As reported with Remicade, incidence of infusion-related events was high in patients with antidrug antibodies than in patients without antibodies. There were no meaningful differences between CT-P13 and EU Remicade in ADA positive and ADA negative subgroups for rates of infusion-related reactions.

We have also obtained preliminary data for immunogenicity from an ongoing randomized control study in patients with moderate-to-severe Crohn's disease. Interim analysis from 109 Crohn's disease patients illustrates that immunogenicity between CT-P13 and U.S. Remicade group was similar. This data further supports 3-way analytical and 3-way PK bridging data between U.S. Remicade and CT-P13. We also believe that these data are of importance to IBD medical community and provide further scientific evidence for extrapolation.

Our data supports CT-P13 having the similar immunogenicity profile to that of Remicade. This

was based on a systematic evaluation of immunogenicity using validated state-of-the-art methods across all clinical studies. A similar proportion of patients developed an ADA through CT-P13 and Remicade in AS, RA, and CD. We have also examined the impact of immunogenicity on PK, efficacy and safety in control phases, and effect on safety and efficacy in extension phases.

As expected, there was a trend for reduction of circulating levels of infliximab in antibody-positive patients in both treatment groups. However, the PK, efficacy and safety were comparable in ADA positive and negative subgroups between Remicade and CT-P13.

Post hoc examination of the effect of methotrexate on immunogenicity profile showed similar findings between CT-P13 and Remicade. The incidence of infusion-related reactions across subgroups was also similar between CT-P13 and Remicade.

Now, I will discuss results of our clinical study in RA patients. A therapeutic equivalence

study in RA was designed following scientific advice with European Medicines Agency in 2009, which agreed with overall design, population choice and the ACR20 margin. This study was pivotal for EU approval.

RA is the most studied indication for infliximab of all the proposed indications. This indication is sufficiently sensitive as evident from magnitude of therapeutic response in efficacy and supported by dose-dependent historical data. A validated primary endpoint, ACR20, was used to establish equivalence. Importantly, an RA patient population, a lower and potentially more immunogenic dose of 3 milligrams was used.

RA study was a multicenter, double-blind, randomized therapeutic equivalence study to confirm similar efficacy, safety and immunogenicity. Patients were randomized 1 to 1 to CT-P13 and Remicade at the approved dose. The analysis of the primary endpoint was stratified by region and C-reactive protein or CRP. The duration of the study was 54 weeks.

Upon completion of treatment, Remicade patients were allowed to transition to CT-P13 and CT-P13 patients continued on therapy. This extension period lasted to week 102, and this design generated single-transition data.

The primary endpoint was ACR20, which was measured at week 30. We also evaluated a series of secondary endpoints including ACR20, ACR50, ACR70 at all time points, DAS28, and collected geographic evidence in inhibiting structural progression.

The prespecified equivalence margin of 15 percent with 95 percent confidence interval and result in power of 80 percent for ACR20 was justified based on absolute treatment difference in historical RA study with Remicade, including the ATTRACT trial, and it was agreed by European Medicines Agency.

When the EU program was presented to FDA in 2014, the agency requested that we justify the equivalence margin using the meta-analysis of randomized control studies with Remicade and was defined using a lower bound confidence interval

that preserves 50 percent of the clinically relevant effect of Remicade. This post hoc analysis led to equivalence margin of 12 percent with 90 percent confidence interval.

Six hundred and six patients were randomized; 302 patients through CT-P13 and 304 patients to EU Remicade. Twenty-three percent of patients in CT-P13 group and 27 percent in Remicade group discontinued the study. The most common reasons for withdrawal was adverse events and withdrawal of consent. Demographic characteristics were balanced between treatment groups.

Looking at the primary endpoint results, we see that a similar proportion of patients in CT-P13 group and the EU Remicade group achieved a clinical response according to ACR20 criteria at week 30, 60.9 percent for CT-P13 and 58.9 percent for Remicade.

The two-point difference in responders has a 90 percent confidence interval of minus 5 to 9 points falling within the 12 percent equivalence margin suggested by FDA. Therefore, therapeutic

equivalence between CT-P13 and Remicade has been established.

The ACR20 response rate attained in Remicade group, highlighted in yellow, was in line with historical data. While these inter-study results has limitations, they provide directional support for efficacy equivalence.

An important design consideration in equivalence trials is the constancy assumption, which is an assessment of the likelihood that the effect of the active to control is similar to past effect.

The results from the RA trial align with historical studies. Importantly, as shown by the narrow arrow bars, equivalence was well within both predefined and FDA-suggested margin derived from the meta-analysis.

We see the time-dependent response rate for CT-P13, in blue, is similar to the results seen with Remicade, in gray, throughout the 54-week treatment period. The response rate was similar between groups for ACR50 and ACR70 endpoints but

without prespecified equivalence margins. Similar responses were observed for a number of secondary efficacy endpoints including DAS28 CRP.

Next, I will review the safety data from CT-P13 clinical trials, focusing on repeat dose, AS and RA studies.

As outlined in FDA guidance, biosimilar products can rely on certain existing scientific knowledge about safety, purity, and potency of the reference product to support licensure as there has been considerable global postmarketing experience with Remicade with more than 4.2 million patients treated globally.

We also should recognize that infliximab is a chimeric monoclonal antibody capable of inducing antidrug antibodies and a range of other risks, which were systematically documented in the reference product label. Comparison of safety across all approved indications reveals consistent frequencies and nature of adverse events.

Over 1,000 patients were treated with either CT-P13 or Remicade in randomized controlled

studies. It is important to note that this safety database aligns with FDA and EMA biosimilar guidances, providing sufficient exposures for confirmation of common events. Whilst we acknowledge limitation of this database in detecting rare adverse events, high degree of structural, functional, and pharmacological similarity to Remicade provide with confidence on overall similar safety profile.

Of this, more 800 subjects were treated with at least one dose of CT-P13. The safety database is characterized by diverse demographies and geographies.

The population profile was in line with ethnicities of regions participating in the studies and patients had representative comorbidities. Of the 800 CT-P13-treated patients, more than 650 were treated for at least 6 months and more than 600 for at least 1 year. At least 230 patients were treated for at least 2 years.

As of 31st of December 2015, postmarketing experience with CT-P13 in ex-US jurisdiction now

consists of more than 58,000 patient-years and continuously growing.

A consistent pattern of safety findings was found in RA and AS studies over a 54-week period. This data is consistent with the Remicade package insert. A total of 4 patients died during the clinical study program: 2 on CT-P13 and 2 on Remicade. The study treatment days on therapy and cause of death are listed here. The treating investigator did not believe they were related to therapy.

Similar proportion of patients reported adverse events leading to discontinuation in CT-P13 group compared to EU Remicade. The most frequently reported adverse events leading to discontinuation match those previously reported for Remicade including infusion-related reactions and infection.

We also see a similar proportion of patients reporting adverse events in CT-P13 and Remicade groups. Across AS and RA data set, upper respiratory infections, latent TB, urinary tract infection, and increase in liver enzymes were most

frequent types of adverse events. These are expected in line with known Remicade profile and usage of methotrexate in RA patients.

Through a CT-P13 clinical development program, we have not identified any new safety signals, and the safety profile appeared to be consistent with that of Remicade.

In line with Remicade prescribing information, we have carefully examined those adverse events of special interest to physicians using TNF alpha inhibitors. This includes infections, all serious infections, pneumonia, active TB, malignancies, and infusion-related reactions.

In order to evaluate relative risk, we compared these adverse events across all integrated safety data set shown as incidence rates per 100 patient-years, including 95 percent confidence intervals and compared to published, randomized, and controlled Remicade studies in RA and AS patients.

We have also examined any new medical

differences at integrated levels and found that that there were no consistent pattern on study level or case event level. These are likely chance findings.

Recognizing there are limitations, we have conducted a comparative safety analysis against historical ITT data in AS and RA patients. There was a high variability in the incidence in some of these adverse events of special interest, but the incidents raised for CT-P13, shown in blue, are consistent with those reported with Remicade for all adverse events of special interest.

We conclude that CT-P13 has a safety profile similar to Remicade as would be expected from highly similar structure, function and PK. There were no clinically meaningful differences between CT-P13 and Remicade in relation to overall safety and immunogenicity.

We have observed similar impact of immunogenicity on PK, efficacy, and safety across all studies. There are robust pharmacovigilance systems in place for continued diligent monitoring

for postmarketing safety surveillance of CT-P13.

Let me summarize CT-P13 efforts to follow a step-wise development approach. The totality of evidence from CT-P13 program supports biosimilarity although high similarity was observed in structural and physicochemical tests and in minor residual uncertainties resolved using robust state-of-the-art functional and biological assays.

High similarity was observed in functional and biological assays. Any remaining residual uncertainty was resolved by a systematic assessment of PK and immunogenicity. No clinically meaningful differences were observed in PK, immunogenicity, efficacy, and safety. An equivalent PK profiles and efficacy was shown in AS and RA studies.

The totality of the evidence supports CT-P13 is biosimilar to Remicade. Consistent with the principles outlined in FDA guidance, Celltrion provided a scientific justification for extrapolation of all indications approved for US-licensed Remicade.

Our comprehensive structural and functional

studies evaluating published mechanism of action involving Fab and Fc regions of CT-P13 demonstrated high similarity.

A number of biological assays were included in a comparative evaluation and were designed to represent different clinical scenarios and specifically those of inflammatory bowel disease, including in vitro models using intestinal cells or in vivo situation in the gut.

Additionally, in line with FDA guidance, differences between conditions of use with respect to mechanism of action or pathophysiology of condition of use do not necessarily preclude extrapolation. We're confident the extrapolation is scientifically justified based on the following:

Our studies demonstrated high similarity of CT-P13 against U.S. Remicade with respect to all known and potential mechanism of action involving Fab and Fc region of the molecule.

Publications demonstrate a linear and predictable PK profile across all approved conditions of use. This includes similarity of

Remicade pharmacology in adults and pediatric Crohn's disease patients.

In CT-P13 studies, highly similar linear and predictable PK profile was demonstrated in three distinct populations, healthy subjects, AS and RA patients.

Finally, similar immunogenicity and comparable safety between CT-P13 and Remicade were demonstrated in AS and RA studies. In addition, the immunogenicity was similar between CT-P13 and U.S. Remicade in Crohn's disease patients.

The consistent immunogenicity and comparable safety profile of Remicade across all conditions of use, as reported in the literature, scientifically justify extrapolation to all indications.

Next, I'd like to invite Dr. Peter Lakatos, a treating physician from Semmelweis University in Budapest, to the lectern to discuss clinical data available with CT-P13 in IBD patients available thus far and his ongoing study with CT-P13 in patients with Crohn's disease and ulcerative colitis.

Applicant Presentation - Peter Lakatos

DR. LAKATOS: Thank you, Dr. Kudrin.

Good morning. My name is Peter Lakatos and I'm the head of the GI service at Semmelweis University of Budapest, Hungary. I will present now real-world CT-P13 data in patients with inflammatory bowel disease, including a prospective nationwide observational study in Hungary that was recently published. This data set has also been submitted to the FDA.

As per December 2015, more than 1200 patients with different forms of IBD were treated with CT-P13. The long-term safety and efficacy data are available for up to 30 to 54 weeks duration in Korea and Hungary. Since I do not practice in the U.S., let me first give you an overview of my experience.

I have been practicing gastroenterology in Hungary for more than 15 years with wide experience treating patients with Crohn's disease and ulcerative colitis. I have conducted and run clinical studies and registries at the national

level using treatment paradigms and products that are available in the United States.

Within the European Crohn's and Colitis Organisation, I was head of the epidemiology committee. Currently, I'm a member of the educational committee and national representative for Hungary. I also assisted in the foundation of the Hungarian IBD study group. As such, I have relationships with companies that develop products to treat IBD. Here are my disclosures.

The Hungarian IBD Study is a prospective nationwide, multicenter, single-arm observational study to evaluate effectiveness and safety of CT-P13. This study was initiated in May 2014 following the launch of CT-P13 in Hungary using the EU label that includes all infliximab indications, including Crohn's disease and ulcerative colitis.

According to the current regulation in Hungary, new patients in need for anti-TNF alpha therapy are required to start CT-P13. New patient definition includes both patients that are naïve, as well as those previously treated with Remicade

but who transitioned to CT-P13 for reimbursement reasons.

Patients are evaluated at baseline, week 13, and then every 3 months to collect long-term efficacy data; and harmonized throughout the centers as mandated by the National Insurance Company. The study will follow enrolled for at least 54 weeks. I will now present data from the induction period through week 14.

To-date, 126 Crohn's disease patients and 84 UC patients have been enrolled. Patient demographics, disease characteristics are representative of patients in Europe and the United States.

Enrolled patients have moderate and severe disease activity and have had their disease for several years ranging from 3 to 11 among those with Crohn's disease and 2 to 12 in UC. Twenty-six percent of Crohn's disease patients have had past surgical resections.

As expected, the enrolled patients have also had extensive use of anti-inflammatory and

immunomodulatory therapy prior to being treated with CT-P13. Twenty-six percent of Crohn's disease patients and 19 percent of UC patients also previously received anti-TNF alpha therapy prior to receiving CT-P13. However, it is important to note that these patients have been off the therapy for at least 12 months and were recommenced on CT-P13 due to relapse.

As you can see, many patients continue to receive concomitant anti-inflammatory and immunomodulatory therapy along with CT-P13. We can see early clinical response and remission at weeks 6 and 14 when looking at available patients with Crohn's disease. We see similar early clinical response and remission are shown in patients with ulcerative colitis. We measured biomarkers including CRP, which showed a decrease along with clinical response in IBD patients.

Mucosal response with CT-P13 was also evaluated at week 14 in the Hungarian study. These rates were consistent with historical data with Remicade in Hungary.

Now, I will show early therapeutic drug monitoring results stratified by prior anti-TNF exposure. We have also determined anti-infliximab antibody responses in patients using a validated ADA assay and found that ADA incidence was consistent with historical data for Remicade.

In patients with prior exposure to anti-TNF alpha agent and specifically Remicade, ADA responses were detected at baseline and at week 14 in approximately one-third of the patients illustrating that ADA cross-react between Remicade and CT-P13.

The next slide summarizes available postmarketing real-world clinical experiences in IBD cohorts in Europe and South Korea, including a global post-approval, parallel design, single-switch Crohn's disease study. Currently, published global postmarketing experiences in IBD patients with CT-P13 exceed 1200 patients with different forms of IBD.

While I acknowledge the limitations of cross-trial comparisons due to methodological

differences, they can have to put these data into context. I will next present comparative analysis of response and remission rates, as well as mucosal healing in patients with Crohn's disease and ulcerative colitis as reported with Remicade in key published clinical trials compared to CT-P13 data.

Here, in blue, we present the clinical response and remission results at week 14 and 30 with CT-P13 in patients with Crohn's disease in the Hungarian and South Korean studies. Shown in orange, historical response and remission data with Remicade show comparable results.

Likewise, here is the comparative analysis for UC studies including additional CT-P13 data from Norway. Again, CT-P13 data are in blue and published Remicade studies in orange.

Mucosal healing is an important clinical measure in IBD, predictive for favorable long-term outcomes, including sustained clinical remission, corticosteroid-free remission, reduced hospitalization, and risk of colectomy.

Here, I illustrate mucosal healing data at

weeks 14 and 30 in patients from UC in the Hungarian and South Korean studies. Again, CT-P13 is shown in blue and historical Remicade data in orange.

Although uncontrolled, these data further support that CT-P13 is effective in inflammatory bowel disease as evidenced by clinical response, remission, mucosal healing, as well as biomarker response rates as shown in the EU and South Korean cohorts. Importantly, clinical data with CT-P13 from more than 1200 patients from Crohn's disease, ulcerative colitis and fistulizing Crohn's disease were documented.

Positive clinical experience with the use of CT-P13 in IBD setting has gained endorsement of EU IBD medical societies and experts. Drug trough and ADA levels are collected in Hungary and are consistent with what we know about the use of Remicade in IBD patients.

While we continue to gather and report data, the data collected to-date suggest that CT-P13 is biosimilar to Remicade in patients with Crohn's

disease and ulcerative colitis.

Thank you. I will now invite Dr. Strand to the podium.

Applicant Presentation - Vibeke Strand

DR. STRAND: Thank you. Good morning.

I'm pleased to be here to provide my clinical perspective on CT-P13. I'm an adjunct clinical professor in the Division of Immunology and Rheumatology at Stanford University, and I've used all of these new biologic and synthetic therapies that have been approved for the treatment of rheumatoid arthritis since 1996.

Serving as a consultant since 1991, I've worked on all the products that have been approved in rheumatology, and I've served as an FDA-invited member on eight Arthritis Advisory Committee meetings discussing draft guidance documents for a variety of rheumatic diseases. Here are my disclosures.

The emergence of biosimilars is an important next step. We know from Europe that biosimilars have increased access to effective expensive

therapies and lowered the cost to society in treating chronic autoimmune diseases. The example of filgrastim in the United Kingdom has allowed broader use of effective doses to prevent febrile neutropenia.

I'm confident in the biosimilarity pathway here in the United States. It does not require large randomized controlled trials, and small residual differences can be assessed in the context of the variability of our currently available biologic therapies.

How do I evaluate this biosimilar? CT-P13 shows equivalent structural and functional characteristics to the reference product. CT-P13 and the reference product have similar efficacy and immunogenicity and comparable safety profiles. And from a patient-reported perspective, I'm going to show you the health-related quality of life data from the RA study using the short form SF-36.

There are eight domains from physical function at 12 o'clock through role physical, bodily pain, and general health perceptions that

are considered the four physical domains. Vitality at 6 o'clock, social functioning, role emotional, and mental health are the four mental domains. They're scored from zero to 100. The higher the score for any domain, the more normative or better the health-related quality of life, the higher the area of the plot. The gridlines are 10 points each, and the minimum clinically important difference is half of that or 5.

Here are the scores for the entire protocol population at baseline, and they are now compared with age and gender match normative scores in the U.S. in patients without disease. You can see the large decrements in health-related quality of life based on active rheumatoid arthritis, not just in the physical domains but also in the mental domains.

Now, at 30 weeks, we see the improvements reported with Remicade treatment and similarly with CT-P13. The SF-60 utility score, which quantifies these changes, were virtually identical between the two products.

Now, quickly, I can show you the health-related quality of life data from the ankylosing spondylitis study. First, we have the baseline and the age and gender match normative scores. Now, we see the improvements with CT-P13 at 30 weeks and similarly with Remicade at 30 weeks. And again, the SF-60 utility scores are highly similar. This further reassures me that the use of this biosimilar would bring significant benefit to my patients.

As shown, the clinical performance is aligned with the reference product. As a rheumatologist and a practicing physician, I'm also interested in hearing about the use of CT-P13 in IBD from my colleague gastroenterologists. It's reassuring to see that extrapolation is further supported by real-world use of this biosimilar product in other countries.

In consideration of extrapolation to psoriasis and psoriatic arthritis, we know that all the TNF inhibitors of different structure are effective and approved in psoriatic arthritis.

Cimzia is currently in phase 3 trials with psoriasis.

Inhibition of soluble and transmembrane TNF is a primary mechanism of action of these agents in both diseases. We know there's a comparable immunogenicity profile between patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis. And there's comparable use of methotrexate in other immunomodulatory therapies across RA and psoriatic arthritis.

In summary, based on my clinical experience, the totality of the evidence indicates to me that CT-P13 has a favorable biosimilar profile. It's been demonstrated to be highly similar to the reference product structurally and functionally by efficacy and immunogenicity with a comparable safety profile.

I think that this supports licensure as a biosimilar to Remicade, extrapolation to all the other clinical indications for which Remicade is approved. Lastly, I would expect that approval would bring significant benefits by improving

access and reducing cost to patients.

Thank you, and I will now ask Dr. Kudrin to return to answer questions.

Clarifying Questions to the Applicant

DR. CAPLAN: Are there any clarifying questions for Celltrion? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific speaker.

We'll start with Dr. Bergfeld.

DR. BERGFELD: Yes, I'm Dr. Bergfeld. The one question I had was there was no mention of impurities. Is that something we could hear about?

DR. KUDRIN: Absolutely. I would like to invite to Dr. Pollitt to respond.

DR. POLLITT: Thank you. Yes. We look at impurities in a number of different ways. We look at the high molecular weight forms, fragments. We also look at the charge variants, but those are all biologically active so we don't consider those to be sort of functional impurities. We also look at whole-cell DNA and the whole-cell proteins that are present in all biological products resulting from

the manufacturing process. And we have very low levels of these in the products, and we've shown that the equivalent or lower than are present in that reference product.

DR. BERGFELD: And they're clean of infectious products?

DR. POLLITT: Sorry?

DR. BERGFELD: Are they clean of infectious agents?

DR. POLLITT: We analyzed the whole-cell banks and the working-cell banks for adventitious agents for all types. We also have five steps in the manufacturing process that are designed to remove or inactivate any adventitious agents that could be present although obviously, our whole-cell banks are clean.

DR. CAPLAN: Thank you. We'll next move to Dr. Brittain.

DR. BRITTAIN: Hi. Yes. I want to ask about slide CC-74. I just want to get -- I think I understood that you originally proposed a 15 percent margin, and FDA is suggesting

12 percent. If I understood correctly from the briefing package, the 12 percent is based on retaining 50 percent of the benefit.

Essentially, you've done a test -- you easily met that test, but essentially you've a done test of saying the new treatment is within -- retaining at least 50 percent of the benefit; is that a correct assessment or interpretation?

DR. KUDRIN: That's a correct interpretation. In our briefing book, we write about 13 percent margin for reasons that meta-analysis we conducted excludes SHIFT study, which was included by FDA. The reasons why we excluded the SHIFT study was that was conducted originally against abatacept as opposed to placebo and also included more severe disease characteristics at baseline.

Nevertheless, in order to align ourselves with FDA briefing book, we also executed analysis with SHIFT study and presented here today. Regardless of whatever equivalence margin we apply,

using 90 percent but in fact, also, was 95 percent confidence interval for 12 percent, we are within this margin, and in fact for not only ITT but also for the protocol population. And also, we're on a number of different sensitivity analyses, which also aligned.

DR. BRITTAIN: I have a quick follow-up. In the historical studies, were they using the same sort of concomitant drugs that -- because I believe I heard that in your studies, there was a lot of concomitant drugs used in addition to the methotrexate. Was it similar in the historical studies?

DR. KUDRIN: Certainly. In the process of conducting meta-analysis, whereas related studies, which were similar or at least we tried to conduct as much as possible, here on this slide, you can see that historical studies included in to meta-analysis aligned in terms of inclusion criteria and usage of methotrexate.

Our study population was quite severely sick based on the fact that we ran the study globally,

including some territories outside of the European Union. So these patients have been exposed to steroids and methotrexate for a long time.

Certainly, looking at the comparison in terms of the severity to other studies, you can see that also comparison of Planetra or RA study from our program to SHIFT study on this slide, you can see that it's reasonably comparable for the baseline characteristics.

DR. CAPLAN: Dr. Gobburu?

DR. GOBBURU: I'm curious as to the need for connecting two trials, RA and AS, and weigh those two.

DR. KUDRIN: Right. Originally, the idea to support this licensure in the European Union was based on the idea that we would conduct PK similarity studies in a population where there is no background immunosuppressive therapy. Also, as I explained in the presentation, a 5-milligram dose was a dose, which was different to our dose employed in RA population.

Having these two studies has actually helped

a lot now because we can see obviously aligned results in terms of different interpretation for not only pharmacokinetic profile but also in terms of immunogenicity data and also looking at the safety.

We examined also carefully in both studies, obviously, impact of immunogenicity and that was similar. But originally, this was an idea to actually try to underpin the downward indication in the label.

DR. CAPLAN: Next up, Dr. Cramer?

DR. CRAMER: Yes. Hi. You mentioned manufacturing process was the same. Can you quickly give us the overview of your manufacturing process?

DR. KUDRIN: Certainly. Dr. Pollitt, please?

DR. POLLITT: The manufacturing process for our product is similar to many monoclonal antibodies. Rather than highlighting our manufacturing process, although the originator's has been published in broad detail in some

publication, but this is just our product development strategy.

It's based on defining the target range for the originator product identifying critical quality attributes, selecting the cell line. We conduct process optimization studies, and obviously, transfer is needed scaled up. But we also looked at suitability of the formulation, which is the same as that for the originated product. Throughout the development, we do look at key criteria in terms of a similarity.

DR. CRAMER: And there's no issues -- quick follow-up -- and there's no issues with doing this in different locations, different scenarios, right? We could get similar performance?

DR. POLLITT: Yes, we can get similar performance. As we scale up, we are deliberately redesigning the manufacturing process to scale appropriately to maintain biosimilarity.

DR. CAPLAN: Thank you. Next up, Ms. Aronson.

MS. ARONSON: Thank you. It's a very

impressive presentation, which I really appreciate. My question is two-part. The first is clarification, which would be nonclinical, and the second would be the clinical studies. The first is, just to clarify, the European version of the biosimilar is approved for RA and AS only; is that true?

DR. KUDRIN: No. European version is approved for all indications of Remicade in the European Union.

MS. ARONSON: And in Canada, it's just RA and --

DR. KUDRIN: In Canada, it's -- RA, AS and also psoriasis and psoriatic arthritis but not inflammatory bowel disease indications.

MS. ARONSON: Thank you. And for the European biosimilar, as far as the label, is there any indication for the patient or understanding about how this might be different than Remicade, the European version?

DR. KUDRIN: For the European product, the label is absolutely identical to that of reference

product in the European Union. Obviously, from what we have seen now in ex-US jurisdictions in 67 countries where the product has been approved and 58,000 patient-years we accumulated experience, the safety is exactly consistent with that of Remicade.

This is the pattern of cumulative exposure shown over a period from launch of the product. You can see that exposure is growing, and we haven't seen anything different from what is known with Remicade.

We have a robust risk management plan in Europe where we have a number of ongoing registries and postmarketing safety studies. And pharmacovigilance systems for this product will be working in conjunction with Pfizer who will be marketing this product, who obviously have a robust and global experience with a number of products.

In terms of differences, no, there are no differences because we provided, today, scientific bridge between European and the U.S. products, which is a 3-way bridge, which is based on two

parts, analytical part where a large of number of orthogonal analytical tests and biological assays have been done to align three products, EU, U.S. and CT-P13, but also 3-way PK study showed today indicates a highly similar PK profile between three products.

DR. CAPLAN: Dr. Shwayder?

DR. SHWAYDER: Dr. Shwayder. I have several questions. Bring up slide 56, please, and nothing more the company will know that I was looking at the slides. How did they come up with 80 to 125; is that the company or is that FDA?

DR. KUDRIN: Well, our margin was defined based on guidance from FDA, but also, we had an ongoing dialogue with agency, and they concurred with this approach.

The principles based here is actually outlined on this slide. The infliximab has a broad therapeutic index, and that allows to use 8 to 125 percent criteria for bioequivalence as opposed to more narrow criteria for equivalence, and the fact that there are no prominent drug-drug

interactions and comparable safety profile.

You can see on this slide the differences in statistically recommendations of PK assessment, which is effectively similar between FDA and the EMA. The confidence interval for biological and biosimilar products are usually -- was 125 percent with justification, which remained in our BLA, and 90 percent confidence interval for geometric means is what is actually recommended. We employed that across all our studies.

DR. SHWAYDER: Next slide, 63. The big problem we have with biologics is after a year, the patients develop antibodies to the drug and we have to stop using it. The 41 versus 36 caught my eye. Do you have data that this divergence continues?

DR. KUDRIN: Right. I think the best way would be to look at also the profile in controlled and extension study at the same time so then we can see how this pattern evolves.

The antibody formation plateaus at week 30 and then remains stable over time. We examined also carefully how this impacts in ADA-positive and

ADA-negative patients in terms of type of response. So you can see, for example, neutralizing antibody formation, which is recognized with infliximab to be largely contributing to antibody response. Again, it's comparable between groups over two years.

Then, looking at the impact on PK, for example, in the 3-way study, you can see that primary analysis wasn't influenced in a sense that all three co-primary PK endpoints were met even in ADA positive subjects, which shows that -- and also in similar manner in AS study, we looked at the -- in RA study, we looked at the impact on PK and efficacy.

Maybe we can have a look at efficacy profile of ACR20 across both two years' period. So this is the impact of ADA's on ACR20, and as expected, there is some reduction of response as expected in ADA-positive patients. And if we look at the proportion of ACR20 responders over two years, you can see how it's distributed in ADA positive and ADA negative subgroups in comparison between CT-P13

and Remicade.

DR. SHWAYDER: Good. Someone thought of it.

Next slide, 69, and this is more of a real-life question. The real-life question we say in psoriasis, when someone tells me they have a 90-percent psoriasis clearance or a 20, I say, but you still can't put on your swimsuit and go to the beach.

So if you have an ACR of 20, you still have to use your walker to get to the store. Why was this a validated endpoint for equivalence? What about the ACR90? Again, do things diverge at an upper end?

DR. KUDRIN: I'd like to invite Dr. Strand to comment on this.

DR. STRAND: Strand, Stanford. Actually, I was part of the outcomes in Rheumatology OMERACT group that helped to develop the ACR criteria. And they were proposed in 1995 and have been used ever since for every rheumatoid arthritis therapy.

Agreed that ACR20 does not seem like a very high bar, but it requires improvement across 5 of 7

different components, three of which are patient-reported, three of which are physician-reported. And asking for that level of improvement is actually a considerable amount of improvement, and we always look at 50s and 70s as well, as you've seen in the pictures.

This is a consistent way -- every rheumatoid arthritis therapy since 1996 has been looked at. And in fact, we do see that once you get a 20, you will get a 40-, a 50- and you will get a 70-percent response. And in general, across all of our therapies, we see in ACR20 of 60-percent, a 50 of 40 percent, and a 70 of 20 percent in patients that are TNF-naïve. It's very consistent with the data here. So we do think that this is actually a significant improvement.

DR. SHWAYDER: Okay.

DR. CAPLAN: I'd like to give some of the other panel members a chance to ask questions, so if you wouldn't mind, we can come back.

Dr. Becker?

DR. BECKER: Hi. As a pediatric

rheumatologist, we tend to be a little bit more liberal with our dosing. And I appreciated the comment from the prior committee member.

I'm curious, do you have any real life data on using higher doses of this agent, like the 10 per-kilo range?

DR. KUDRIN: Thank you very much. Considering that PK was linear and predictable in both AS and RA studies at 3 and 5 milligrams, we conducted PK modeling exercise, obviously acknowledging limitation of this approach.

What we did, we combined data set for the AS study; it was 5 milligrams using 3-compartment model and accounting for intra-individual variability for clearance and volume of distribution.

Then we also looked at the similar PK data set in RA study and predicted, based on these two data sets, that at 10 milligrams, we would have similar peaks and similar predictable PK profile. Acknowledging limitations of PK modeling, we also collect diligently data on safety from patients

with inflammatory bowel disease and also in RA.

Limited data in safety has been collected currently from extension study in Japan at 10 milligrams and also in Korean postmarketing study. Largely, this data focused around treatment-emergent adverse events, and they are consistent with those observed with 5 milligrams. So we haven't seen anything new there.

DR. CAPLAN: Dr. Schiel?

DR. SCHIEL: Yes. I have question for Dr. Pollitt. I was actually looking at the various analytical assays in the fragment species that were identified. So CE-SDS is the only assay that I'm seeing that actually could look at these fragment species, which at some point, of course, this could eventually lead to a decrease in efficacy.

I'm curious, if there has been -- in looking at alternative assays such as a non-reduced intact mass spectrometry or other assays to identify what the cause of this is. And second is this part of the control strategy, at what limits are we going to control the free light-chain fragmentation.

DR. POLLITT: Thank you. Yes, we look at the fragmentation primarily by CE-SDS. We haven't applied other methods specifically to look at the fragments. What we can say is, actually, we've seen incredibly low levels of these non-assembled or fragments forms, and they are at the same levels as in Remicade.

The predominant fragment is H2L1 form. That's the predominant fragment. But obviously, we do see very low levels of H2 and L1 forms. Yes, it predominantly CES. Yes, we haven't looked specifically at other methods.

DR. CAPLAN: Thank you. Next up, Dr. Fuss?

DR. FUSS: Thank you for this complete presentation. I do have some clarifying questions, the first actually to Dr. Lakatos.

The question I have is, in some of the material that was sent to us, there were reports not only from your study from Hungary but also from Norway from Dr. Jahnsen. In that study -- and this will relate to a second part of this question if you'll bear with me.

The first, in the Jahnsen report, they do note that there were 8 patients, 4 Crohn's and 4 UC patients, that were, what appeared to be, at least as written, naïve to TNF who developed very high ADA levels. They do not report the ADAs for the entire study. They also do not report what was the clinical response in these patients. They do report that the trough levels were very low.

In a similar fashion to this question, there were two reports from Poland in pediatric inflammatory bowel disease patients in which there were dropout of patients -- in both, more so in UC than in Crohn's -- due to adverse event reactions. They do not comment on ADAs. I do not know if they were measured. Can you comment on these studies?

DR. LAKATOS: Yes. Thank you for the question. Dr. Lakatos from Hungary. First, the Norwegian study, first of all, this was a mixed population of patients being partly already treated in remission and some others were having an active disease at transition.

You're very right that there were very few

patients that had had antibodies in the naïve group and some of them had high antibodies. I had a personal conversation with the author. They couldn't give me the exact data, so I can't comment further on this.

But we have also measured antibodies in the Hungarian study. And what you see here is that we had some patients in the naïve population who were antibody positive. And I dare say these were very low level antibody positivities to only midrange, and they didn't affect so they were transient antibodies. They disappeared with therapy in the naïve group. So this is what we have seen. High antibody titers were only seen at later time points and in patients with previous infliximab exposure.

As far as the mentioned Polish pediatric study, this is a study when they transitioned due to reimbursement issues, and this was mandated by the given hospital, so the three hospitals that were included in the study.

From the 40 patients, about 10 were in the induction period, about 30 were already in

remission at the time of transition. And what the authors looked at were clinical endpoint, the evolution of the clinical activity score in the pediatric group and also the biomarker values. These were not changing in general.

So before, at the time of the switch and two treatment cycles after the switch, the clinical remission was maintained, as well as the biochemical response was maintained. They didn't measure antibodies and trough levels.

DR. FUSS: Just a quick follow-up on that, just in the pediatric UC population, the two studies at least didn't seem congruent in that you had one study, which showed some efficacy of the use of CT-P13. However, in a second population group, there was not much change in PUCAI score or at least decreased enough to see significant response or remission.

DR. LAKATOS: Right. But as I said, the 30 patients were already in clinical remission, so actually, they have shown that the remission was maintained with low PUCAI scores and that the

patients who were switched during the induction, they actually -- 67 or 70 percent were going into remission with the next two treatment cycle in this given paper that is now in press, online in the JCC.

DR. KUDRIN: So maybe I'd like to remind that we have also data on ADA from week 40 in our randomized controlled study in Crohn's disease. This is obviously interim analysis but showed similar ADA rates. We haven't seen anything unusual there.

But in terms of reports you were referring to are largely case report studies and obviously anecdotal evidence by and large. The populations included in some of those cohorts are relatively small and also not well defined in terms of baseline characteristics. So I would caution in terms of drawing any conclusion out of this and draw attention to extension period, which is probably the largest data set available now from RA and AS studies. We have up to 2-year treatments.

Also, NOR-SWITCH study, which was funded by

the Norwegian government is currently running. Dr. Jahnsen is actually collaborating as an investigator this study.

Obviously, the study is currently still ongoing. It's going to be available probably around third quarter of this year, but there are no concerns from investigators as such that there is any problem with switching. In fact, the only reason there's been delay because they're actually struggling to recruit into Remicade-treatment group as a comparator group because of the large use of CT-P13 now in Norway.

DR. CAPLAN: We're going to move on. We have a number of folks who have questions, so we will have an opportunity after the break to continue these.

I'm going to take -- I'm going to entertain Dr. Moreira, and then we'll have Dr. Siegel introduce himself, and then we'll have a break and continue with questions afterwards.

DR. MOREIRA: Thank you. Thank you for the presentation. I think I have two questions

probably for Dr. Pollitt. One is question is a follow-up to Dr. Cramer's question in terms of manufacturing sites and just clarifying that the data that we have seen today in terms of the production and the lots of manufacture are from the site where the product will be sourced from going forward.

DR. POLLITT: That's correct. The lots included in the 3-way similarity studies are manufactured at the same sites as commercial lots would be manufactured for the U.S.

DR. MOREIRA: Thank you. Then the other question was, as shown, some of the quality data, there are some differences in some cases relative to the reference product, for instance, higher molecular weight, percentage compounds, differences in glycosylation.

These types of parameters are typically -- can be modulated by the cell culture conditions or purification strategies. I was wondering if A) there were studies attempting to bring them closer to the reference product, and

B) if there are critical process parameters that have been identified to make sure that these quality attributes will stay within the ranges that have been identified.

DR. POLLITT: Absolutely. I think the first thing that we have to highlight is that what we do see in our similarity studies is consistency of CT-P13, and we are showing that. At least the similarity study data are showing that the lots that we have included in the similarity studies are consistent. So we aren't seeing any wide variation, and that gives us confidence at least in our process controls.

Now, obviously, we will be further evaluating manufacturing processes and parameters to see if, yes, there is any possibility of tweaking them. But ultimately, it's actually about release specifications, which is what we, at the end of the process, are using to say yes or no to; is this within the criteria. And the criteria are based partly on our own experience but also in the reference product values that we've obtained in

these similarity studies.

DR. CAPLAN: Dr. Siegel, if you wouldn't mind introducing yourself, and then we'll give you an opportunity to ask a question after the break?

DR. SIEGEL: Sure. Thanks. Sorry I was a little bit late. My name is Richard Siegel. I'm the clinical director of NIAMS and also a senior investigator running lab largely studying TNF family cytokines at NIH.

I just had a clarifying question about anaphylactic reactions. In table 42 from the briefing materials, you had a similar rate of anaphylactic reactions in the treatment-emergent adverse events. But then in some of the more detailed tables of discontinuation and also in the narrative, all the cases were from the CTP patients.

Is that just different pools of studies that were analyzed to get those different results?

DR. KUDRIN: Thank you very much. Just to explain, this table summarizes actually the proportion of different patients using

infusion -- this is the different type of infusion-related reactions. In the course of our studies, we have analyzed infusion-related reactions in anaphylaxis using several criteria.

When we actually submitted our application, we applied broader term to capture a greater number of infusion-related reactions. Then European Medicines Agency requested us to reanalyze this using different criteria. Then we came to FDA, they were interested in Sampson's criteria.

We actually conducted a range of different analyses, but regardless of this analysis, the incidences are comparable. The principle, with Sampson criteria here, has outlined how we combined those criteria, and this is very much been described by Sampson. And this is for the capture rules of the infusion-related reactions. So criteria 1, 2, and 3, they have to be fulfilled -- or two criteria should be fulfilled for the anaphylaxis definition.

We examined very carefully these events also on case basis, all of them. Whatever analysis we

did, they were all comparable between groups, not only through control phases but also through extension phases. But we acknowledge the number of really severe reactions, which required resuscitation, for example, was really small.

DR. SIEGEL: So the events that are in table 42 were just not as severe and they didn't make it into the table 58 and 59?

DR. KUDRIN: Right. That's right.

DR. SIEGEL: Okay.

DR. CAPLAN: Okay. We'll now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:35.

(Whereupon, at 10:20 a.m., a recess was taken.)

DR. CAPLAN: We're going to go ahead and get started. Let me ask that folks please take their seats. I'd like to introduce Kurt Brorson from the FDA to present the product quality review of

CT-P13.

FDA Presentation - Kurt Brorson

DR. BRORSON: Good morning. I am Kurt Brorson from CDER's Office of Biotechnology Products, Division 2. I will present our perspective on the product quality of the applicant's proposed biosimilar to US-licensed Remicade. My talk will cover the infliximab structure and mechanism of action, CT-P13 manufacturing, the design of studies to support high similarity, and the results of our analytical similarity assessment.

Remicade is the originator product marketed by Jannsen Incorporated. It is a chimeric IgG 1 kappa monoclonal antibody that binds and neutralizes human tumor necrosis factor alpha. It has a molecular weight of around 149 kilodaltons. The antibody is produced by a recombinant mammalian cell line and possesses heterogeneity typical of mammalian cell culture-derived monoclonal antibodies.

TNF alpha is considered to be a master

cytokine critical for the function of the immune system, as well as inflammatory responses. It exists in both a soluble and transmembrane bound form that can be produced by a range of immune-related or other cell types. The consequences of effector functions of TNF alpha are also varied and include tissue destruction, activation of proinflammatory cytokines, and cell death.

Thus, this regulation of this master proinflammatory cytokine can have multiple clinical consequences in diseases like rheumatoid arthritis or inflammatory bowel disease.

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

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

include reverse signaling of membrane TNF-positive cells, as well as ADCC and CDC of membrane TNF-positive cells.

It is possible that the relative role and importance of infliximab activity for each of these mechanisms may differ between indications. Potential infliximab mechanisms have been summarized in recent review articles, and in vitro models for infliximab activity by these mechanisms have been developed.

In this slide, we categorize them as "likely" or "plausible" based on the totality of evidence, including whether there are or are not published in vivo or biopsy immunofluorescent staining or in vitro studies using cultured clinical isolates that suggest that infliximab may function in this way in patients. For example, reverse signaling of membrane TNF-positive cells in IBD tissues falls under the category of "likely" based on public literature.

The CT-P13 drug substance is an antibody solution that is manufactured by standard

bioprocessing. It is produced by engineered mammalian cells in bioreactors and purified by chromatography, filtration, and other common bioprocessing steps. Viral safety procedures required for biotechnology products are in place.

Over the past five years, multiple batches of the drug substance have been produced with some process optimization over this time. The product has been shown to be consistent after each of these minor changes.

The applicant has identified a set of critical quality attributes that are typical of monoclonal antibody products. The drug product is a sterile lyophilized dosage form in stoppered glass vials. It has the same strength and formulation as the US-licensed reference product. Expiry dating is based on stability studies.

An analytical similarity program was designed utilizing the proposed biosimilar, CT-P13, US-licensed Remicade, the reference product, and EU-approved Remicade. The program had two goals. First, a comparison of the propose biosimilar to

US-licensed Remicade was needed to support a demonstration that it was highly similar to the reference product.

Second, pair-wise comparison of CT-P13 US-licensed Remicade and the EU-approved version was needed to justify the relevance of data generated using EU-approved Remicade as the comparator in some clinical and nonclinical studies.

The applicant designed and qualified or validated a panel of assays to compare the three products. Many are orthogonal methods that measure the same CQA, or critical quality attribute, but from different perspectives. Based on a comprehensive review of potential Remicade mechanisms of actions, a panel of in vitro biological assays were also developed and implemented as well.

Amino acid sequence identity is one component of a conclusion of analytical similarity. This was evaluated by multiple orthogonal methods. Because TNF alpha binding is the main mechanism of

action of infliximab, two measurements of this activity, by a TNF binding ELISA and a TNF neutralization bioassay, were chosen for the most rigorous statistical test, equivalence testing.

Other attributes were analyzed by, us, using quality range analysis. Here, the data from the applicant's product lots were compared to the quality range data set generated by the applicant's analysis of multiple lots of the US-licensed reference product. Some assays are more qualitative than quantitative. For example, traces from two-dimensional structure tests like FTIR or circular dichroism. These were subjected to a qualitative, more visual assessment.

The applicant was able to source more than 40 batches of both reference product and EU Remicade. These were compared to a total of 26 lots of their proposed biosimilar. For assays that assessed Remicade mechanism of action and were tested using equivalence testing, the applicant had more than a dozen lots.

Amino acid sequence was compared by using

tryptic peptide mapping. As you can see in these reverse phase HPLC chromatograms, the proposed biosimilar and the reference product displayed the same peak pattern. The amino acid sequence match was confirmed by other orthogonal methods like two-dimensional mass spectroscopy and amino acid sequencing.

TNF binding and neutralization, the primary infliximab mechanism of action, were subjected by us to equivalence testing. My colleague, Meiyu Shen, will discuss the results of the statistical analysis of the data from the 13 to 27 lots each of CT-P13 US-licensed Remicade and EU-approved Remicade.

FDA Presentation - Meiyu Shen

DR. SHEN: Thank you, Dr. Brorson.

My name is Meiyu Shen, the CMC statistical reviewer from Office of Biostatistics. I'm presenting statistical equivalence analysis of two highly critical quality attributes for biological activity. For this submission, the review team focused on two assays that assessed the parameter

in Remicade, the mechanism of action for independent equivalence testing: One is the TNF alpha binding affinity ELISA and then the other is the in vitro TNF alpha neutralization.

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

We concluded this quality attribute passes equivalence test if 90 percent confidence interval for the mean difference between the test and comparator falls within the equivalence margin defined by approximate as 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 affinity. The Y-axis represents the TNF binding affinity percentage. The spread of these three products are similar to each other as shown in the graph. However, the mean of the US-licensed Remicade is a few percentages higher

than those of CT-P13 and the EU infliximab.

TNF alpha binding is considered to be a primary mechanism of action of infliximab. The TNF alpha binding is measured by ELISA in multiple lots of these three products as this data is subject to rigorous equivalence testing.

The table here presents the equivalence test results for TNF alpha binding affinity. The first column is the pairs for comparison. Second column is the mean difference between the test and the comparator. Third column is the 90 percent confidence interval for the mean difference between the test and comparator. The next is equivalence margin, and the last column is the conclusion of the equivalence test.

These results are graphically presented below. For all three comparisons, 90 percent confidence interval for the mean difference between the test and the comparator falls entirely in the corresponding equivalence margin.

Now, let's look at in vitro TNF alpha neutralization. This slide presents the data graph

for in vitro TNF for neutralization. The spread and the mean of these three products are similar to each other. In vitro TNF neutralization is subject to equivalence testing also.

The table here presents the equivalence test results for in vitro TNF neutralization. This table is very similar to the table we just discussed for TNF alpha binding. These results are graphically presented as for all three 3-way comparisons; 90 percent confidence interval for the mean difference between the test and the comparator falls entirely within the corresponding equivalence margin.

Based on our independent analysis of the applicant's data, we concluded that all 3-way comparisons for both TNF alpha binding affinity and the in vitro TNF alpha neutralization passed equivalence test.

Hence, the statistical equivalence testing results of TNF alpha binding and the in vitro TNF alpha neutralization support that CT-P13 is highly similar to the US-licensed Remicade and also

support the analytical bridge between all three products.

This slide presents a methodology of a quality range analysis. The quality range equals the sample mean plus or minus X times sample standard deviation of the reference product. The reference product data are measured by the applicant.

If high proportions, for example 90 percent, of the observed batch values of a quality attribute, for the test fall within the quality range, the comparison of test and comparator regarding that quality attribute supports a finding of high similarity.

Next, Dr. Brorson will continue presenting quality range analysis for several quality attributes and others.

FDA Presentation – Kurt Brorson (continued)

DR. BRORSON: Thank you, Meiyu. For the sake of brevity, I will present examples of quality range assays that address potential infliximab mechanism of action where we paid particular focus

during our review. For many of these assays, a dozen or more of the proposed biosimilar and reference product lots were tested by the applicant to provide sufficient confidence in the reference product quality range and the subsequent comparison.

The antibody-mediated reverse signaling is a potential drug mechanism of action where the antibody cross-linked or bound cells may undergo apoptosis or be inhibited from secreting proinflammatory cytokines. Binding of TNF would transduce a reverse signal to membrane TNF-positive cells.

As discussed before, there is some published literature that suggests that infliximab may function this way in IBD patients, for example, by down modulating immunocyte over responsiveness to gut flora LPS or by inducing apoptosis of proinflammatory cells.

This contention is supported by in vivo or biopsy immunofluorescent staining studies, as well as in vitro studies using cultured clinical

isolates subjected to immunofluorescent staining and/or TUNEL assays.

The applicant developed reverse signaling assays including an in vitro reverse signaling assay measuring LPS-induced TNF alpha release from PMBCs. Here, three concentrations of the CT-P13 and U.S. and EU Remicade were used to pretreat PBMCs. These cells were then washed to remove the excess antibody and tested for TNF alpha production in response to LPS. The cells are considered to be reverse-signaled if their LPS responsiveness is diminished by the TNF blocker pretreatment.

The applicant's results of these assays were re-evaluated by the review team in an independent statistical analysis using the quality range statistical approach. One hundred percent of the CT-P13 lots were within the quality range set by the applicant's data on the U.S. reference product as determined in this case by the mean plus or minus 3 standard deviations.

The red bars represent the reference product quality range determined in this manner, in this

slide and following slides as well. Of note, results from CT-P13 and US-licensed Remicade tested in the other apoptosis reverse signaling assay format were found to be overlapping as well.

As stated before, the main activity of infliximab is believed to involve TNF alpha binding and neutralization and plausibly reverse signaling, all mediated via the variable region CDR surface. However, infliximab also has an Fc portion that can mediate effector functions like antibody-dependent cellular cytotoxicity or ADCC or complement-dependent cytotoxicity, CDC, in inflamed sites in diseased tissues.

A hint that this may be the case exists when the broad class of anti-TNF alpha products are examined. As shown in the third row, all listed TNF antagonists have demonstrated efficacy and are approved for treatment of RA. However, as shown in the following row on Crohn's disease and ulcerative colitis, etanercept, which has low ADCC activity, is not approved for treatment. Published literature supports lack of efficacy in Crohn's

disease based on a small study using a dose-approved in rheumatoid arthritis.

In addition, Cimzia, or certolizumab pegol, which has no Fc region or ADCC activity, achieved clinical response but not clinical remission achieved by other approved TNF antagonists. Although it is possible that other factors contributed to this outcome such inadequate dosing, it also raises the question as to whether absence of Fc effector functions, including ADCC activity, could have played a role.

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

Fc-gamma R3A, also known as CD-16, is the main form of Fc-gamma receptor on NK cells, a highly potent type of immune cells that target antibody-bound tumor or virally-infected cells. ADCC activity may vary with the avidity of Fc-gamma receptor, Fc bridging, which in turn seems to be

dependent on the glycan composition of the antibody.

The applicant designed a panel of three ADCC assays to compare the activity of their product with the US-licensed and EU Remicade. The three assays used combinations of PMBC or purified NK cells as effectors and membrane-positive transfectomas or LPS-activated macrophages as targets. They found that only when using the transfectomas were they able to detect ADCC activity with either form of infliximab.

I will show results from two of the ADCC formats. The first is where PMBCs are used as effectors and transfectomas as targets. Peripheral blood mononuclear cells are a complex population of cells, which could include natural killer cells.

PMBCs would also include other cell types that may also serve as effector cells for ADCC, as well as potential regulatory cells that may modulate NK cell activity. The applicant argues that this population is more physiologically relevant than purified populations and enriched NK

cells.

As can be seen, 100 percent of the lots of the proposed biosimilar are within the quality range of the reference product, again, as defined by the mean plus or minus 3 standard deviations of reference values.

Another assay format was developed using enriched NK cells as effectors and transfectomas as targets. It is possible that this format assay could more precisely measure the activity of the effector cell type most likely to mediate ADCC via infliximab if this activity occurs or is important for down modulating inflammation at disease sites.

Between 26 and 35 lots of the three antibodies were compared at three different concentrations. While considerable overlap exists between the lots of the product, a small downward shift is evident in ADCC activity by CT-P13 in this assay format. Nevertheless, greater than 90 percent of the lots of the proposed biosimilar are within the quality range of the reference product.

C1q binding is the first step in the activation of the complement system that executes complement-dependent cytotoxicity. Here, it can be seen that C1q binding of 100 percent of the lots of the proposed biosimilar are within the quality range of the reference product. There is no direct in vivo evidence that CDC is either involved with infliximab function, nor is there direct evidence that it does not play a role in therapeutic response.

In summary, the applicant developed a panel of biological assays to address each of the potential mechanisms of action of infliximab. Most importantly, TNF alpha binding and neutralization, believed to be the primary function of infliximab, have been shown to be statistically equivalent between CT-P13 and the US-licensed reference product.

Other mechanisms like reverse signaling and CDC are within the quality range set by the reference product with no shift in activity evident between the tested batches of CT-P13 and

US-licensed Remicade.

In the case of ADCC, there was a small downward shift in ADCC activity by CT-P13 in one of two assay formats using NK cells as effectors. There was no shift in the other assay formats using PMBCs as effectors. However, despite the small shift in the NK cell assay format, greater than 90 percent of lots of the proposed biosimilar are still within the quality range of the reference product.

Thus, we have concluded that the applicant's evaluation of each potential mechanism of action of Remicade in an in vitro assay using both CT-P13 and US-licensed Remicade as part of the totality of the evidence supports the conclusion that CT-P13 is highly similar to the reference product.

Further, the data submitted by the applicant supports the conclusion that CT-P13 and US-licensed Remicade have the same mechanisms of action for specified indications to the extent that the mechanisms of action are known or can be reasonably be determined.

As seen in these select examples I presented, the applicant's analytical exercise in the 3-way analysis also established a bridge between all three products. This justifies the relevance of data compared using EU-approved Remicade as the comparator in some clinical and nonclinical studies.

The applicant also performed an extensive comparison of the three products post-reconstitution for proteinaceous particles in the 1-25 micron range. This analysis is helpful because the immune system can be sensitive to particles in this size range.

A finding of similarity for this attribute would support the relevance of immunogenicity data obtained using EU-approved Remicade to support a demonstration of no clinically meaningful differences to US-licensed Remicade. They employ two methods, micro-flow imaging and light obscuration.

I will show only the MFI data, but the orthogonal method of light obscuration yielded

similar conclusions. As can be seen, there is considerable spread between different product lots but no consistent pattern of more or fewer particle levels in any of the three products.

This observation, in conjunction with the overall protein analytical results from the 3-way analysis, establishes an adequate bridge from the standpoint of potential antigenicity and justifies the relevance of immunogenicity data obtained using EU Remicade to support a demonstration of no clinically meaningful differences with U.S. Remicade.

In summary, the extensive comparison of the functional, physical, chemical, protein biochemistry and high-order structured attributes of CT-P13 and US-licensed Remicade lead us to the conclusion that the proposed biosimilar is analytically highly similar to the reference product. We have also concluded that an adequate analytical bridge has been established as part of the scientific bridge to justify the relevance of certain data obtained using EU Remicade to support

a demonstration of biosimilarity to U.S. Remicade. Thank you.

FDA Presentation – Le He

DR. HE: Good morning. My name is Lei He. I'm from the Office of Clinical Pharmacology. I'll be presenting the clin-pharm component of this submission.

The objectives of the clinical pharmacology program are to evaluate the pharmacokinetic similarity between CT-P13 and the US-licensed Remicade and to assess if the PK element of the scientific bridge between CT-P13 US-licensed Remicade and the EU-approved Remicade has been established to allow the use of data generated to use in EU-approved Remicade.

As such, three studies were conducted to assess PK similarity, including study 1.4, a pivotal 3-way PK bridging study in healthy subjects, and two supportive studies: study 1.1, a PK study in AS patients, and study 3.1, a comparative clinical study in RA patients.

In brief, our assessment shows that the PK

similarity was demonstrated between CT-P13 EU-approved Remicade and the US-licensed Remicade.

Study 1.4 is the 3-way PK bridging study. It's a randomized, double-blind, 3-arm parallel, single-dose clinical study. A total of 213 healthy subjects were enrolled and randomized to 3 parallel arms with 71 subjects in each arm. All subjects received a single-dose of either CT-P13 U.S. Remicade or EU Remicade at 5 milligram per kilo through IV infusion on day 1. Blood samples were collected throughout the study for PK assessment.

The primary PK endpoint includes Cmax, AUC-t, and AUC-infinity. The study design elements and the PK similarity assessments were aligned with the FDA guidance for industry clinical pharmacology data to support a demonstration of biosimilarity to a reference product, which was published in May 2014.

The PK results of study 1.4 is presented in this slide. The plot on the left panel is the PK profiles following administration of CT-P13, U.S. Remicade, and EU Remicade. The inserted graph on

the top is enlarged profiles in the first two days. As you can tell, following different treatment, the PK profiles of all three products are well overlapped.

On the right is the PK similarity analysis table. We compared the CT-P13 versus U.S. Remicade, CT-P13 versus EU Remicade, and EU Remicade versus U.S. Remicade for Cmax, AUC-t, and AUC-infinity and presented to the geometric mean ratios with 90 percent confidence intervals for these comparisons.

Our analysis shows that the PK similarity was demonstrated for all the comparisons. This is consistent with the applicant's data analysis.

Study 1.1 is a randomized, double-blind, parallel group study in AS patients. The primary objective is to evaluate the PK similarity at a steady state between week 22 and week 30. Patients were randomized to receive either CT-P13 or EU Remicade at 5-milligram-per-kilo through IV infusion at weeks 0, 2, 6, and then every 8 weeks through week 54. PK samples were collected

pre-dosed at the end of infusion and one hour after the end of infusion for all nine doses.

Extensive PK samples were collected following dose 5 between week 22 and week 30 for a steady state PK similarity assessment. The primary PK endpoint includes the steady state Cmax and AUC. You will also hear the efficacy result presentation from the statistical reviewer, Dr. Levin, later on.

Here, I present the PK results of study 1.1. The plot on the left panel is PK profiles of CT-P13 and the EU Remicade following dose 5. As is shown, the PK profiles following the administration of CT-P13 and the EU Remicade are pretty much overlapped, and the data analysis also indicated the PK similarity was demonstrated at a steady state in AS patients.

Study 3.1 is a randomized, double-blind, parallel group comparative clinical study. It was designed to assess efficacy similarity following multiple-dose in RA patients. Patients were randomized to receive either CT-P13 or EU Remicade at a dose of 3-milligram-per-kilo through IV

infusion at weeks 0, 2, 6, and then every 8 weeks through week 54 with co-administration of methotrexate and folic acid.

The primary endpoint was the proportion of patients achieving clinical response according to the ACR20 criteria at week 30. Sparse PK samples were collected pre-dose at the end of infusion and one hour after the end of infusion for all nine doses.

As is shown in the PK comparison following dose 5 as an example, the concentrations of both products are comparable at each time point. This was also observed following all other doses.

In summary, the PK similarity has been demonstrated between CT-P13 and the US-licensed Remicade. The PK data also support the scientific bridge between CT-P13 US-licensed Remicade, and EU-approved Remicade to justify the relevance of comparative data generated using EU-approved Remicade. The overall PK results supported the demonstration of no clinically meaningful differences between CT-P13 and US-licensed

Remicade.

Thus, the PK results along with the analytical data support the establishment of the scientific bridge between CT-P13 US-licensed Remicade, and EU-approved Remicade to justify the relevance of data from EU-approved Remicade in the CT-P13 clinical program.

Next, you will hear Dr. Levin about the clinical efficacy component of this submission. Thank you.

FDA Presentation - Gregory Levin

DR. LEVIN: Good morning. My name is Greg Levin. I will be discussing the comparative efficacy results, which support the evaluation of whether there are clinically meaningful differences between CT-P13 and US-licensed Remicade.

Here is an outline of the topics I will cover. I will describe the design and results of two clinical studies that compare the efficacy of CT-P13 and EU Remicade. I will then address a few potential statistical issues that we have explored as part of our review and will end with some

conclusions based on the totality of the comparative clinical data.

Study 3.1 was a 54-week randomized, double-blind, parallel group, comparative clinical study in 606 patients with active rheumatoid arthritis despite treatment with methotrexate. Patients were randomized 1 to 1 to CT-P13 or EU Remicade.

There were investigators in Europe, Asia, and Latin America, but there were no sites in the United States. The primary endpoint was the ACR20 response at week 30. ACR20 is a binary endpoint defined by achieving at least 20 percent improvement in the tender and swollen joint counts in addition to at least 20 percent improvement in 3 of 4 measures of signs or symptoms.

Secondary endpoints included the ACR 50 percent and 70 percent improvement criteria, the disease activity score based on an assessment of 28 joints or DAS28, the components of the ACR response criteria, and the radiographic joint score.

Study 3.1 was completed before any correspondence with FDA, but the applicant did have a statistical analysis plan documented prior to study completion. The applicant's planned primary analysis was based on comparing an exact 95 percent confidence interval for the absolute difference in week 30 ACR20 responses to a similarity margin of plus or minus 15 percent. The applicant later revised the margin to 13 percent based on FDA feedback.

We carried out a number of additional analyses to support those performed by the applicant. First, FDA generally expects the type 1 error rate of a test of similarity to be controlled at the overall 5 percent rather than 2.5 percent level, so we based our primary analysis on a comparison of a 90 percent rather than a 95 percent confidence interval to the margin.

Second, we used the similarity margin of plus or minus 12 percent. I will discuss the justification of this margin shortly. We also carried out additional analyses of key secondary

endpoints in addition to sensitivity analyses to address the potential impact of missing data.

The determination of a similarity margin is critical because the margin determines what magnitude of difference in efficacy needs to be statistically ruled out with high confidence. We believe that a margin of plus or minus 12 percent on the absolute difference scale is reasonable. Our selection of this margin was based on an examination of historical data on the effect of Remicade in addition to weighing the clinical importance of various differences in efficacy against the feasibility of different study sizes.

The lower bound of the proposed similarity margin of minus 12 percent also corresponds to the retention of approximately 50 percent of conservative estimates of treatment effect sizes relative to placebo for Remicade based on the lower CI bound of 24 percent from an FDA meta-analysis.

The lack of an agreed upon similarity margin between FDA and the applicant a priori is not problematic in this case because the primary

analysis rules out the 12 percent margin that we consider reasonable.

Here, I display the primary efficacy results from study 3.1. Among all randomized patients, 61 percent of patients on CT-P13 were ACR20 responders at week 30 as compared to 59 percent on EU Remicade.

As shown in the red box, the estimated difference between arms was 2 percent with a 90 percent confidence interval of minus 5 percent to plus 9 percent. This confidence interval ruled out both the plus or minus 13 percent margin proposed by the applicant and the plus or minus 12 percent margin we consider reasonable.

The lower CI bound of minus 5 percent also corresponds to the preservation of approximately 80 percent of a conservative historical estimate of the effect of Remicade. Responses were also similar between treatments when restricting to the subset of patients who adhered to the protocol.

Here, I display mean differences between treatment arms for several important continuous

secondary endpoints that capture different disease symptoms, quality of life, and radiographic progression. Mean improvements from baseline were similar between CT-P13 and EU Remicade for all key endpoints.

One important secondary endpoint is the composite disease activity score, DAS28. Each arm showed similar improvements from baseline of around 2 units, and a 95-percent confidence interval ruled out large differences in efficacy. In particular, the upper CI bound of 0.16 is considerably lower than 0.6, which has been specified by EULAR as a threshold for a moderate within patient response.

The similar improvements in DAS28 over time on the two treatment arms is also evident in this figure, which displays mean scores at baseline in weeks 14, 30 and 54.

We also reviewed results from study 1.1, a 54-week randomized, double-blind, parallel group clinical study in 250 patients with ankylosing spondylitis. The primary goal was to compare the pharmacokinetic profiles of the two treatments with

efficacy and safety evaluations considered secondary objectives.

Among patients who completed the study, 71 percent and 72 percent of patients on CT-P13 and EU Remicade achieved an ACR 20 percent response for an estimated odds ratio of 0.91. Response rates were also similar between the arms in a supportive FDA analysis in all randomized patients.

Mean changes from baseline on key patient-reported measures of disease symptoms were also similar between the treatment arms in study 1.1 with confidence intervals ruling out large differences.

In summary, results from study 1.1 in AS were generally supportive of results from the larger comparative clinical study in RA.

The potential effect of missing data was one of the statistical issues we explored during our review. There was considerable patient dropout in study 3.1 with around one-quarter of patients withdrawing during the 54-week study and 15 percent withdrawing prior to the week 30-visit.

We note that such a large amount of withdrawal is likely preventable because it was primarily caused by the study design, as the protocol specified that patients who discontinued treatment early were to be withdrawn from the study. Overall dropout rates, in addition to the distributions of reasons for withdrawal, were similar between the treatment arms.

The primary endpoint was a composite measure of treatment success defined by remaining on treatment and achieving an ACR20 response. Comparing treatments with respect to this composite outcome may confound differences between treatments in efficacy with differences in tolerability. Therefore, it is important to evaluate the components of the composite endpoint, which includes an assessment of ACR20 at week 30 regardless of adherence to treatment.

The considerable patient dropout is potentially problematic for this evaluation, as well as for evaluations of important continuous secondary endpoints like DAS28 because analyses in

completers rely on the strong and unverifiable assumption that outcomes in patients who drop out are missing at random.

Therefore, we conducted tipping point analyses to explore the sensitivity of results to violations in the assumptions about the missing data. We estimated differences in efficacy between the treatments under varying missing, not at random, assumptions about the unobserved outcomes.

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

This table displays estimated differences between CT-P13 and EU Remicade in the ACR20 response at week 30 regardless of adherence, with varying assumptions about the differences on each treatment arm between outcomes in patients who withdrew from the study early and outcomes in patients who completed the study.

The red box describes scenarios in which the 90 percent confidence interval fails to rule out a 12 percent loss in the ACR20 response. For this to occur, the response among CT-P13 dropouts would need to be around 70 percentage points lower than the response among CT-P13 completers, while the response among EU Remicade dropouts would need to be similar to the response in EU Remicade completers.

This roughly corresponds to the assumption of a zero percent ACR20 response among CT-P13 dropouts as compared to a 60 to 70 percent response among EU Remicade dropouts.

Given the similar distributions of reasons for withdrawal, in addition to the similar baseline characteristics between dropouts on the two treatment arms, this assumption seems implausible. Therefore, the tipping point sensitivity analyses largely support the findings of the key efficacy analyses in study 3.1.

The last potential issue I will discuss is the importance of the assumptions of assay

sensitivity and constancy. To reliably evaluate whether there are clinically meaningful differences between two products, a comparative study must have assay sensitivity or the ability to detect meaningful differences between the products if such differences exist.

A reliable evaluation of the degree to which the proposed biosimilar preserves the effect of the reference product also relies on the constancy assumption, which is the assumption that estimates of the effect of Remicade from historical trials are unbiased for the setting of the comparative study.

As discussed in the ICH guidelines, historical evidence of sensitivity to drug effects in trials with similar design and conduct to the comparative study, in addition to appropriate conduct in the comparative study, can help support the validity of these assumptions.

This table presents the results of five historical randomized clinical trials comparing ACR20 responses between Remicade and placebo in

patients with active RA despite methotrexate use. Examining the far right column, we can see that there were relatively large and reasonably consistent treatment effects observed across the five trials.

We also found that important aspects of the design and conduct of study 3.1, such as inclusion criteria, concomitant medications, baseline disease severity, and within-group response rates were largely similar to those characteristics of the five historical studies.

We also did not identify any issues with study conduct with the exception of the high withdrawal rate that has already been discussed. Therefore, the totality of available information generally supports the assay sensitivity of study 3.1 in addition to the constancy assumption.

I finish with some concluding remarks. The applicant's large, comparative clinical study in RA demonstrated similarity between the treatment arms with respect to the primary and key secondary efficacy endpoints, and these results were

supported by findings from a smaller comparative study in AS.

As part of our review, we identified and explored a few important statistical issues but do not believe that these issues affect the overall conclusions. Therefore, the collective evidence from the clinical studies 3.1 and 1.1 supports a conclusion of no clinically meaningful differences between CT-P13 and U.S. Remicade with respect to efficacy in the studied indications. Thank you.

FDA Presentation - Juwaria Waheed

DR. WAHEED: Good morning. My name is Juwaria Waheed. I will be discussing the safety and immunogenicity results from the clinical program for CT-P13.

The bulk of the safety data is derived from clinical studies using EU Remicade as a comparator. As previously discussed, the applicant has established a scientific bridge to justify the relevance of the safety data generated from using EU Remicade in the CT-P13 clinical program.

The safety population in the clinical

program comprised of over 800 individuals, including healthy subjects in patients using two different dosing regimens. Overall, the safety database is adequate to provide a reasonable comparative assessment of safety and immunogenicity using two approved dosing regimens of Remicade in two distinct patient populations.

The safety analysis did not identify any new safety signals compared to the known safety profile of Remicade, and the incidence of deaths, anaphylaxis, and immunogenicity were similar between treatment groups.

This table provides an overview of the safety profile in the core control studies. At the top of the table, going across are randomized, controlled, repeat-dose studies 3.1 in RA, 1.1 in AS, and the single-dose study 1.4 in healthy subjects.

In each study, the overall incidences of treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation, infections, serious infections, infusion-related

reactions, and anaphylaxis were similar between CT-P13 and the comparator products.

In the context of the known adverse event profile of US-licensed Remicade, specific risks were characterized as adverse events of special interest, listed in the far left column. This table provides a summary of the FDA comparative analyses of adverse events of special interest during the 54-week double-blind, controlled treatment periods of studies 1.1 and 3.1.

Within each study, the cumulative incidence of each event and the on-treatment incidence rates per 100-person years were calculated, as well as the relative risk. Results from the integrated relative risk for each adverse event of special interest is presented in the far right column.

For certain rare adverse events, like active TB and pneumonia, relative risk was increased, but the number of events was small and the confidence intervals were wide, resulting in considerable uncertainty. Also, based on the high degree of functional and analytical similarity between the

two products, we believe these results are likely a chance finding.

Similar analyses were conducted for the extension studies 1.3 in AS and 3.2 in RA as summarized in this table. In each extension study, patients previously treated with CT-P13 during the control studies continued on CT-P13, and patients previously treated with EU Remicade underwent a single transition to CT-P13. This comparison addresses the safety of the clinical scenario where non-treatment-naïve patients may be transitioned to CT-P13.

Realistically, the main adverse events that we were concerned about this setting are immune-mediated reactions such as infusion-related reactions and anaphylaxis. Incidence of infusion-related reactions did not increase following the transition.

Anaphylaxis is not listed in this table because a relative risk of anaphylaxis could not be calculated as there was only one case of anaphylaxis reported in the extension studies. The

single case occurred in a patient who continued on CT-P13 treatment, and no anaphylaxis cases were reported in patients who transitioned from EU Remicade to CT-P13.

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 a required component of a 351(k) licensing application.

Because antidrug antibodies against Remicade have been implicated and reduced clinical efficacy, hypersensitivity, and infusion reactions, and the CT-P13 development program, immunogenicity of CT-P13 was prospectively assessed in the RA and AS controlled studies, and their respective extension studies in healthy subjects, and in patients with Crohn's disease.

This next table describes the incidence of ADA formation at prespecified time points during the control studies in RA and AS, studies 3.1 and 1.1, and the respective open label extension

studies, 3.2 and 1.3. Of note, the RA patients have concomitant immunosuppression with methotrexate and the AS patients were not on any background immunosuppression.

In the control studies, the rates of immunogenicity assessed as a proportion of antidrug antibody or ADA positive patients at all time points were similar between the CT-P13 and EU Remicade treatment groups.

In the two extension studies, the rates of ADA positivity measured at baseline, week 78 and 102 were also similar between patients who remained on CT-P13 and those who underwent a single transition from EU Remicade to CT-P13, providing reassurance that non-treatment-naïve patients could be transitioned safety to CT-P13.

Overall, assessment of antidrug antibody incidence at multiple time points in clinical study populations reflects the proposed chronic administration of CT-P13.

The impact of ADA formation in the CT-P13 controlled and extension studies can be summarized

as follows. Similar rates of ADA formation were observed between CT-P13 and EU Remicade at all time points in both the RA and AS studies. ADA formation had similar impact in both CT-P13 and EU Remicade-treated patients with respect to exposure, efficacy, and immune-mediated safety outcomes, including infusion reactions and anaphylaxis.

Immunogenicity was also assessed in the PK study 1.4 in healthy subjects. ADA positivity was measured at week 8 after a single dose of either CT-P13, EU Remicade, or U.S. Remicade was administered.

The analysis demonstrated similar incidences of ADA-positive subjects in the CT-P13 and EU Remicade arms with lower incidence of ADA-positive subjects in the U.S. Remicade-treatment arm, which was unexpected. On further review, no assay or subject-related factors could be identified to explain the apparent lower incidence of ADA-positive subjects in the U.S. Remicade group.

In evaluating the significance of these imbalances, the agency considered the following. The lower ADA incidence rate with U.S. Remicade in study 1.4 was unexpected given the established analytical bridge between all three products. Also, this lower incidence is not consistent with published literature comparing U.S. Remicade and EU Remicade that showed higher immunogenicity rates in a similar setting.

Importantly in this study, the observed ADA differences did not correlate with infusion reactions or hypersensitivity and also did not differentially impact PK. In light of these additional contextual pieces, the results of study 1.4 are considered unlikely to represent a real or clinically meaningful difference between CT-P13 and US-licensed Remicade.

To further support similarity in immunogenicity between CT-P13 and US-licensed Remicade and to mitigate any concerns arising from the differences observed in study 1.4, the applicant submitted an interim analysis of

immunogenicity in patients with Crohn's disease from ongoing study 3.4 summarized in this slide.

Study 3.4 is a randomized, double-blind, controlled study in patients with active Crohn's disease comparing efficacy, safety, and immunogenicity of CT-P13 with U.S. Remicade and EU Remicade after multiple doses of 5 mgs per kgs. The applicant has only submitted the interim immunogenicity from study 3.4. The study is not discussed further in the FDA presentation.

This interim analysis shows the incidence of ADA formation was similar between CT-P13 and U.S. Remicade in patients with Crohn's disease treated with 5 mgs per kgs dosing regimen. Of note, the ADA incidence was numerically higher in the EU Remicade-treatment arm, likely due to the small sample size of the subgroup.

In conclusion, with respect to immunogenicity, similar immunogenicity was observed between CT-P13 and EU Remicade in two different settings, RA and AS, using two approved dosing regimens, 3 and 5 mgs per kgs with or without

concomitant immunosuppression with methotrexate. Similar immunogenicity was also observed between CT-P13 and US-licensed Remicade in patients with Crohn's disease based on interim analysis results.

As previously noted, an analytical bridge, including analysis of product quality attributes that could potentially impact immunogenicity, has been established between CT-P13, EU Remicade, and U.S. Remicade. Therefore, the data from the immunogenicity studies adds to the totality of evidence to support a demonstration of no clinically meaningful difference between CT-P13 and US-licensed Remicade.

In summary, safety outcomes, including immunogenicity, were similar between patients treated with CT-P13 or comparator products. No new safety signals were identified in the CT-P13 clinical program compared to the known safety profile of Remicade.

Further, the accumulated clinical safety data from ongoing registries and observational studies in RA, AS, and IBD submitted by the

applicant appear consistent with the safety seen in the CT-P13 clinical development program.

The safety and immunogenicity results add to the totality of evidence to support the conclusion that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade. Thank you.

FDA Presentation - Nikolay Nikolov

DR. NIKOLOV: Good morning again. In the next 10 minutes or so, I will cover a concept that may not be very familiar to some, specifically the concept of extrapolation. I should acknowledge that the review of this application and the considerations for extrapolation were a collaborative effort among multiple disciplines and subject matter experts within the FDA, including our gastroenterology and dermatology colleagues.

CT-P13 is being developed for the same indications for which U.S. Remicade is licensed. The clinical program, however, provides clinical efficacy and safety data primarily from clinical studies in patients with ankylosing spondylitis and

rheumatoid arthritis.

This approach is consistent with the abbreviated regulatory pathway, which permits a biosimilar product to be licensed based on less than a full complement of product-specific preclinical or clinical data. Therefore, one of the key concepts that distinguishes a biosimilar development program from a standalone drug development program is the concept of extrapolation.

As a scientific matter, the agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more additional indications for which the reference product is licensed based on data from a clinical study, or studies, performed in only one indication such as rheumatoid arthritis, and in the case of CT-P13 program, also ankylosing spondylitis.

To better illustrate this, I will compare and contrast the standalone drug development versus biosimilar development programs. The goal of a standalone development program for innovator

biological products is to demonstrate that the product is safe and effective. Drug development starts with the preclinical research, moves to phase 1, then phase 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 biosimilarity 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 product, which represents a different paradigm in drug development and we would like to committee to consider.

To support extrapolation of data, an applicant needs to provide a sufficient justification, which should address issues like potential differences in mechanism of action, pharmacokinetics and biodistribution, immunogenicity and safety in 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 conclusion that CT-P13 is highly similar to the US-licensed Remicade with respect to primary, secondary, and higher-order structures, post-translational profile and in vitro functional characteristics, purity, stability and potency, including TNF alpha binding and neutralization.

Further, the clinical data submitted support the conclusion that no clinically meaningful differences exist between CT-P13 and US-licensed Remicade based on similar clinical pharmacokinetics, similar efficacy, safety and immunogenicity in patients with rheumatoid

arthritis and ankylosing spondylitis using two approved dosing regimens.

Next, consistent with the principles outlined in the FDA guidance documents and previously discussed by the FDA today, the applicant provided scientific justification for extrapolation of clinical data from studies in patients with rheumatoid arthritis and ankylosing spondylitis to the additional indications sought for licensure.

With respect to pharmacokinetics, no notable differences were observed in the pharmacokinetic parameters or profile for US-licensed Remicade in Crohn's disease patients as compared to patients with other conditions of use, including rheumatoid arthritis and plaque psoriasis.

Additionally, pharmacokinetic characteristics were similar between pediatric and adult patients with Crohn's disease or ulcerative colitis following the administration of an approved dose of 5 milligrams per kilogram of US-licensed Remicade.

Since similar PK profile was demonstrated between CT-P13 and US-licensed Remicade, as discussed earlier by Dr. Lei He in the FDA presentation, a similar PK profile and biodistribution would be expected for CT-P13 in patients with psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis.

The next slide addresses considerations on safety and immunogenicity in different patient populations. In general, immunogenicity to the US-licensed Remicade was affected primarily by the dose used and the use of concomitant immunosuppressive therapy rather than by patient population.

Consistent with these considerations, the applicant provided data demonstrating similar immunogenicity and safety, including immune-mediated adverse events such as infusion-related reactions and anaphylaxis in two different settings, in patients with rheumatoid arthritis and ankylosing spondylitis using two

different approved dosing regimens, 3 milligrams per kilogram and 5 milligrams per kilogram, either with or without concomitant immunosuppression with methotrexate.

Further, an interim analysis of the ongoing randomized controlled study in patients with Crohn's disease showed similar incidence of antidrug antibody formation between CT-P13 and US-licensed Remicade in patients following the administration of 5 milligrams per kilogram dosing regimen.

Accordingly, similar immunogenicity and safety profiles would be expected for patients with psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis receiving CT-P13.

The applicant provided data to support the conclusion that CT-P13 and US-licensed Remicade have the same mechanisms of action for a specified indication to the extent that the mechanisms of action are known or can reasonably be determined as summarized in this table, and that these mechanisms

of action meet the similarity acceptance criteria between CT-P13 and US-licensed Remicade.

Next, I will summarize the scientific considerations for extrapolation of data specific to psoriatic arthritis and plaque psoriasis. The primary mechanism of action of Remicade is direct binding and blocking of TNF receptor-mediated biological activities as already discussed. The scientific literature indicates that this mechanism of action is the primary mechanism of action in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

The data provided by the applicant showed similar TNF binding and potency to neutralize TNF alpha supporting the demonstration of clinical similarity pertinent to this mechanism of action. Further, similar pharmacokinetics, safety, and immunogenicity profiles are expected for CT-P13 in patients with psoriatic arthritis and plaque psoriasis as those seen in rheumatoid arthritis and ankylosing spondylitis.

Therefore, based on the above

considerations, the agency believes that it's reasonable to extrapolate clinical data of CT-P13 from rheumatoid arthritis and ankylosing spondylitis to support a demonstration of biosimilarity of CT-P13 in patients in the psoriatic arthritis and plaque psoriasis.

Next, I will summarize the scientific considerations for extrapolation of data specific to the inflammatory bowel disease indications. As noted by Dr. Brorson earlier in the FDA presentation, there were small differences between CT-P13 US-licensed Remicade, and EU-approved Remicade in glycosylation, specifically a-fucosylation, Fc-gamma receptor 3 binding, and some NK based ADCC assays.

In assessing whether the apparent fractional differences may translate into a clinically meaningful difference in inflammatory bowel disease indications, the agency has considered the following.

The biological functions that the subtle Fc-gamma receptor 3 binding differences might

impact, specifically ADCC, are within the quality range of the reference product based on the applicant's data. Two, the mechanism of action of TNF inhibitors in treating inflammatory bowel disease is certainly complex, and ADCC is only one of several plausible mechanisms of action.

Importantly, the historical inflammatory bowel disease clinical trials, including those for Remicade, often utilize doses and timing of primary endpoint assessment that are in the therapeutic plateau. And thus, clinical outcome measures, such as clinical response or clinical remission, lack discriminative capacity to assess the effect of small differences in ADCC and Fc-gamma receptor 3 binding such as those seen in CT-P13 program.

Further, TNF alpha binding and neutralization, reverse signaling, and Fc region-mediated potential mechanisms of action of Remicade in inflammatory bowel disease indications are highly similar between CT-P13 and US-licensed Remicade, supporting the demonstration of same potential mechanisms of action for inflammatory

bowel disease. Similar pharmacokinetic, safety, and immunogenicity profiles are also expected for CT-P13 in patients with inflammatory bowel disease.

Therefore, based on the above considerations, the FDA believes it is reasonable to extrapolate clinical data of CT-P13 from rheumatoid arthritis and ankylosing spondylitis to support a determination of biosimilarity of CT-P13 in the inflammatory bowel disease indications.

In the last slide, I would like to summarize the FDA findings. Based on the FDA review of the CT-P13 biologics license application, the totality of the data submitted by the applicant supports a conclusion that CT-P13 is highly similar to the US-licensed reference product, US-licensed Remicade, and no clinically meaningful differences exist between CT-P13 and US-licensed Remicade.

The data submitted in the BLA also support a conclusion that the scientific justification for extrapolation of clinical data supports a finding of biosimilarity for all indications for which US-licensed Remicade is licensed.

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. Thank you.

Clarifying Questions to FDA

DR. CAPLAN: Thank you. Are there any clarifying questions for the FDA? Please remember to state your name for the record before you speak. If you can, please direct your questions to a specific speaker. Ms. Aronson?

MS. ARONSON: Diane Aronson, patient representative. I guess this is a question to the FDA. I'm wondering because Canada did not approve for CD and UC, did you have access to any information from Canada? Do you share information, and would you know if they have extrapolation in their process?

DR. NIKOLOV: This is Nikolay Nikolov.

First, we did not have access to that information, and we cannot really speak for other regulatory agencies. We provided our assessment based on the data submitted to the FDA, so we cannot really comment on anything else.

We knew that this might be a point for discussion since this has been in the public domain, and there are differing recommendations by the EMA and Health Canada. But we certainly don't want this committee to feel as adjudicators for the case, as we presented the data that was submitted to us.

DR. CAPLAN: Dr. Long?

DR. LONG: My question is addressed to Dr. Pollitt. Is that appropriate at this point? I didn't get to ask it before.

DR. CAPLAN: We'll come back to those but first, FDA comments.

DR. CURTIS: Hi. Sean Curtis. I had a question for Dr. He on the clin-pharm data. One of the slides you show, I think your fourth slide showed the study results 1.4. Was there a look at

individual patient data? I'm just trying to get a sense of the variability.

Obviously, the mean results look very -- clearly meet the biosimilarity criteria, but I was curious what sort of sensitivity analyses might've been done on the individual patient data to confirm that similarity.

DR. JI: Ping Ji from the FDA. The inter-individual variability from the study is less than 30 percent, so we do look at the individual data.

DR. CAPLAN: Please wait to be recognized by the chair. Next speaking will be Dr. Brittain.

DR. BRITTAIN: Yes. My question is for Dr. Levin. I really liked your tipping-point analysis. Can we go to slide 5 of his talk?

So the good news is that 80 percent of the benefit has been retained, at least when we assume that the missing data would be the same in both groups. But I guess I'm curious about why the margin was chosen as a 50-percent benefit.

I understand that's the strategy you used in

inferiority, but non-inferiority feels different to me than this, when we're talking about wanting to basically find a substitute for something. And I didn't know if it was really driven by feasibility. And also the 90 percent confidence interval, I was sort of surprised by that as well. I was just wondering if you could comment on what drove you to that approach.

DR. LEVIN: Yes. We had lots of internal discussions between statistical and clinical colleagues about what would be the appropriate margin for these studies. And looking at the historical data and thinking about what the margin would correspond to in terms of percent preservation of effect was only one of many considerations.

So it just turns out that it was about 50 percent, which I know has been used for a lot of non-inferiority studies. But that was just one of many considerations, and you mentioned some of the other ones.

Feasibility was one of them. Thinking about

the relevance of different thresholds on the absolute difference scale and how concerned people would be with those differences was another.

Thinking about how big the point estimate for the difference could be while still ruling out the margin was another. So the largest point estimate you could have with a 12-percent margin in an adequately powered studies would about 6 percent. The point estimate should be within about 6 percentage points, and people were pretty comfortable with that.

But there were many considerations that led to our determination that that 12 percent was reasonable. And it is additionally reassuring that the confidence interval actually rules out smaller than 12 percent differences.

DR. CAPLAN: Dr. Miller?

DR. MILLER: Don Miller. My question is for Dr. Brorson. It's kind of clear that there is quite a bit of variability from lot to lot for any kind of product. How does FDA assure that any biologic product does not drift in quality or

characteristics over time?

DR. BRORSON: Certainly. Thank you for that question. As part of manufacturing, there are process controls placed on all the unit operations used to make a biotech product. Those maintain control within a certain range during manufacturing.

Then after manufacturing, there are quality control tests that are performed on both drug substance, which is the bulk protein solution, as well as directly on drug product, which is the protein in the vial. Those have set acceptance criteria that don't change over time unless the FDA reviews them.

The assays that are used to test products on a lot-to-lot basis are subject to a procedure called validation, or assay validation, where the robustness, the precision, the accuracy, the specificity of the assay itself is very carefully evaluated to make sure that the assay itself is very specific and precise and doesn't vary over time.

Finally, when processes do change -- occasionally, manufacturers will change their processes deliberately; for example, they might scale up or they might move to another manufacturing site -- they perform what is called a comparability study, where they take a set number of batches of product produced, prior to the change and produced after the change, and test them in a battery of biochemical and other kinds of assays. Usually, the lot release assays that are performed routinely, plus other more structural assays as well.

Then finally, all manufacturing plants that produce biopharmaceuticals in the world that market to the United States are inspected every other year or so for conformance to what are called good manufacturing practices.

As part of that inspection, the assays are given another evaluation. The manufacturing process is reevaluated to make sure it conforms to the product license, and general manufacturing practices are looked at. So FDA has a very

rigorous program in existence to make sure that products don't drift over time.

DR. CAPLAN: Thank you. Next up, Dr. Shwayder?

DR. SHWAYDER: Dr. Shwayder. I have a question I'd like to ask of the FDA but could be just as well asked of the company. The 1 to 4 percent of positive antidrug antibody in naïve patients fascinates me.

Do we have an explanation? Are we just seeing an auto-antibody effect to the human kappa chain? Here are my questions.

Well, first of all, what is it and why is it there? Secondly, should we be screening patients before we give them this medicine? And lastly, if we eliminate the auto-antibody patients from the group that they were testing, does the incidence of antidrug antibodies go down and does the effect of the drug lengthen?

DR. KOZLOWSKI: So there are situations where you see preexisting antibody in patients. They're usually very low titer. There are rare

examples. I think cetuximab is a case where preexisting antibodies can lead to reactions, but that's a rare situation. So I think it's something we consider. It's looked at. It's evaluated. And if there is a concern that preexisting antibodies will be a problem for a product, I think it's something that gets discussed.

DR. CAPLAN: Dr. Siegel?

DR. SIEGEL: In comment on your last question, we published a study recently collaboratively between us and NIAID. Steve Holland's group had defined the patients who actually make auto-antibodies against cytokines that cause immunodeficiencies.

We did have a cohort of rheumatoid arthritis patients in there, most of whom the antibodies were -- actually, the therapeutic antibody is in their blood. But a very small percentage of patients, more in lupus than in rheumatoid arthritis, do make anti-cytokine auto-antibodies.

Now, whether this assay would detect a specifically antidrug versus anti-cytokine, the

company would have better information, but anti-cytokine antibodies can occur.

I did have, though, one other question, more about extrapolation. So this is a general question, and if it came up in the early morning, I apologize if I missed that. But are postmarketing surveillance or studies different for the indications, which are extrapolated versus non-extrapolated? Just a general question that might not apply here.

DR. NIKOLOV: We don't expect different pharmacovigilance for indications that are studied and for the ones that are extrapolated. Again, this was partly covered early in the morning by Dr. Christl. But we don't anticipate requiring additional postmarketing studies just because this is a proposed biosimilar. It would undergo the routine pharmacovigilance as any other biologic product.

DR. CAPLAN: Dr. Mager?

DR. MAGER: Don Mager from the University of Buffalo. This is question for Dr. Nikolov.

Slide 7 on the extrapolation slides, you indicate no notable differences in PK parameters in CD patients as compared to patients of other conditions.

It seems there are some reports in the literature that there could be differences in pharmacokinetics, in particular perhaps pre-infusion C-reactor protein and other factors that could influence PK parameters in other diseases. I was wondering, what is the basis for that statement and what analysis was done to check PK parameters across all diseases.

DR. NIKOLOV: So the statements on this slide are derived from Remicade's FDA-approved labeling. These are general statements based on data previously reviewed but they're in the labeling.

Just to go back to the very basics of the extrapolation, the question for us is whether there are any differences between the products that we would expect to result in differences in PK biodistribution in the different patient

populations, and we don't really think that there are.

DR. MAGER: Can I follow up --

DR. JI: Sorry. This is Ping Ji from FDA. So numerically, you could see some differences in PK parameters across different diseases, but all of them are in the same ballpark, like the half-life for infliximab across different diseases about like a 7 to 9 hours. So it's numerically consistent differences.

DR. CAPLAN: Dr. Curtis? Jeff Curtis?

DR. CURTIS: I had a question for Dr. Waheed on slide 9 about immunogenicity in study 1.4. On the bottom row by ELISA, the differences in the incidence of antidrug antibodies of 27 versus 11 percent, I just wanted to make sure I followed the thinking on that.

So it seemed like there was relative comfort given this data cited in 2014 that perhaps the 11 percent is artificially low. I guess I wondered if there was more than just that, because I think that's a Pfizer abstract that's actually smaller

than the 70 patients in this study.

Then I didn't fully understand the last point. It didn't correlate with infusion reactions or hypersensitivity, but these people never got a second infusion. So I wanted clarification on those two points.

DR. JI: We think some differences for immunogenicity in study 1.4 could be a random effect because of the limited number of subjects in the study.

DR. CURTIS: And then on the next slide, with the study 3.4, of the 12 people who got EU Remicade, 2 out of 12 had antidrug antibodies, but 2 out of 12 isn't 33 percent. So I don't know if that's a typo or this is correct, and the study report is incorrect.

DR. NIKOLOV: The number is 2 -- maybe the calculation was wrong. It's 2 out of 12.

DR. CURTIS: Okay.

DR. CAPLAN: Dr. Mager, do you want your follow-up question or did you no longer have one?

DR. MAGER: I can wait for the discussion on

extrapolation.

DR. CAPLAN: Any other questions?

DR. CRAMER: Steve Cramer. This is for Kurt. I guess my question is about the range of product-related impurities. So we see this difference in the charge variants; we see there's a little difference in the aggregates. There are differences, and yet when we do the other studies, we go, well, we don't really care because in vivo, the C-terminal lysine will be cut, et cetera. But yet we're going to be using analytics for release criteria and everything, so I'm just a little confused.

If the analytics is the foundation and we're using that for everything, but yet the work we've done here at some level says, well, the analytics are important but not so important. What really is important is the clinical result. I'm a little confused. What would be the release criteria and how will I think about that?

DR. BRORSON: You're correct. There will be a lot release program for this product. It extends

beyond just the assays that I presented in my presentation. I focused on the ones that we felt that are very important for mechanism of action for purposes of this presentation. However, the other attributes, like you mentioned aggregates, are part of their lot release program.

In general, the level of aggregates, even though for this product is slightly higher than is present in the innovator product, is within the range that's typically seen in biotechnology products. So many of the attributes that you mentioned are attributes that we have quite a bit of experience with in the broad portfolio of products that we review within our office.

That's all handled as part of the review process when we evaluate the application. It's not as if we're picking out specific assays, thinking some are more important than others. It's just that they're all -- the other assays are handled as a part of the review process.

DR. KOZLOWSKI: This is Steve Kozlowski, FDA. What Dr. Brorson said is correct, that we

look at a variety of these things. I think the idea of ranking the risk of the attributes is a very important part of this exercise because as analytics get better and better, you can measure more and more deeply, and you can always find differences.

So the question really is the judgment, which differences matter? A lot of thought goes into differences based on the history. Again, monoclonal antibodies, Dr. Brorson mentioned. We have lots of them.

We understand these attributes. They may be different in each context, but there's an ability to make good risk-based judgments about what will matter.

DR. CAPLAN: Thank you.

DR. RANGANATH: Veena Ranganath. I had a question if there is the consideration going back to the fact that we're talking about 3 milligrams per kilogram and then extrapolating. Are we thinking about the extrapolation for 10 milligrams per kilogram that we see with some of our

rheumatoid arthritis patients?

DR. NIKOLOV: This is Nikolay Nikolov. The extrapolation would apply to any clinical setting if the product is licensed or approved for that indication, and that would include dosing and dosing regimen in that indication, even though the clinical studies might have been done with the 3-milligram-per-kilogram regimen.

DR. CAPLAN: Thank you. We have just a few minutes to go back to the questions for the sponsor, and first up is Dr. Long.

DR. LONG: I have a question for Dr. Pollitt about the ADCC results. This is one parameter where there was a difference, a small difference. I agree that there is no particular reason to think that ADCC is important, so no reason to think that a small difference is going to be important. But there is a difference.

So I wanted to look at the primary data, which is in your report but I don't think it was on the slides. I find it a little difficult to interpret. In figure 50, for instance, that

displays the lysis of lamina propria mononuclear cells by NK cells, and there's no significant lysis. But that's corrected, of course, for spontaneous lysis.

That's usually understood as no antibodies, no NK cells. But the level of spontaneous lysis is very important. If it's very high, then the data is less reliable. And figure 49, to me, suggests that there is high spontaneous lysis, although there, the controls are not really specified, so it's hard to know.

DR. POLLITT: Thank you. I'd like to invite Dr. Ben-Horin to come and discuss this study because this study was conducted in his laboratory using cells taken from his patients.

DR. BEN-HORIN: Thank you. My name is Shomron Ben-Horin. I'm director of IBD gastroimmunology laboratory at Sheba Medical Center in Israel. I'm associate professor of medicine in Tel Aviv University, also in Israel.

The last 10 years, I've been doing research on biologics efficacy and immune mechanisms in

immunogenicity. In light of our chair's directive, I have to confide that I've received personal fees from the sponsor, as well as research grant.

Regarding this question, what we have done actually in these experiments -- and I believe you're referring to the slide that was on the BP but was not shown, given in the presentation today yet.

This is an experiment whereby we took cells, which are lamina propria intestinal cells from the gut of patients with IBD during colonoscopy by biopsies, and we incubate those cells with both CT-P13, as well as infliximab, Remicade, the RP, and also in IgG control. Thereafter, we incubate them for 4 hours with NK cells to determine ADCC activity.

I draw your attention to the left-hand side, which are the bars that represent those results, and what we could see is actually no activity of ADCC in these experiments.

Now, the top of that bar that looks quite high on the right-hand side is actually juxtaposed

just as a control because one may say perhaps this is due to not -- it has nothing to do with ADCC but rather to the NK activity per se in those patients whereby we took the NK cells from the same IBD patient.

Just to rule out there was no defective NK cell-mediated cytotoxicity for those patients, we used the canonical K562 assay whereby the NK cells are mediating killing of these K562. And indeed, you see robust killing sort of refuting the possibility that wherever we see no ADCC is due to an NK cell defect.

Therefore, I think it strongly supports the fact that there was no ADCC in what I believe to be one of the most physiologically relevant models for infliximab mode of action in the lamina propria of the gut.

DR. LONG: My question was more about the accuracy of the results because the level of spontaneous lysis is not shown. And figure 49, if you can go to that one, suggests -- although it's not clear from the data presented -- that there is

very high spontaneous lysis.

DR. BEN-HORIN: Can I get to the slide to refer to? This is actually presentation of the same data, but not in a conjoined manner, in a conjoined format, but rather looking at each and every patient that was recruited for this study.

You can see that we are taking cells from both ill mucosa, denoted by I; and healthy mucosa, denoted by H.

What we see here is actually percentage of cell death; that is if I understand correctly what you're asking about, is this percentage of cell deaths comparing for each patient for each experiment, the cell death mediated as opposed to lamina propria cells incubated alone, just to show the differences in each patient for CT-P13 and Remicade, and there was no such difference for any of the patients studied.

DR. LONG: Right. But what happens if you leave out the NK cells or if you leave out the IgG? This could be natural killing due to the NK cells. You would see that even without the antibodies. Or

it could be spontaneous lysis, which we would see with -- so I just don't see those comparisons.

DR. BEN-HORIN: I totally agree, and perhaps I'm not clarifying it enough. As you can see, of course, it's limited by the amount -- as you well know, we are limited by the amount of biopsy material we can obtain during colonoscopy, and the harvesting of the cells is sometimes challenging. Usually, you get about 500 K cells on average.

So in not all the patients we could both controls of LMPC alone and LMPC plus NK. But in some of the patients, as you can see, that was the case. And this did not result in any spontaneous cell mediated killing above the spontaneous cell death of LPMC alone.

DR. CAPLAN: Okay. Thank you. We'll now break for lunch. We will reconvene again in this room in one hour from now at 1:15 p.m. Please take any personal belongings you may want with you at this time.

Committee members, please remember that there should be no discussion of the meeting during

lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:18 p.m., a lunch recess was taken.)

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

(1:17 p.m.)

Open Public Hearing

DR. CAPLAN: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes 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 relationships 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 the 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 options.

One of our goals today is for this open public hearing to be included in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

record? Thank you.

DR. EPSTEIN: Thank you. I'm Dr. Michael Epstein from Annapolis, Maryland. Celltrion sponsored my travel here today, but I'm not compensated for my time.

Officers of the FDA and members of the Arthritis Advisory Committee, thank you for allowing me to address you today. I'm speaking today representing my own practice as a gastroenterologist who treats adult and pediatric patients with inflammatory bowel disease on a daily basis. I also have over 30 years' experience as clinical research scientist encompassing most of the biologics, and I have served on FDA advisory boards in the past.

Access to biologics such as infliximab and others are critical to caring for my patients with Crohn's and ulcerative colitis. The 351 pathway was developed allowing a rigorous scientific approach for biosimilars to enter the market to ensure biosimilarity and to reduce the residual uncertainty regarding structure and function.

The Celltrion biologic license application has more than fulfilled the requirements for biosimilarity according to the data that I have heard and seen presented here today. I am confident that this product would be safe and effective in my patients with inflammatory bowel disease.

Once therapy has begun and if a patient is responsive with infliximab, that therapy must be continued indefinitely. The cost of this indefinite therapy, however, is prohibitive and increasing.

Since I began infusing, in my own office, Remicade, the cost has increased unchecked twice a year from an average wholesale price of $382 per vial to over $1,000 per vial, a single-dose vial. This has made the goal of offering biologic therapy, unfortunately, out of the reach for many of my patients and has affected their ability to treat their disease and live normal lives.

My patients are also affected by rising deductibles, which in our practice have increased

by an astounding 67 percent, shifting this cost right on to the patients. International experience with biosimilars has shown that biosimilars like CT-P13 will cost up to 30 percent less than the reference product on the market today.

The totality of the information presented shows that this product is safe and is effective as the marketed infliximab and can be extrapolated to patients who suffer from IBD. I would encourage you to consider that extrapolation. Thank you.

DR. CAPLAN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and organization you represent for the record.

MR. GINSBURG: Seth Ginsburg, Global Healthy Living Foundation and Creaky Joints. I have no disclosures to make today regarding my travel here. And on behalf the nonprofit Global Healthy Living Foundation and its arthritis organization, Creaky Joints, I want 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 Ginsburg, and I'm the co-founder of Creaky Joints and the Global Healthy Living Foundation. I was diagnosed with spondylarthritis when I was 13.

For us patients, biosimilars represent hope as well as fear. We hope for expanded treatment options through a broader formulary. We fear being switched from a drug that works to one we don't know without participating in the promised cost reductions.

Our community is carefully processing these two emotions because biologics transform lives, whether it's Mariah (ph) from Colorado who is able to finish her master's and law degrees, or Cindy from Texas who took one last road trip with her elderly father before we passed away.

In addition, our community fears biosimilars could represent losing the biologic treatment we've searched years to find and worked tirelessly to gain access to, in the case of Brenda from North Dakota, a decade.

A biosimilar may be essentially equivalent to you scientists, but not to the biologic patient whose life has been transformed forever. 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 patient-powered research network, we will vigilantly tract patient-reported outcomes.

FDA is working to include patients in the regulatory process. PCORI represents a natural extension of the patient voice with PCORnet, which is a national resource for real-world evidence collection.

In order to achieve the promise originally intended by the PBCIA in 2010, we are addressing patient and physician confidence. We believe the FDA and biosimilar manufacturers can support this effort by closely examining their supply chain and support services to ensure continuity of support and product, creating unique naming and clear labeling to allay fears, as well as a finalized

interchangeability rule that eliminates payer level switching.

We also think the FDA needs to allow extrapolation unless the mechanism of action for the extrapolated indication is not clearly understood or the drug is considered scientifically or therapeutically outdated.

Patients are okay with extrapolation as long as you are extrapolating the best-in-class therapy. We want biosimilars to be an improvement of what we have and not the lowest common denominator of what we know.

Other countries, such as Canada, held back full extrapolation by not including IBD. Science is only part of biosimilar success. Use and satisfaction is where success also will be measured.

We thank the FDA for emphasizing the value of the patient perspective through public meetings like this, and we continue to mobilize our patient community to create a better life for those who will benefit from biosimilars. We welcome input

and collaboration, and thank you for your commitment to the patient.

DR. CAPLAN: Thank you. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

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

MS. ARNTSEN: Thank you. Kathleen Arntsen. I'm here as a patient. I have nothing to disclose. I am just a patient and an advocate who knows firsthand that we desperately need new drugs to treat complicated autoimmune diseases like lupus. Biosimilars hold tremendous promise and therapeutic advantages for people like me with diseases of unmet need.

Besides lupus, I suffer from several other autoimmune disorders and comorbid conditions. I take 38 medications a day and have unique allergies

and sensitivities to inactive ingredients in drugs, requiring careful monitoring by my healthcare providers. My entire digestive tract is impaired, and it takes five different drugs to allow me to eat each day, and I have refused a colostomy at this point.

I have an infusaport for bi-weekly 7-hour infusions and I'm blind in my right eye from shingles and adverse drug reactions. I have a very expensive prosthetic device now. Due to the heterogeneous nature of autoimmune diseases, no two cases are alike and treating complicated patients like me is like balancing on a pinhead.

Given that the FDA has not yet finalized guidance on issues that impact patient safety, please keep in mind complex autoimmune patients like me who do not fit the norm and are labeled "outliers" by their treating physicians.

You must remain vigilant in protecting patient safety while promoting unfettered access to vital and innovative treatments by recognizing the complexity of biologics, as well as the intricacy

and vulnerability of the potential patient populations.

At this initial juncture of biosimilar development, it is critical for patients and physicians to be confident that these drugs are safe and as effective as the innovator product. It is essential to validate that the chemical, structural and biological parameters are highly similar to the reference product and consider whether the similarities have meaningful clinical relevance. It is your responsibility to review the science and the analytical data and determine the acceptable amount of uncertainty.

Please understand no one-size-fits-all products exist for complex autoimmune patients. Our immune response to treatments is unique, contrary, and at times adverse. Biosimilars are not precise replicas of the originator biologic. Subsequently, their performance may be not equivalent in every disease population, resulting in unexpected divergent effects.

I strongly believe that each biosimilar

should be considered individually by each disease population, not combined together as a variable group. Patients like me are so hypersensitive that even the slightest change in manufacturing, dose, or method of delivery can provoke immunogenicity and disease complications. There must be sufficient proof of clinical efficacy, purity, safety, potency, and tolerability provided for each distinct disease patient population to grant indication extrapolation, not just projected clinical data.

As millions in the lupus, autoimmune, and unmet disease communities fervently await the development of these new therapies, we also recognize that much like these complex conditions, the biosimilar approval process is intricate and warrants a thoughtful, innocuous, and vigilant course.

I think thank you for this opportunity, and thank you for continually recognizing the importance of the patient voice.

DR. CAPLAN: Thank you. Will speaker

number 5 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

DR. CAPLAN: Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. SIEGEL: I'm Dr. Jay Siegel. I work for Johnson & Johnson whose companies develop, manually and sell Remicade.

Mr. Chairman, distinguished members of the committee, FDA officials, thank you. Johnson & Johnson has long supported the implementation of biosimilars pathways that place the highest priority on ensuring that patients receive drugs, which are safe and effective.

Over two decades' experience in the development, study, manufacture, and use of Remicade have provided our scientists and physicians substantial insights relevant to today's proceeding. I will focus on issues regarding the

use of CT-P13 in IBD.

CT-P13 differs from Remicade with regard to a number of chemical and physical attributes, including glycosylation, glycation, and aggregation. These differences impact FcR binding and have the potential to impact various drug functions important in IBD. There is a substantial body of evidence that Fc-mediated functions, and not just binding of soluble and transmembrane TNF, are important in the treatment of IBD with Remicade.

While some functional assays found differences and others were less sensitive to differences, there is little or no basis for concluding that the less sensitive assays are more physiological. None of the assays are validated for predicting responses to a drug in a patient.

Not only does Remicade's mechanism of action differ in IBD compared with RA and AS, so too do its pharmacokinetics, site of action, typical dosing, concomitant medications, immunogenicity, and safety profile. All raise questions about

extrapolation.

Trials of CT-P13 to-date do not adequately address residual uncertainty regarding use in IBD. It has been demonstrated that clinical trials of anti-TNFs in arthritis are not sensitive to detect differences that emerge in treating IBD. While all approved anti-TNFs perform well in RA and AS, those with lower or no Fc-mediated activity appear to perform less well in IBD.

Studies of switching from Remicade to CT-P13 provide varied results and no valid basis for concluding that patients that switched did any better than had they been switched to placebo, as the limited data in patients discontinuing chronic Remicade maintenance in IBD indicate persistent remission is not uncommon.

Uncontrolled induction studies using CT-P13 also provide varied results and for several reasons support no valid comparison of response rates to those of Remicade. Only direct clinical comparisons of CT-P13 and Remicade in active IBD can provide the requisite assurance that CT-P13 is

similarly safe and effective.

We urge the FDA and the committee to await and consider, at a minimum, the results of ongoing Celltrion study 3.4, comparing the drugs in IBD, before making the determination about CT-P13 in IBD. I thank you and urge you to read our detailed written testimony.

DR. CAPLAN: Thank you. Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. SIMMON: Thank you. My name is 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 regarding my appearance here today.

On behalf of our members, I would like to thank and commend the agency on its continued progress in its implementation of the Biologics Price Competition and Innovation Act. We greatly appreciate the work the agency has done to create

an environment that maximizes access and savings for patients.

The Biosimilars Council works to ensure a positive environment for biosimilar products and to educate the public, patients, and providers about biosimilars. We're focused on the regulatory environment, reimbursement, legal affairs, and advocacy. Member organizations include companies and stakeholders working to develop biosimilar products with the intent to compete in the U.S. marketplace.

The council recognizes that development, production, and approval of biosimilar products must be grounded in sound science. As part of the BPCIA, FDA was granted important discretion to determine scientific requirements on a case-by-case basis to ensure safety and efficacy. Therefore, FDA can require any information that is necessary to support a determination that a biosimilar product is highly similar and has no clinically meaningful differences.

In making these determinations, the agency

relies on the same scientists that assess applications for new biological products and who are experienced. Thus, the scientific underpinnings for biosimilar approvals will represent all necessary robust and rigorous scientific approaches as determined by the agency.

We are confident in the FDA and in the process. From a scientific and regulatory perspective, the active substance of the biosimilar is another version of the active substance of the innovator or reference product. And for that reason, the council supports the use of longstanding conventions for naming all products with the same active ingredient with the same international nonproprietary name or INN. This methodology has been endorsed by numerous scientific bodies, including the U.S. Pharmacopeial Convention as in line with traditional scientific standards.

Additionally, extrapolation of data is already an established scientific and regulatory principle that has been utilized for many years by

the innovator industry. For example, in the case of major changes in the manufacturing process of innovator biologics, FDA has used comparability or extrapolation information for nearly 20 years.

In such cases, clinical data are typically provided to confirm safety and efficacy of one indication and taking into account the totality of information gained from the comparability exercise. Based on the acceptable outcome of the comparability and clinical evaluations, the data may then be extrapolated to other indications.

In conclusion, the council applause the agency for its effort to support the biosimilar pathway in the United States, and we look forward to attending many more meetings and further patients' access to these important medicines. Thank you.

DR. CAPLAN: Thank you. Will speaker number 8 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. CAPLAN: Will speaker number 9 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. LaMOTTE: Yes. Hello. My name is Larry LaMotte. I'm with the Immune Deficiency Foundation, and I'm here on behalf of the Patients for Biologic Safety and Access, which is a 23-member national patient -- a coalition of national patient organizations who are interested in the biosimilar pathway.

As representatives of millions of American patients and their families, we, the members of Patients for Biologic Safety and Access, are here to give you input on the perspective of patients as you consider this important application.

We've heard several times today, and we've heard in the past from the FDA, that the FDA is only interested in establishing biosimilarity and not safety and efficacy. We, at PBSA, implore that patient safety and efficacy should be the drivers in these deliberations, not just the similarity.

That's what our patients are interested in, making sure that they are safe and effective for them to use.

Ultimately, of all the stakeholders in this whole entire process, the one with the most risk are patients, and they need to be assured that they have the safest product that they can have. And that requires not just statistical studies or analytics, as what you all call, but also clinical work, too.

The data that FDA has suggested at this advisory has raised some questions that should probably be answered before this committee votes today. Why did the FDA not consider real-world patient experience with Inflectra instead of rely on extrapolation of clinical data on only two of the conditions?

Why weren't all studies on the use of the biosimilar, the European-approved biosimilar, included the manufacture's submission to the FDA, including at least one study in Ireland that found significantly worse patient outcomes after taking

the biosimilar? That has not, to my knowledge, been mentioned even at all today even though it's presented at the ECCO symposium in Barcelona a year ago.

Why did the FDA open the door to one-time switching of patients in this biosimilar when Congress expressly required a finding of interchangeability for switching?

Why did FDA choose to approve the biosimilar for use in IBD when Health Canada refused this request? Now, I heard the statement with the question earlier before and was kind of really kind of shocked that there was no interest from the FDA on that issue.

We just assure -- we want the FDA to use patient safety as the primary driver in this deliberation and not cost, which is prohibitive from your taking into consideration but has been raised here. I thank you very much for your time.

DR. CAPLAN: Thank you. Will speaker number 10 step up to the podium and introduce yourself? Please state your name and any

organization you are representing for the record.

MR. PHILLIPS: My name is Thair Phillips. I'm the president and CEO of RetireSafe. I have nothing to disclose. RetireSafe is a nationwide nonprofit advocacy organization for older Americans. I'm here today representing our 300,000 supporters and almost 50,000 email activists.

RetireSafe looks forward to the promise of increased access offered by biosimilars, but we continue be concerned about safety. Our supporters, in response to a survey, overwhelmingly voiced their desire for what they viewed as common-sense safeguards when it comes to the naming, labeling, switching, approved indications, and the open communication required for biosimilars. Our statement today will deal with safety issues, both with the biosimilar being discussed today and with the overall biosimilar approval process.

In reference to today's biosimilar, we are concerned that the FDA did not consider real-world patient experience and instead relied on

extrapolation of clinical data for two of the conditions, RA and AS, for approval of the other six conditions. The applicant apparently cites some small studies, but it bears FDA didn't consider those studies.

We also found it troubling that at least one public available study that found significantly worse patient outcomes after taking the biosimilar was not included in the manufacturer's submission.

We share the concerned voice by the panel member as to the lack of any evaluation or discussion as to why Health Canada refused to approve this biosimilar for use in children and adults with Crohn's disease.

The most troubling issue, however, is that FDA seems to have opened the door to a one-time switching of patients to this biosimilar when Congress has expressly required a finding of interchangeability for switching. This tacit reassignment of status is a dangerous precedent-setting action that threatens biosimilar safety at several levels.

The overall biosimilar approval process remains a threat to safety. We are concerned and baffled by FDA's failure to release final guidance in many basic areas. We cite the following areas where the lack of final guidance and precedence established so far in the approval process threaten safety: the extrapolation of indications referenced above; the seemingly lack of requirements for a clinical data to back the use for each indication; a doctor's label that may offer little or no information on use for a specific indication, especially in differences from the reference product; the lack of specificity in the assignment of J codes that will hinder adverse event tracking; the projected lack of resources available to FDA to effectively approve biosimilars and to monitor their subsequent manufacturing and use.

Americans trust the FDA. I personally heard Dr. Woodstock say in a house hearing last week that safety would not be sacrificed when it comes to biosimilars. I take her at her word.

As a voice for the people you protect, we ask that the questions and issues cited above be given appropriate consideration. To do otherwise would undermine the trust Americans have in the FDA. Thank you.

DR. CAPLAN: Thank you. Will speaker number 11 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. BANFIELD: Good afternoon. My name is Matthew 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 members about the science of biosimilars is critical.

The Biosimilars Forum is a nonprofit 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 that the U.S. as a competitive, safe, and sustainable biosimilars 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. In fact, about 70 percent of the 57 proposed biosimilar products currently advancing with the FDA are sponsored by members of the forum.

Members of the forum recognize 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 patients about the science behind biosimilars.

Vital to our goals, the ability for biosimilar sponsors to engage with FDA and have a productive dialogue leading to timely product approvals, 2015 was a watershed year as the agency approved the first ever biosimilar medicine for the U.S. market. In 2016, we anticipate the review and approval of several more biosimilars and possibly including the first ever interchangeable biosimilar medicine.

The introduction of biosimilars in the U.S. can help expand the access to high quality treatment options for clinicians and patients, as well as reduce cost to families, caregivers, payers, and the healthcare system. We appreciate that FDA has worked hard to implement this new abbreviated licensure pathway, taking steps to include issuing multiple guidance on biosimilars, and we expect more in the coming months.

The biosimilars program is new, and it is crucial that we maintain the current momentum and build on our experience as we move forward. As FDA continues to implement the biosimilars approval

pathway and we begin discussions surrounding the review of and possible changes to the biosimilars user fee program, 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 the field advances in the days ahead. Thank you.

DR. CAPLAN: Thank you. Will speaker number 12 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. LAYTON: Good afternoon. My name is Dolottie Layton. I have nothing to disclose.

I stand here before you today speaking on behalf of people with Crohn's disease. This disease is a chronic inflammatory bowel disorder that affects the lining of the digestive tract. It can't be cured, but it is treatable by professionals with medication.

In my case, Dr. Michael Epstein who saved my life by prescribing a PICC line, Remicade, and

nutrition -- however, due to the cost of this medication and high deductibles with the health insurance, many problems occurred. Remicade was substituted with Humira and later with Lialda, which my body rejected completed.

So I'm pleading with each of you, for myself and all those that need greater access to these kinds of medications, to approve CT-P13 that would work in the same manner as Remicade but that is less costly. Will you all do this for us, please? Thank you on behalf of myself and all Crohn's patients everywhere.

DR. CAPLAN: Thank you. Will speaker number 13 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SCHIMIZZI: Thank you very much. My name is Greg Schimizzi, a practicing rheumatologist for 34 years, and I'm representing the Coalition of State Rheumatology Organizations.

Rheumatologists are keenly aware of the expense, as well as the life-changing benefits of

biologic agents that have improved the lives of millions of seriously affected autoimmune disease patients. We also welcome the entry of potentially lower-priced biosimilar alternatives to the market but have concerns about safety and the uncertainties surrounding these products. My comments will be restricted to the monoclonal antibodies infusion proteins today such as Remsima, CT-P13, and Remicade.

The beneficial effects and properties of monoclonal antibodies infusion proteins not only are dependent upon correct amino acid sequencing but are also affected by a wide array of post-translational changes that affect the tertiary and quaternary structure of these proteins. I have outlined many of the protein modifications affecting protein structure and function in my written statement to this committee.

These protein alterations may be responsible for differences in heterogenicity, immunogenicity, binding properties, and the differential effects in different populations with diseases that have

different pathophysiologies and the mechanisms of the disease action.

We urge the committee to make the following recommendations to the FDA.

Number 1. Avoid automatic indication extrapolation for this and other complex biosimilar medications since these extremely complex medications can never be totally identical to the innovator compound, and additional studies are needed in each one of the diseases they're applying for. Small changes in the structure can create dramatic changes in efficacy, immunogenicity, and adverse effects.

Number 2. Adopt a naming system. We recommend that the FDA adopt a naming system with the distinct nonproprietary names so the biosimilars and even interchangeable biologics can be readily distinguished from the innovator compound.

Number 3. Develop new pharmacovigilance mechanisms to address the potentially more complicated immediate as well as late sequela that

will possibly develop with biosimilar agents, especially with regards to these attributes.

Number 4. Discourage nonmedical switching in the strongest possible terms and language to prevent payers from interfering with the appropriate care of patients with crippling, disabling and life-threatening autoimmune disease.

Number 5. Request that CMS revisit its decision and provide separate J codes for each biosimilar product. This will bring CMS into total agreement with a distinct proprietary naming, a system that has already been recommended by the WHO.

Number 6. Include labeling that is specific for each biosimilar agent and not simply a reiteration of the innovator product information.

Number 7. Consider the difficulties patients have like you've just heard just a moment ago. A lot of our patients move from state to state, live part time in one part of the country and another portion of their life in another part of the country.

What happens to them with switching and different pharmacies, different benefit plans? What happens to patients who change insurance plans? What happens to insurance companies that change providers, medication providers faster than the weather changes in Washington?

Number 8. We recommend that patients and physicians be informed in a timely manner if a medication being dispensed is or is not, in fact, what was actually prescribed, especially if the agent is deemed non-interchangeable.

The FDA needs to create new and different guidelines for the most complex of biologics being developed since these are truly different from whatever has come before the FDA in the past. I thank you for your time, and thank you very much for your consideration.

DR. CAPLAN: Thank you. Will speaker number 14 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. CAPLAN: Will speaker number 15 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. SMITH: Good afternoon. My name is Liz Smith, and I'm a volunteer with the Arthritis Foundation.

The fifth of my sixth children, Emily, was diagnosed with juvenile idiopathic arthritis before her third birthday. We were fortunate. We only waited a few months for a diagnosis. But getting to that diagnosis meant blood work, bone scans, x-rays, fear, and a series of doctors' appointments.

Emily was the first of our children to be diagnosed with arthritis. Since then, one of our sons, David, has also been diagnosed with rheumatoid arthritis. And 17 months ago, our youngest daughter was diagnosed with Crohn's disease and Crohn's-related arthritis. Both my mother and my mother-in-law have rheumatic diseases, so arthritis is truly a family affair.

Arthritis can be very complex to treat, and patients often have to try multiple drugs before they find the one that works best for them. One estimate of RA patients who took one of the three first generation biologics for at least six months showed that between 40 and 50 percent of them failed to meet the American College of Rheumatology 50 percent improvement criteria.

Of patients who fail on a biologic, rheumatologists switch their patients to another biologic 90 percent of the time. Biologics gave Emily her childhood again. She went from struggling to walk, to being able to run up and down the soccer fields with her peers. Unfortunately though, she's had to move from one biologic to another, and yet another, for a variety of reasons, including some very unwelcomed side effects.

As we consider biosimilars in the future, I want my kids to always know what biologic medicine they're on just as they do now, and I want their providers to also know what medication is being

dispensed.

Biosimilars could represent a great opportunity to increase access and lower costs, but patient safety must be the highest priority. That's why we would like to reiterate our position that there should be unique names for all biologic products. Unique names are critical to ensuring robust pharmacovigilance and to promoting high levels of patient and provider transparency, which we believe are key components of overall patient safety.

Should this drug get approved, the FDA should make postmarket surveillance a high priority, ensuring effective, robust ways to report adverse events and track patients responses to the drug.

Prescribing the correct biologic -- and I suspect the correct biosimilar -- to meet a patient's needs is often an experiment in trial and error even for the most accomplished physician. Thank you very much for the opportunity to speak at this meeting.

DR. CAPLAN: Thank you. Will speaker number 16 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WORTHING: Hi. My name is Angus Worthing. I'm grateful to speak on behalf of the American College of Rheumatology, representing over 8,000 rheumatologists, and I'm a rheumatologist myself.

We see the benefits of biologics in our patients every day, and we eagerly await and anticipate increased access to treatments with more affordable biosimilars. By the way, I have no disclosures.

ACR strongly believes that safe and effective treatments should be available to the patients at the lowest possible cost. In the absence of other large scale levers to control U.S. biologic drug prices, FDA approvals of biosimilars may be the only tool to keep costs within reason. As we have seen today and in published data, CT-P13 has performed effectively in multiple diseases, and

it could be the first biosimilar approved for rheumatologic diseases in the U.S.

Decisions regarding approval of biosimilars should be driven by sound science and take into account several observations and guiding principles, which I'll list.

Number one, in addition to adequate pharmacokinetic and pharmacodynamic studies, clinical data are necessary to ensure safety and efficacy of biosimilars and to provide the necessary level of confidence for their use by patients and providers. Furthermore, collection of long-term postmarketing data for each individual biosimilar is necessary to monitor for less common but important adverse events.

Two, biosimilars must have distinct names, allowing them to be distinguished from each other and the reference products. This will ensure correct prescribing so that I know what I'm prescribing, correct dispensing so that we can avoid inappropriate switching, and aid in postmarketing pharmacovigilance, prescriber

confidence, and ultimately enhance the market uptake.

Three, extrapolation of indications for biosimilars may be pursued with caution but should not be granted routinely by the FDA based solely on FDA-approved indications of the reference product and in the absence of safety data specific to the biosimilar agent and patient population in question.

Four, FDA labels should clearly indicate whether or not a biosimilar is interchangeable with the reference biologic. FDA labels should also clearly delineate all indications for which a biosimilar is approved and specify whether the supporting clinical data for the indication are derived from studies of the biosimilar or the reference biopharmaceutical.

Thank you again for the opportunity to share the views of the American College of Rheumatology. ACR stands by ready to discuss biosimilars further with FDA officials, other scientists and providers, and patient groups in order to help create the most

effective healthcare for American patients. Thanks.

DR. CAPLAN: Thank you. Will speaker number 17 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. EICHELBERGER: My name is Bernadette Eichelberger. I am with the AMCP, Biologics and Biosimilars Collective Intelligence Consortium, the BBCIC. I have no disclosures to make. On behalf of the AMCP BBCIC, I would to thank FDA for hosting this meeting today and for its consideration of the approval of biosimilars in the United States.

The Academy of Managed Care Pharmacy convened the BBCIC to provide active, postmarketing surveillance of biosimilars and/or innovator products in the U.S. Similar to the United States experience with the introduction of generics, we expect that as biosimilars come to the market, and as you've heard here today, that physicians, patients, and other stakeholders will have

questions about the safety and effectiveness of these products.

Currently in the U.S., we do not have an active post-approval process that is built for purpose to monitor biosimilars and biologics. To meet this need, the BBCIC was convened in May of 2015 as a public service initiative that will draw on large data sets of de-identified pharmacy and medical data to provide unbiased scientific information on the safety and effectiveness of marketed biosimilars and their corresponding novel biologics.

The BBCIC is a multi-stakeholder consortium that is science-driven and leverages distributed research network technology to conduct research an active surveillance of biosimilars and biologics. It will supplement the country's current passive reporting system such as the FDA Adverse Events Reporting System. We believe that the public and the healthcare community's understanding of biosimilars will be enhanced by the BBCIC's balanced scientific approach.

The BBCIC is the only distributed research network dedicated to monitoring biosimilars and their corresponding innovator biologic products. The BBCIC framework will apply the same scientific analysis methods that are used with the FDA's Sentinel Initiative, which is a postmarket surveillance system comprising more than a hundred million lives that tracks the safety of pharmaceuticals and therapies once they reach the market.

Our charter for the BBCIC, which is available at www.bbcic.org, describes the transparent process that we will use to characterize patient populations and generate evidence for biologics and biosimilars in a manner that promotes robust and relevant scientific research and exchange. The BBCIC launched our research activities last month.

The BBCIC involves a collaboration of some of the country's largest managed care organizations and integrated delivery systems, as well as pharmacy benefit management firms, research

institutions, and pharmaceutical companies. These organizations are providing the broad financial and in-kind support needed to support our research activities. In addition, three public representatives from patient advocacy and medical society sit on our BBCIC planning board.

Our initiative reflects the consortium's commitment to public safety and health. Once again, the BBCIC thanks the FDA.

DR. CAPLAN: Thank you. Will speaker number 18 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GEWANTER: Good afternoon. My name is Harry Gewanter. I'm the current chair of the Alliance for Safe Biologic Medicines, and they've both financed my travel and I receive honorarium from them.

ASBM is an organization of patients, physicians, pharmacists, manufacturers of both innovative and biosimilar medicines, and others working together to ensure patient safety is at the

forefront of the biosimilar policy discussion.

I have more than 30 years of practice as a pediatrician and pediatric rheumatologist caring for children and youth with rheumatic and other chronic and disabling conditions. Biosimilars provide the opportunity for increased access and options to these miracle treatments at hopefully a reduced cost.

Since CT-P13 would be the first biosimilar of a monoclonal antibody approved by the FDA, it warrants especially careful consideration and input from all the stakeholders. I appreciate you opening this process today.

Given the known variability in patient response with chemical-generic medications, prescribers, pharmacists, and patients desire clear product identification, accurate transparent labeling, and all additional relevant information to feel comfortable and confident in the use of these reverse engineered unique proteins for all available approved indications.

In 2015, prior to the approval of Zarxio,

ASMB conducted a survey of 400 U.S. physicians experienced in the use of biologics. Eighty percent of these clinicians wanted to know for which approved indication was approval based on clinical studies versus which were extrapolated from studies in other indications.

In other words, they wanted to know which of the approved indications had actual in vivo data as compared to the assumptions based on in vitro information.

Ninety percent considered it highly important, or very important, that the product be identified as a biosimilar. Seventy-nine percent wanted to have postmarket surveillance data on the biosimilar, distinguishable data between reference and biosimilar product, and whether the biosimilar is interchangeable with the reference product.

We've obtained similar results over the past three years from physicians in Canada, Europe, and Latin America, as well as U.S. pharmacists. These data and others support the FDA's traditional emphasis on clear product identification and

transparency in labeling.

ASBM believes that when considering approval of a biosimilar such as CT-P13, the FDA should include within its deliberations not just analytical information but also factors of importance to patients and physicians such as clinical safety data for all approved indications, transparency regarding biosimilarity, postmarket surveillance data, indication extrapolation, and interchangeable status to ensure the safe use, wide adoption, and confidence in biosimilars.

Thank you again for including us in this conversation on this important issue. We are more than happy to collaborate, as with the ACR, with the FDA on these and other important matters. Thank you.

DR. CAPLAN: Thank you. We are now at speaker number 19 -- no, excuse me. Do we have 19? Yes. Please step up to the podium and introduce yourself. Please state your name and any organization you are representing for the record.

DR. STOLOW: Thank you. I am

Dr. Joshua Stolow, a practicing rheumatologist for 27 years from San Antonio, Texas. I am representing the Alliance for Patient Access. The AFPA is a national network of physicians dedicated to advocating on behalf of patient access to approved therapies.

In my practice, I use biologic medications to treat a wide variety of rheumatic and inflammatory diseases, including IBD. As the parent of a 20-year-old son now in college who was diagnosed with ulcerative colitis at age 2 and who has been on a biologic for the past four years, I can truly appreciate the incredible life-changing benefit of these medications from a clinical and a personal vantage point. I am wary of the substitution of a biosimilar if it has not been fully studied in the disease state for which it will be prescribed.

I prescribe all the approved biologic medications for rheumatoid arthritis, lupus, and related disorders. I am pleased that the FDA is considering approval of a second biosimilar

medicine as these medicines may provide broader treatment options and may reduce healthcare cost.

As you move towards approval of additional biosimilar medicines, I wish to focus on two issues that could have direct impacts on patient safety and prescriber uptake, labeling, and indication extrapolation.

First, labeling information should contain the data provided by the applicant, and not only the reference products data, that the FDA relies upon in making an approval decision. Providing the clinical data package of the applicant will give physicians clear information about what disease states have been tested and what the clinical outcomes and potential side effects of the approved product are for that indication.

Reliance on analytical data for biologic medicines may not be appropriate. Real-world clinical data is critical to understand the safety and efficacy.

Second, I urge the FDA to continue to move carefully when considering approving applications

that request indication extrapolation. Complex biologic medicines may have the ability to treat a variety of unrelated serious medical conditions. However, because these medications and the biosimilars that follow them are not produced in the same manner and have different structural attributes that may not work in the same manner nor have the same effect, manufacturers should be required to provide substantial clinical data supporting their request.

A biosimilar testing for one or two indications of an innovator product should not automatically qualify that biosimilar for other indications for which the innovator product is approved.

Ultimately, the clinician is responsible for the clinical care of a patient requiring biologic medications and should be informed of all available data and before a stable innovator product is changed to a biosimilar. Thank you.

DR. CAPLAN: Thank you. Will speaker number 20 step up to the podium and introduce

yourself?

(No response.)

DR. CAPLAN: Will speaker number 21 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SMITH: Thank you. My name is Gideon Smith. I am board-certified dermatologist practicing at Massachusetts General Hospital in Boston and on the faculty at Harvard Medical School, and I'm here today representing the American Academy of Dermatology or AADA. I have no conflicts of interest to report.

Thank you for the opportunity to speak before this distinguished committee. The AADA represents more than 13,000 U.S. dermatologists, many of whom treat adult patients with chronic severe plaque psoriasis, one of the indications for infliximab.

The biologics are some of the most important recent developments in therapeutics in dermatology. Unfortunately, the expense of biologics often

limits patients' access to them. Drug pricing has been identified by the ADA as one of our most important issues, and we hope that biosimilars will reduce total healthcare expenditures as they have in Europe.

Infliximab, a TNF alpha inhibitor, however, is a very complex molecule. Production of large glycoproteins such as monoclonal antibodies is incredibly difficult, and the process by which they are produced is fundamentally more complex than the manufacture of smaller drugs.

As prescribers, we are particularly concerned about both the safety and efficacy of any biosimilar. The FDA process only requires analytical studies for similarity, animal studies for toxicity, and clinical study for immunogenicity, pharmacokinetics, and pharmacodynamics. This is a significantly reduced requirement than we currently have for new drug approvals.

While we do support this approach, the approval of CT-P13 depends critically on the

quality of the biosimilarity evidence. We recommend caution with approval of any treatments involving the immune system as we are all aware of the consequences of the TGN1412 trial in which highly reassuring preclinical studies failed to anticipate disastrous consequences in human subjects.

If the biosimilarity evidence is strong by extension suggesting safety and efficacy, the AADA would support approval based on considerations in both healthcare cost and drug access for patients. However, we strongly recommend long-term postmarketing monitoring of clinical practice and registry data to identify issues related to immunogenicity, efficacy, and safety, which may not emerge in limited preclinical trials. Without effective postmarketing surveillance and studies, patients will be put at risk.

Thank you again for this opportunity to share our concerns. The AADA looks forward to continuing to work with the FDA on issues that impact our patients. Thank you.

DR. CAPLAN: Thank you. Will speaker number 22 step up to the podium and introduce yourself? Please state your name -- will speaker number 23 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. BECKER: Hi. I'm Cindy Becker. I don't have anybody to associate with. I am a parent of a child with Crohn's disease. I also facilitate two support groups for parents of children with IBD, inflammatory bowel disease. I'm here to share our stories about what it's like to be a parent of a child with IBD.

Having IBD is about courage. It's an 18-year-old going off to college who's terrified that she's going to be hospitalized and be alone, but she goes anyway. It's about waiting for the results of your 14-year-old's liver biopsy because the last IBD medication she was on damaged it.

It's about adjustments. It's a 10-year-old travel soccer player having to quit because he's too weak to play, but in a couple of years when he

has a little more strength, he becomes a referee instead. It's that same young man at the age of 13 who can't absorb any nutrients from food, so he can't eat anything. Instead, he adapts and he gets hooked up to a machine every night for his nutrition.

Having IBD is about compassion. It's an 8-year-old girl at Camp Oasis, which is a camp just for kids with IBD, showing her ostomy bag to a 15-year-old girl that's going to have surgery in another month, that same surgery.

It's about pain. It's a mom walking into her kitchen and finding her 16-year-old on the floor unable to stand up. It's a 3-year-old boy holding his stomach and saying, "Mom, tummy, ouch."

Mingled with the pain of sadness, it's a mother noticing that her preschooler is the only one in the preschool pictures not smiling. When she asks her daughter about it, her daughter says, "Mom, it hurt too much."

This disease is about medication. It's morning pills, leaving your class for your

middle-of-the-day pills, evening pills, weekly injections, infusions, and explaining this to a 6-year-old child.

Having IBD is about caring. It's a family that takes turns going on a liquid diet because their 7-year-old son can't eat and has to be on liquids.

It's about celebrating the little things, the tears of joy while a mother watches her 9-year-old daughter rock climb for the first time because she's finally healthy enough to do so.

It's about money. This disease is expensive. My family, we budget for it because me and most every family I know, we max out our health deduction every year.

From a parents' perspective, it's about fear, afraid your child is going to flare, be in pain, have an obstruction, need surgery. But you've got to choose. You can be paralyzed by it or you can go on in spite of it.

Having IBD is hard. Being a parent of a child with IBD is hard. We need drugs that can

help, and I'm here to ask you to do your part to make sure that the drugs are safe for our children, obtainable and affordable, and reach the market so we can all be a little less afraid. Thank you.

DR. CAPLAN: Thank you. Will speaker number 24 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. BUCHANAN: Hi. I'm Sarah Buchanan with the Crohn's and Colitis Foundation. I appreciate the opportunity to speak today.

As CCFA is the leading voluntary health agency advocating for the 1.6 million Americans with Crohn's disease and ulcerative colitis, otherwise known as inflammatory bowel diseases, I've appreciated the patients and the families that have come here today to describe the disease to you and their experience looking for a drug that will work, how biologics have really transformed the care for patients with IBD, trying to cover the cost for biologics, and then also hoping that they can stay on the biologics for as long as possible

without a loss of response.

CCFA supports innovation, and we welcome all FDA-approved therapies for patients with IBD. We recognize that biosimilars pose an important opportunity to increase competition in the marketplace. We are hopeful that any cost-savings that will result will be passed on our patients because the cost of care is the biggest barrier to care for our community.

Biologics are complex, and we do have some safety concerns. Our leading medical advisors drafted a written statement that we submitted to you last week, so I encourage you to take a close look at that. I will point out three key points.

One, for indication extrapolation, CCFA has refrained from advocating for extra IBD-specific evidence when approved for another condition has been deemed sufficient by FDA. We are willing to accept FDA approval of therapies indicated for Crohn's disease and ulcerative colitis by extrapolation based on studies in other conditions, especially rheumatoid arthritis.

Two, we are very concerned about immunogenicity and loss of response. I've heard a lot of discussion about that topic today, so please ensure that biosimilars would not incur additional immunogenicity or loss of response as compared to the reference product.

Then lastly, CCFA is very concerned about the lack of awareness and understanding about biosimilars that we've observed in the field among both patients and physicians. We're afraid that misunderstanding could lead to a slower uptake of biosimilars or their misuse, so we strongly encourage FDA to partner with stakeholders to educate physicians and patients about these products. Thank you for your consideration.

DR. CAPLAN: Thank you. Will speaker number 25 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. SPIEGEL: Good afternoon. My name is Andrew Spiegel. I'm representing the Global Colon Cancer Association, and I have no disclosures.

I have been in the patient advocacy community for 17 years now, and I have witnessed firsthand the impact biologic medicines have had in the colon cancer community. Seventeen years ago, there was one medication for colon cancer, which had been around for 30 years and was highly ineffective. Today, there's more than 10, five of which are biologic medicines.

Since biologics have become the mainstay of treatment for colon cancer, the life expectancy of colon cancer patients has tripled. We've gone from a death sentence of less than a year to live to now the sickest metastatic patients living nearly three years on average, and many are living much, much longer. So you can see that we have stake in seeing safe and effective biosimilars come to the United States.

We're excited about the introduction of these biosimilars because not only do they bring new treatment options but they do so at a proposed reduced cost. Reducing costs should translate to greater access to these life-saving treatments.

But in order to feel comfortable using biosimilars, the patient and prescriber communities want to be sure that they are as safe and effective as their reference products. Although the drug being discussed today is not for colon cancer, this discussion is very important to the community I represent.

The biosimilar monoclonal antibody we are discussing today is much more complex than filgrastim-sndz, which was approved last year by the FDA, and therefore warrants much more scrutiny. Unfortunately, currently available clinical data on this drug, while good, remains limited. Lack of adequate clinical data and its efficient transparency regarding that data can be obstacles to patient and physician confidence and a potential barrier to widescreen biosimilar adoption.

As you already heard today, my organization agrees with the need for accurate labeling of each product as a biosimilar along with the appropriate data for each specific medicine. Similarly, we believe it important to distinguish which approved

clinical indication is based upon extrapolation or direct clinical data. In short, the more transparency, the better, as it will facilitate confidence in the usage of biosimilars.

A final issue of concern was raised by the FDA's recent public documents implying that a single medication switch could be made for nonclinical reasons. We would hope that only prescribers and patients would make any switching decisions after fully considering all options.

We thank you for inviting patients and other stakeholder groups to comment on these important issues and the FDA's continued efforts to keep patient safety at the forefront of these policy discussions. Thank you.

DR. CAPLAN: Thank you. And finally, will speaker number 26 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. MELMEYER: Good afternoon. My name is Paul Melmeyer, associate director of public policy at the National Organization for Rare Disorders. I

have no disclosures to make.

I'm here today on behalf of the men, women, and children in the United States suffering with one of the 7,000 known rare diseases that, in aggregate, affect approximately 30 million Americans. NORD, a 501(c)(3) organization, is a unique federation of voluntary health organizations dedicated to helping people with rare orphan diseases and assisting the organizations that serve them.

NORD's mission is to ensure that all people with rare diseases have access to diagnostics and therapies that extend and improve their lives and that the United States maintains a regulatory environment that encourages the development and timely approval of safe and effective diagnostics and treatments for patients affected by rare diseases.

Biologics represent the future of rare disease treatments. Biologics treat rare and chronic diseases in an innovative and rejuvenating manner the small molecule-treatments are unable to

do so. NORD is a proud member of the Patients for Biologic Safety and Access, and we would like to reiterate many of their established positions.

We are concerned that the agency has not yet issued final guidance on various biosimilar policies that impact patient safety such as interchangeability, naming and labeling. NORD also supports the institution of unique and nonproprietary naming to eliminate confusion among patients and prescribers.

We support the complete labeling of biosimilars to identify the product as a biosimilar and indicate if it is interchangeable with the reference product. We encourage the FDA to provide greater educational services to rare disease patients and their physicians to better understand the unique nuances of biosimilars.

Outside of our collaborative efforts with the PBSA, we are also concerned with the FDA's decision to discuss the potential determination of biosimilarity of CT-P13 in a pediatric ulcerative colitis indication. This orphan indication in the

reference product holds orphan drug exclusivity until September 23, 2018.

For over 30 years, NORD has fiercely defended the Orphan Drug Act and its valuable incentives for the innovative development of orphan therapies. Actions that weaken the exclusivity protections within the program are thus particularly troubling. This potential weakening of incentives for orphan development could lead to fewer products being developed for the rare disease patient community.

While we have our concerns with extrapolation, if extrapolation is to occur, then it needs to be carefully and definitively precluding in the extrapolation to an ODA-protected indication. This very issue is at stake today. By putting it on the agenda for discussion, FDA has implied that there is less than 100 percent commitment to honoring the ODA in these circumstances.

We urge you to make clear in your comments on this question that you consider extrapolation to

a protected orphan indication as unacceptable. Thank you again for the opportunity to participate in today's hearing.

Clarifying Questions (continued)

DR. CAPLAN: Thank you. With that, we have concluded the OPH session, and we're now going to return to some of the outstanding questions that panel members had raised or have yet to raise. I'm going to recognize Dr. Jonas for the first of these questions. Could you please identify who you'd like the question directed to specifically?

DR. JONAS: Jonas from UNC. I'm not exactly sure who to address this to. This is for the sponsor. We saw some data, and all the data we looked at today was a single switch from EU Remicade to CT-P13. My question is, are there data available regarding multiple switching from EU Remicade to CT-P13 and potentially back? Are there data available that you could share?

DR. KUDRIN: Thank you very much. Just to emphasize that within this biological license application, we are not claiming interchangeability

status. We have only data currently from single transition, and data on alternate switching or multiple switching are currently absent. But within European Union, where we have a number of ongoing registries and also we capture a large postmarketing safety now, obviously, different scenarios of alternating switching are carefully looked at.

One thing for reassurance of the public would be that for the last 10 years of extensive experience with biosimilars in the European Union, where more than 22 products now have been approved, the safety of switching has been very positive and also safety of using biosimilar products across different classes. And certainly more recently with this particular product and also with now more recently another complex product fusion protein, a biosimilar being approved, safety profile and immunogenicity profile was very positive.

DR. CAPLAN: Thank you. Next up, we have Dr. Jeff Curtis.

DR. CURTIS: Jeff Curtis from UAV. I have

two questions about Celltrion's 3.4 IBD study perhaps to Dr. Kudrin. The first was to understand a little bit more about the background. Although we've seen some immunogenicity data, from my understanding, this is a comparison trial of more than 200 people with the primary result being efficacy and safety outcomes are being looked at.

So it's not just an immunogenicity study, and it was launched after regulatory approval of the product in Europe. I guess my question is, is what was the motivation for this study, and was it based on the need for additional clinical data? What is it a regulatory request? That's question one.

Then the second is a little bit forward-looking as I understand that this probably will read out in a year. If that indeed is the case and we have new clinical data for IBD, if in fact the study does not meet its primary clinical efficacy endpoints and its safety endpoints, what the company's position is on what to do with that information in IBD, especially in countries where

it already has an IBD approval and yet you now would have data in IBD that had failed its main endpoint.

So what's the thinking about what might happen if that were to occur?

DR. KUDRIN: Right. Thank you very much. The 3.4 study of Crohn's disease study has not been designed upon request of any authority. No Health Canada or European Union European Medicines Agency requested this studied at any point.

The only reason the study has been designed, together with Hospira or Pfizer by Celltrion, is to exactly assist public and stakeholders and particularly gastroenterology community with understanding of extrapolation and positioning of the product on the market.

Certainly, we heard today that there is a lot of concerns surrounding extrapolation, so the data there is only to educate prescribers and help with placing this across the globe.

As we know now, this product has been already approved in 67 countries. And with data

coming with more than 2,000 patients in inflammatory bowel disease, we do not expect the study to fail. For that reason, we do not anticipate that those will be any surprising findings from the study.

We're not even thinking about the consequences of a failed study because with highly similar analytical, structural and functional characteristics for this biosimilar, there is no reason to think that there will be a surprising finding in this trial.

Certainly, from the findings presented today by Dr. Lakatos and also data from a lot of different cohorts and studies, we know that response rates, remission rates, and mucosal healing rates are in line with what's been reported with Remicade.

I think that's what we can say.

DR. CAPLAN: Next up, Dr. Mager.

DR. MAGER: I had a question for the sponsor, again, about the pharmacokinetics. You had shown in response, I think, to one of the

questions, the population, a pharmacokinetic model. And I was wondering if you could share with us -- I was curious to know whether you identified similar covariate relationships in that analysis as has been reported in the literature. In particular, I'm interest in whether or not pre-infusion C-reactive protein had any correlation with the clearance of the drug.

DR. KUDRIN: We have done an extensive subgroup analysis of PK data looking at different covariates. We haven't examined specifically effect of the protein you mentioned. But for example, impact of demographic factors such as age, gender, weight -- and we also looked at the racial and regional factors -- have been looked at the primary results of ankylosing spondylitis trial.

Whatever analysis we did, the subgroup analysis didn't find any notable differences between CT-P13 or Remicade except that, of course, in some subgroups, the number of subjects was reasonably small. Like with this particular impact of races, the one subgroup was small. For that

reason, the confidence intervals were wider.

But whatever other covariates we looked at, both products look comparable.

DR. CAPLAN: Next is Dr. Fuss.

DR. FUSS: These questions are actually in follow-up to Dr. Long's questions about some of the in vitro studies. I'm not sure -- this is addressed to the sponsor.

The first question was in the data set that you had sent us, there was some information given that PDMCs and LPMCs were purchased from genetically-identified patients.

First question is, were there any differences in the genetic make-up of the PBMCs and the LPMCs that you obtained in the patient population? Were they uniform? Were there any abnormalities, any differences?

DR. POLLITT: Just to clarify, yes, we looked at a number of -- we looked at the Fc-gamma receptor 3 polymorphisms. When we were designing the ADCC assay, we wanted to ensure -- because we know that there were differences between cell type,

cells from different donors, and so we looked at a number of different donors and looked also at the Fc-gamma polymorphisms.

As you can see here, there were relatively low ADCC activity for some of the donors with FF allotype and higher with the VF allotype. We actually chose to use a single donor for all our studies, and that includes PMBCs and the NK cells. And this was the VF polymorphism with donor number 4.

DR. FUSS: The follow-up to that and my last question is, again, relating to some of the ADCC and the membrane-bound TNF type studies, ADCC as we've heard here is a very complex issue, very complex pathway, but there were a lot of other signaling pathways that actually can affect the ADCC pathway.

When you've done your studies predominantly, they were add-mixtures of the cell types and the sample monoclonals, with or without sometimes LPS. Were any other cytokine stimulants or other stimulants used to try to stratify these types of

data or to normalize the ADCC type response or the membrane-bound TNF expression responses? In particular, IL 6, IL 27, or some of these other cytokines.

DR. POLLITT: For the ADCC assays, we did look at the level of transmembrane TNF present on the cells. We looked at what those present were on the transmembrane, transfected Jurkat cells, and we also looked at the level of -- that we had on our LPS-stimulated cells.

We also looked at LPMC from patient mucosa. And just to show the results -- and this is one of the reasons why we think that we see ADCC activity with the engineered cells, these overexpressing Jurkat cells, but we don't see it with the LPS-stimulated monocytes and macrophages. And again, we haven't been able to detect ADCC at significant levels in IBD patient mucosa or the LPMC.

The reserve signaling activities, we looked at TNF levels, but we also had -- in our Caco-2 cell model, we looked at IL 8 and IL 6 expression

to see whether we were actually dampening down the effects of those cells, the expression of those. I think I may have shown you this before, but just to highlight, we do see highly similar activity. This is IL 8, but we also looked at IL 6 in our two-way studies.

DR. CAPLAN: Dr. Gobburu?

DR. GOBBURU: This question, I think, is for the sponsor. Regarding the in vitro potency -- I'm looking at slide CC-43 -- there is a distinct difference in the distribution, meaning the central tendency for CT-P13 is towards the lower, consistently, the three concentrations compared to the U.S. -- let's talk about the U.S. Should I be concerned about it?

DR. POLLITT: We believe not, because this is a very highly -- a rather artificial cell system. We include this assay because we're required to conduct our assays at the highest sensitivity that we can. But this isn't necessarily what we would consider to be the best model of a physiological system because we don't

often have purified NK cells in the physiological system. And we also don't have these very high expression levels of transmembrane TNF.

I would like to invite Dr. McGuckin to discuss ADCC and what's known about it in the literature.

DR. McGUCKIN: Professor Michael McGuckin from the University of Queensland in Australia. I'm a mucosal immunologist, and I've got research interest in intestinal inflammation and also in experimental therapeutics.

I guess something that hasn't been discussed so far around this question of the subtle difference in ADCC and NK cell assay is that it disappears completely in the presence of serum.

If you take this into the physiological situation, I think this in vitro assay, given that very high level of transmembrane TNF that has been modified genetically so it can't be cleaved, it's an unnatural molecule if you like, that it won't leave the cell surface.

On top of that, if you take it in a more

physiological situation either by putting serum in that assay or using whole LPMC as effector cells, then that points out to me that this is very unlikely to be recreated in the mucosa of an IBD patient.

Another issue, I guess, that hasn't been discussed today is that from the few studies where researchers have looked in the mucosa of patients before and after commencing therapy, the cells that express high levels of transmembrane TNF are actually macrophages, myeloid cells. And the cells that die in response to the therapy are T-cells. And those T-cells have very low or no level of transmembrane TNF. And I can show you some of that data if you like.

This is a study that was published by Marcus Neurath's group in gastroenterology, and they map this out in patients before and after therapy. The fluorescence is not showing up very nicely in this room here, but what those fluorescent dyes are telling you is that the cells that express transmembrane TNF are myeloid cells.

So if ADCC was occurring when you commence therapy, you would expect that the cells that underwent apoptosis or died would be those myeloid cells, but in fact, it's T-cells that die. And they provide a very nice explanation for this in that the T-cells express TNF receptor 2, and the macrophage expresses the transmembrane TNF and sends a survival signal to the T-cells. Then in vitro, if you block that survival signal by blocking the transmembrane TNF with infliximab, what happens is that the T-cells undergo activation-induced cell death and die.

So this is a very plausible explanation around why transmembrane TNF is important but also why ADCC doesn't seem to be the key to the cell death that happens in the mucosa.

DR. GOBBURU: Yes, but if you're talking about the experiment itself, why is there a selective differential behavior for CT-P13? Whatever limitations that you have alluded to would apply for both, wouldn't they?

DR. McGUCKIN: No, there's nothing selective

about CT-P13. It's acting exactly as Remicade would, so it will block transmembrane TNF in the same way that Remicade does. But the point is that it's not doing that in Fc-dependent manner. So this small change in glycosylation in what is less than 2 percent of the product is not having a bearing on that particular inhibitory function.

DR. CAPLAN: Dr. Feagins?

DR. FEAGINS: Linda Feagins. For our patients with IBD, we often check infliximab drug levels, as well as antibody levels to guide our decisions how to take care of our patients. And I'm just curious, have the commercially available assays for these been compared between infliximab, Remicade, and the biosimilar agent? And basically, will we able to use these interchangeably when we take care of our patients?

DR. LAKATOS: Yes, thank you very much for the question. Indeed, it has. Before we embarked on the study, you have to know that there's a harmonized follow-up and monitoring in Hungary necessary clinically, biochemically. So we used

CDIA regularly; we use CRP, not just for the study purpose but in all patients who are treated with the biologicals, with the originator for CT-P13.

On top, we validated the Theradiag assay from France to check for both Remicade antibodies and the CT-P13 antibodies so it was formally validated. We did the same for U.S. assay as well. So yes, indeed it was validated.

DR. CAPLAN: I'd put my name down as the next one at the time I thought of the question. This is a follow-up, really a two-part question. The first is a follow-up to Jeff's because I didn't feel like I could reliably rearticulate the response. And that is, if in these clinical studies that are ongoing in IBD, if you have a different response, a different outcome than what you expect, because this is science and that's what sometimes happens in science, then what will the sponsor do with that data? And then, again, what would the FDA do with that data if they became in possession of that?

DR. KUDRIN: As I think we don't anticipate

any surprises from the study as I mentioned, but obviously, if there's any unusual finding, we will be sharing this data with the agency and working with them through this. But the principle of extrapolation as today is not based on this study. And for that reason, this study has not been part of this biological license application.

As extrapolation, based on foundation of highly similar functional characteristics of the entire molecule, including Fc and Fab functions included in highly similar ADCC for this product, we believe that this is not going to be the case that in this study we're going to find anything unusual.

One of the features in the study, which also pursues long-term safety in IBD in patients in a controlled manner, is looking at the -- if I may have the slide back please?

We would like to examine also safety in switching between CT-P13 and Remicade in a randomized manner. This is will be examined following week 30. And also, dose escalation of

10 milligrams is allowed in the study.

DR. NIKOLOV: Dr. Caplan, maybe I -- if I can follow on the second part of your question --

DR. CAPLAN: Yes, please.

DR. NIKOLOV: -- what's the FDA take on this.

Just to begin, no, we cannot really comment on hypothetical scenarios, and we would certainly like to see the data regardless of what it is. We do this for any biologic, not just for the biosimilars. We review any clinical data that gets submitted to us. We've had other situations where even approved therapies do not really yield expected results in clinical trials.

With that set aside, we don't really -- we have reviewed the data just to address some of the comments from the public speakers, and we didn't really present the data from the IBD postmarketing studies. One is because to avoid redundancy in the presentations; two, even though the data is overall reassuring about the safety and efficacy of the product in IBD indications, this is open label,

uncontrolled data, and we cannot really provide definitive conclusions based on those data.

But three, which is probably more important, is that we didn't really consider, that clinical data in inflammatory bowel disease indications or any of other indications that we considered for extrapolation, is necessary for the discussion today and for potentially a regulatory decision.

We didn't require, for example, the controlled clinical study that Celltrion is conducting. As Dr. Kudrin mentioned, no other regulatory agencies have required that data. This is mostly to reassure the practicing clinicians that the drug might be working, which we all expect it would, based on what we know so far.

DR. CAPLAN: Okay. We're going to take a break now. The duration will be 15 minutes, and then we will resume. We have a number of folks that have requested additional questions.

Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the

audience. The plan is to resume at 3:00 p.m. Thank you.

(Whereupon, at 2:46 p.m., a recess was taken.)

DR. CAPLAN: I'd like to now call on Nikolay Nikolov to make some comments and provide us with a charge to the committee on behalf of the FDA.

Charge to the Committee- Nikolay Nikolov

DR. NIKOLOV: Good afternoon, everyone. Again, my name is Nikolay Nikolov. As we prepare for the committee's discussion and voting this afternoon, I want to provide a brief reminder with the issues, the regulatory framework, and the underlying decision-making for 351(k) marketing applications for proposed biosimilar products and the questions to be discussed and voted upon.

As discussed earlier, Section 351(k) of the Public Health Service Act defines the term "biosimilar" or "biosimilarity" to mean that the biological product is highly similar to the reference product, notwithstanding minor

differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product.

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 conclusion that CT-P13 is highly similar to US-licensed Remicade 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;

Two, whether the clinical data submitted support the conclusion that no clinically meaningful differences exist between CT-P13 and US-licensed Remicade; and

Three, whether the applicant provided sufficient scientific justification for the extrapolation of clinical data from studies in rheumatoid arthritis and ankylosing spondylitis to

the additional indications sought for licensure.

Consistent with these considerations, the first question to the committee is to discuss the adequacy of the data to support a demonstration that CT-P13 is highly similar to the reference product, US-licensed Remicade, notwithstanding minor differences in clinically inactive components.

Then the committee will be asked to discuss the adequacy of the data to support a conclusion that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use, rheumatoid arthritis and ankylosing spondylitis.

The last discussion question is whether there is a sufficient scientific justification to extrapolate data from the clinical studies of CT-P13 in rheumatoid arthritis and ankylosing spondylitis to support a determination of biosimilarity of CT-P13 for the following additional indications for which U.S. Remicade is licensed. These are psoriatic arthritis, plaque

psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis.

The FDA is also requesting the committee's discussion on specific concerns with extrapolation and what additional information would be needed to support extrapolation, if any.

Question 4 is a voting question on the committee's recommendation whether based on the totality of the evidence CT-P13 should receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which U.S. Remicade is licensed and CT-P13 is eligible for licensure. These are listed in the parentheses: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult ulcerative colitis.

The voting will be followed by discussion on the reasons for your vote and for those who voted no, a discussion on whether this was applicable to all or some of the indications and why.

Thank you and I will now turn the meeting to

you, Dr. Caplan.

Questions to the Committee and Discussion

DR. CAPLAN: Thank you. We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at specific request of the panel.

The first question open for discussion now, does the committee agree that CT-P13 is highly similar to the reference product US-licensed Remicade, notwithstanding minor differences in clinically inactive components? If you could just wave to Ms. Begansky, then she will put you on the list. Dr. Cramer?

DR. CRAMER: I just wanted to make one additional comment about the product-related variants. It seems to me that when I look at the analytics, there is a difference in the charge variants form, a difference in the aggregate form.

I see these differences, and I said earlier, I've been assured by the discussion here that it's

not a problem in terms of the clinical side of that. I just want to make the observation that there is a difference, and I just want to know what we're going to do about it.

DR. CAPLAN: Dr. Gobburu?

DR. BRORSON: Well, this is Kurt Brorson. I'm the product reviewer. I can address that.

DR. CAPLAN: Go ahead.

DR. BRORSON: These are all reviewed during the review cycle of the BLA. Also, during the review cycle of a BLA, there is a process where we work with the sponsor to address certain issues and perhaps negotiate tightening of the process or the product.

I can't comment on specifics of what happened on this particular application because it's all trade secret, but that is part of our review process and the review cycle.

DR. CRAMER: Having said that, I just follow up I do believe that they are clinically not a big deal from all the clinical data that I've seen, but I'm still curious.

DR. CAPLAN: Dr. Moreira?

DR. MOREIRA: Again, on this topic, I believe that we do see some differences, but I'm reminded by the comments from Dr. Brorson earlier that they have looked at these, and they are within what we see for other biological products.

Also, I asked earlier, the sponsor, about in-process controls and the critical parameters and critical quality attributes. I believe that perhaps I can ask again if they have indeed established those, and when they look at their productions systems, if indeed they can assure that there are in-process controls that are taking care of the critical parameters and they have been relative to the quality attributes as ranked as the highest criticality warrants, and there can be the processes under control and keep these variations within the accepted limits that the FDA has agreed to.

DR. CAPLAN: Now, to Dr. Gobburu.

DR. GOBBURU: Thank you. My question -- I still do not know if I'm concerned, but my question

about the in vitro potency is still, well, in my mind.

Can I ask the FDA to maybe help me why I should not be worried about the findings, SPR or the ADCC, with respect to this distinctly different distributions in vitro? Let me tell you why I'm asking this question.

Clearly, the expectation for the analytical comparison is at the bottom of the triangle with 48 font. The clinical study is at the 8 font for a reason. So I want to make sure that I am not missing or we are not missing something important because this is one of the sensitive tests.

DR. KOZLOWSKI: So I think that when we evaluate these, again, we considered the risk and the potential implications of things. There was however differences in the average value of an attribute, but a patient doesn't see the average value of the attribute. They see the distribution. And I think one other way of thinking about that is looking at the distributions and how different they are in terms of what a patient sees.

Also, as Dr. Brorson mentioned, what you see here is the exercise to look for similarity. There's also a whole manufacturing control process and control strategy that tries to make sure attributes stay within a certain range. So that's an additional layer upon that distribution that may give confidence about individual manufactured lots of product.

DR. GOBBURU: So in other words, Steve, if you have some of these lots that have results which are, let's say to the left-hand side of these goal posts, they may not be released?

DR. KOZLOWSKI: Again, a control strategy could prevent that from happening. And part of what we review, which again is a trade secret, is the manufacturing process, the quality control, the process controls. I think the sponsor may want to comment.

DR. GOBBURU: Okay.

DR. POLLITT: May I answer this point? Just to clarify that, yes, we recognize that in the meta-analysis are certainly on the Fc-gamma

receptor 3A, and we have tightened the limits after discussion with FDA to ensure that actually, in future, all lots will be within the 3 standard deviations of U.S. Remicade. Hopefully, that provides you with some assurance.

DR. CAPLAN: Thank you, Dr. Pollitt. Comments from the panel?

(No response.)

DR. CAPLAN: Does anyone have any questions that they think might prompt discussion around this topic, about the similarity?

DR. GOBBURU: I can put a stake in the ground if that helps to motivate people to speak up. I'll opine on this question.

I don't have any clarifying questions left, but by looking at the totality of evidence, looking from the physicochemical, structural point of view, as well as the in vitro assays, the pharmacokinetics, and the clinical study -- I don't know if I need to even look at the AS study, but the RA is adequate. But so be it, you have data for the AS, too.

Looking at these five components together, I think that the CT-P13 is highly similar to the reference product. There you go.

DR. CAPLAN: Just a comment from the chair. It seems to me that a lot of the endpoints focused on the RA study rather than the AS study. I didn't see any BASFIs or BASDAIs, or I don't recall if there was an ASAS20.

Can anyone comment on a little bit more detail there?

DR. KUDRIN: Certainly, quite a number of secondary efficacy endpoints in the AS study, so may I have maybe some ASAS20 and ASAS40 data from -- no, I would like to see efficacy data from ankylosing spondylitis study.

These obviously were not predefined in terms of any equivalence or non-inferiority margin because this was a PK study. But you can see that ASAS20 and ASAS40 assessed throughout two years looked comparable between CT-P13 and Remicade and also in maintenance in switch group. You've also seen today data presented by Dr. Strand with

quality of life in ankylosing spondylitis patients.

Maybe also, if we have a list of secondary efficacy endpoints for AS study. So there was a range of different parameters assessed using primarily descriptive statistics. Here, you can see assessment of those features. They all look comparable throughout first and second year.

DR. CAPLAN: Dr. Solga?

DR. SOLGA: Steve Solga. Do you mind if I just ask a question to the FDA about the comparator label? I wonder if the FDA has considered updating the label for infliximab and the other biologics labeled for IBD.

All of them contained the awkward concluding clause "moderately-to-severely active disease in patients who have had an inadequate response to conventional therapy."

That awkward clause really made some sense 20 years ago, but today, biologics are considered conventional therapy. And it causes some confusion for docs and their patients and also creates delay when trying to get access to these patients with a

pair when you have a patient with severe flare and you haven't yet proven to the pair they've failed prednisone, mesalamine, leaches, that kind of stuff.

DR. NIKOLOV: This is Nikolay Nikolov, and I'll take it as a rheumatologist to answer this question. The indications in products like Remicade, which were initially approved in the 1980s, include really lengthy indications. These are currently legacy indications, which we no longer preferred, and we prefer the description of the clinical data in the clinical study section where the prescribers can actually get the actual information, what was done and what was studied.

With respect to this probably archaic or outdated language, changing an indication is really an uphill battle in general. We're trying to prospectively change this practice, not just for the inflammatory bowel disease indications but for other indications as well.

DR. CAPLAN: Thank you for that clarification. Do we have any other comments from

the panel members?

(No response.)

DR. CAPLAN: Are there any comments from the patient representatives around this or any additional questions that you may have had?

DR. HORONJEFF: Not at this time. I think some clarification in later discussion.

DR. CAPLAN: Okay. Dr. Maloney on the telephone, can you please proceed with your question?

DR. MALONEY: Mine is actually a comment. I am slightly comfortable at the beginning of that statement but when we get to "notwithstanding minor differences in clinically inactive components," I'm not 100 percent sure that RA can say that the differences might not be clinically inactive.

I'm very happy with the first part of the statement because I think there's been good data. But I'm not so sure I'm very happy with the sentence following the comma.

DR. NIKOLOV: This is Dr. Nikolov again. I just want to clarify that the question was phrased

to track with the statutory language or the language that's in the law, which is exactly what we have on the slide.

Maybe I can ask my product quality colleagues to add to that.

DR. BRORSON: Okay. We've discussed ADCC quite a bit and the NK cell assay for ADCC. We'd like to point out that after testing the multiple lots that the applicant has tested and in our evaluation using quality range analysis, despite that small shift, greater than 90 percent of the proposed biosimilar lots are within the quality range of the reference product as defined by plus or minus 3 standard deviations.

We came to the conclusion on the basis of this kind of analysis that the product is highly similar. It's important to remember that the standard is highly similar, not absolutely identical. That's the thing to keep in mind, and maybe Steve can elaborate on that a little bit.

DR. KOZLOWSKI: I think that's exactly right, that highly similar does not mean the same.

It's particularly written that way. Therefore, minor differences are beyond what highly similar is, but I think there is space in highly similar. Some of our statistical tools are part of that, but some of it is judgment in terms of highly similar. And then the minor differences in clinically inactive components are issues beyond that. And I don't think our interpretation of that leads to a problem with this data set.

DR. BRORSON: So for example, Steve mentions C-terminal lysine content. C-terminal lysine is an amino acid at the very end of an antibody that gets clipped off right after infusion. That would be an example of a clinically inactive component that would be different between -- that could be different between the different products.

DR. CAPLAN: Comment by Dr. Cramer?

DR. CRAMER: Just briefly. I mean, I think it's semantics to some extent. If you want to be really noogie about it, you would collect the peaks from the ion exchange like the deaminated product, the first peak, which is not a C-terminal lysine, I

believe, and you'd actually test that individual charge variant, whether it was clinically active or not. But I think that's beyond the scope for what we're doing here.

DR. BRORSON: Well, the sponsor did not mention -- they can expand on this after my comments. But they did perform an analysis where they selectively enriched for certain impurities of the product that we were asking them about, concerned about. And they enriched for the impurities including the ones that we've discussed and tested them in various biological assays, and found that, essentially, they had the same activity in a whole panel of different biological assays. But it looks like you're going to expand on that, so go ahead.

DR. POLLITT: I can show you the data if you would like to see it. We did purify specific impurities to see what the impact of them would be. We also looked at forced degradation studies to see at what point various -- the attributes have an effect on -- start to have an effect on biological

activities.

I show you here, we looked specifically obviously at Fc-gamma receptor 3a binding affinity, and we looked -- this is showing the high molecular weight forms and also the H2L1 levels. So these are a form of non-assembled forms or fragmented forms.

As you can see here, you we can the levels up to quite high levels, you know, 10 percent or 20 percent, and we don't see any impact on either Fc-gamma receptor 3a or a significant effect on NK ADCC.

DR. CAPLAN: Thank you. Dr. Brittain?

DR. BRITTAIN: I think my comment has been addressed, but since I don't really understand the immunology of this at all, I want to understand if amongst the panel, are there some people who believe that we don't really know whether the differences may have a clinical impact?

DR. CAPLAN: We'll have a little bit more time to reflect on that as clinically meaningful differences is the topic of the second discussion

question.

DR. KOZLOWSKI: Steve Kozlowksi, FDA. One issue with the antibodies is we all have lots of antibodies with lots of variations. Many of the variations that you see here exist in our immunoglobulin. So I think when it comes to immunogenicity concerns about structural changes, there's a lot of information we have about the natural variants we see in antibodies. And I think that can give some comfort about a small structural change in a product being so different from what are endogenous immunoglobulin is that it will present in immunogenicity risk. It's usually the specific part that binds to the TNF or target that's an issue.

DR. CAPLAN: Dr. Schiel?

DR. SCHIEL: About the comment on the general use of analytical technology that characterize these proteins and sort of a suggestion in that same light to Celltrion in their submission form that was the briefing material that we received, so the analytical methods will often

pick up changes in a product far before some of the biological assays will. They're more sensitive; they're very selective for specific attributes of the products, so you may see various small changes in a product that you might not pick up on biological assays or in vitro.

I can't highlight enough the importance of having very robust analytical assays and again that it's not unlikely that we're going to see changes in these various attributes using the wide variety of analytical methods.

One of the things, I think, going forward in this field and as a suggestion to the current briefing materials from Celltrion would be to present some of the data, the analytical data, in a quantitative format.

For example, table 15 definitely lists an exhaustive tool box of analytical methods, but I think it would be very useful rather than showing the percentage of lots that either made or fit within a quality acceptance range in tier 2 analytics to also show graphical representative

data, especially of those species that are different, so we can actually see what the variability is very similar to we did with some of the biological assays.

I think looking at the data and understanding the 3 standard deviation for tier-2 type analytical methods, it makes sense that there's a very exhaustive characterization platform there. But visualization in these briefing materials, I think, would be very helpful to reviewers.

DR. CAPLAN: We're going to go to the telephone now and allow Dr. Eric Tchetgen to make a comment or ask a question.

DR. TCHETGEN TCHETGEN: Yes, thank you. My question is regarding trying to get a sense of the uncertainty in of some of these data. We had a discussion about the impact of missing data in study 3.1. The emphasis of that discussion was really around the analysis, the tipping-point analysis, which I think is fairly compelling in the sense of reassuring us that missing wasn't random

and you do not have any issues.

However, given that this is biosimilarity trial, I think the other concern is whether basically the missing data is adding uncertainty in the endpoints in both arms, making them, let's say, less likely basically in terms of adding noise to finding the differences.

This particularly pertains to ACR20, and I wonder if anyone could address that either from the sponsor or FDA, whether there were any sort of analysis that were done to assess the impact of missing data on not so much the magnitude of the differences but rather the uncertainty around those differences.

A related question, if I might add, is part of the rationale, part of the explanation as to why there was such large high dropout in the same, in each arm, which is pretty high by any measure. But part of the explanation was that this was due to design in the sense that folks who were not adhering were discontinued, which is a bit of a strange design for randomized trials. Usually, for

head-to-head comparison, when you want to do it [indiscernible - phone interference] in any case. I wonder if the rationale for such as design can also be explained?

DR. CAPLAN: First, let's have the sponsor --

DR. LEE: Then I'll turn it over to the FDA after my answer. My name is Sang Joon Lee, vice president of Celltrion. I'm in charge of the statistics and data management.

First, Celltrion conducted a variety of missing data imputation method to examine the impact of missing data on showing therapeutic equivalence, and it turns out to be there's no impact at all.

First, what you see in the screen is our primary endpoint of ACR20 at week 30. There are several methods; first one is original, is the protocol, which is non-responder imputations. Basically, we consider all missing data is imputed as non-responder. Method A or LOCF is the last observation carried forward method, which is the we

used the responder information as a last observed barrier.

In the nature of week 30, there's only week 14 response variable that offer -- still, there's missing data. In that case, we consider them as non-responder. That's method B, which you can see in the figure. It's showing here the 95 confidence interval is all within 12 percent margin no matter what we use.

Now, FDA shows the tipping-point analysis, which is a very robust way to show what's going to happen. Celltrion also conducted tipping point analysis in a very similar way, but I want to show you something, a more strong measure here.

There are 47 missing data in CT-P13 in comparison to population to ITT. For EU Remicade group, there are 45 missing data. True dimension here is a possible combination of outcomes.

Here, you can see the blue region is the tipping point, which satisfies equivalence. What you can see here is actually there's a binary process. No matter what kind of value we observe

in the combination of missing data, the probability on meeting equivalence is 97.3 percent. With a 50 percent margin, the probability is 99.9 percent, supporting there's no clinically meaningful differences between CT-P13 and Remicade.

DR. CAPLAN: Did the FDA also want to respond?

DR. LEVIN: Yes. This is Greg Levin. I'll just add a couple of things. I'm not sure if I caught all of the questions that were asked, so follow up if I don't address them. But I think that missing data always adds uncertainty to the conclusions, but we're comfortable in this case that it would take highly implausible assumptions about the missing data for the conclusions about the similarity comparisons from the RA comparative study to change. So we're comfortable that the conclusions of similar efficacy are credible despite the missing data.

I do agree with the comment that it was due to the design. I mean the patients who discontinued treatment were not followed up by

design, and that echoes what has been done in historical studies as well. So the rates of treatment adherence in the study are similar to what was observed in historical studies, so we're comfortable with that as well. But if I didn't answer any of the questions, please follow up.

DR. CAPLAN: Hearing none, let's have a comment from Dr. Shwayder.

DR. SHWAYDER: There were several comments in the open public hearing part this afternoon about does the similar medicine work, first up and does it work in flip use; I think speaker number 9, certainly J&J, at least one other.

My first thought is we'll have 10,000 patient users when we have 10,000 patient users. In the meantime, does what we have so far help the FDA be reassured that the medicine, the biosimilar medicine works, first up; and as a flip med from Remicade, there were some data, but they were small numbers.

DR. NIKOLOV: Was that a question or a comment?

DR. SHWAYDER: Well, can you reassure the people who say, okay, you compared it biochemically, but does it work when we give it first up for IBD?

DR. NIKOLOV: I think the question 1 refers to the highly similar standards for the analytical similarity. I guess we're shifting towards the discussion of second question of no clinically meaningful differences.

I think we laid out our considerations for why the differences that were seen between CT-P13 and U.S. Remicade are first not sufficient -- or sufficient to say that the products are highly similar, and then these minor differences, we do not expect that they would impact any of the clinical activity in inflammatory bowel disease, based on everything that we know about the molecules, how similar they are, the PK or the exposures that were similar between CT-P13 and U.S. Remicade, and the efficacy and safety and immunogenicity data in two different patient populations.

Based on all of this information, we do not have concerns that these differences represent or would represent a clinically meaningful difference in inflammatory bowel disease.

DR. CAPLAN: So I'm just going to reiterate that the focus here is on the similarity with regard to the analytics. So are there remaining questions about that? You have some comment on that? Okay. This is Dr. Siegel.

DR. SIEGEL: I want to respond -- this is a question that sort of crosses over from the analytical to the clinical. I think maybe the person on the phone, the first caller, the issue is, is there a minor difference in clinically inactive component. I think we're not talking about an impurity but the -- I think, to me, it really does come down to the glycosylation of the Fc region and binding to Fc receptors is that I think -- and that's a hard one. I guess in my mind as an immunologist and within immunologists, if you don't study Fc receptors, that can be a daunting area because there's a lot of variations as we've

been talking about. It's a challenge thing to know.

The one thing that leads to a somewhat clinical question -- so I guess I'm still uncertain, and I think there is a degree of uncertainty that doesn't prevent me from still thinking that when you take the totality, it's a small point.

But one thing that I went back to in the briefing was the fact that there does seem to be a genetically controlled binding difference and the V allele potentially looks more different than the F allele.

So the question I had for the sponsors was -- and I might've missed it in the data is, are there any clinical studies that use that as a gating variable? Maybe you could comment on that if there have been or plan to be, the Fc receptor polymorphism.

DR. POLLITT: Thank you. Yes. When we look at the Fc-gamma receptor 3a binding, we looked at binding to both V and F allotypes. As you can see

here, there's some spread in U.S. Remicade lots. We see some CT-P13 lots have actually slightly lower binding affinity. The numbers here on the bottom, they go from high on the left-hand side to low on the right-hand side. And it's known that the IgG1s bind to Fc-gamma receptor 3a V type but higher affinity than the F type.

What you also see here is that the difference between Remicade binding to V and F type is obviously much greater than any small difference between CT-P13 and Remicade.

The reason why we think that's probably an important point is because, yes, we know about the different binding affinities of IgG1s for these different allotypes, but also, there's been clinical studies, which have showed with infliximab, that there's no difference in clinical responses dependent on patient allotypes. There have been studies conducted in certainly Crohn's disease, rheumatoid arthritis, and psoriatic arthritis.

Also, can I also have the comparison for the

TNF inhibitors, please? Thank you.

I think something else that we would like to show you is that on the left-hand side here, we have NK ADCC assays, and I've said that's a very sensitive system. We've compared CT-P13 against Remicade in this assay but also against Humira, Simponi, Cimzia, and Enbrel. And as you can see, the levels in CT-P13, Remicade, Humira, and Simponi are approximately the same. If anything, actually, CT-P13 is slightly higher than Simponi on this. We know and we weren't expecting to see high levels of ADCC for Cimzia and Enbrel.

On the right-hand side, you can see the same assay with PBMC used as effector cells.

DR. SIEGEL: And just to confirm, we discussed it earlier, but that data is where you're comparing different drugs in the same donor?

DR. POLLITT: All of the effectors cells were all from the same donor.

DR. SIEGEL: Okay.

DR. POLLITT: We have done other studies, which have used different donors. But yes, that's

all from one donor.

DR. NIKOLOV: I would like to add to this discussion. If we can pull slide 11 from the back up on extrapolation slides.

Before they pull the slide, there has been the notion that Fc-gamma receptor 3 polymorphism has been associated with differential clinical responses in Crohn's disease, and this comes from a paper published in 2004 by Louis, et al.

However, the same group subsequently published -- and that's in 200 consecutive patients with Crohn's disease of convenient sample. The same group subsequently analyzed the 344 Crohn's disease patients from the ACCENT 1 study, one of the registrations trial, if I'm not mistaken, and found no association between the Fc-gamma receptor 3 polymorphism and the clinical response to infliximab.

There was only a trend toward the greater decrease in C-reactive protein after infliximab treatment in the high affinity phenotype.

If you can move to the next slide, I just

want to point out that C-reactive protein, based on my conversations with my gastroenterology colleagues, is not really used as a marker for monitoring clinical response to therapy and certainly not an endpoint that we use for assessment of efficacy in IBD trials.

In a follow-up paper by Moroi, the same observation was confirmed that there might be an association with decrease in CRP from baseline. This is the highlighted section on the slide, from baseline, much higher decrease in CRP in the VV phenotype, which is the high affinity receptor phenotype compared to the other two phenotypes. That was seen only at week 8. However, infliximab treatment resulted in CRP decreased to the same level in all three groups, both at week 8 and week 30.

Next slide. More importantly, the baseline CRP values in the high affinity receptor group, phenotype was almost twice as high as that compared to the other two phenotype groups, which actually brings the question whether the patients with the

VV or high affinity phenotype have higher disease activity rather than if infliximab had a differential effect on the biological responses as measured by CRP.

There are several components. One is CRP is a surrogate maybe of a biological response, and then these data specifically raise the question not whether the infliximab impacted CRP differentially but whether these patients just have a different phenotype.

DR. CAPLAN: Dr. Curtis?

DR. CURTIS: I had a question on the tipping point analysis. Is it possible to put that data up, which I think was slide 13 in Dr. Levin's presentation?

So I think that the scenario that we were called to consider was the scenario in the upper right where under what was described to be probably unlikely scenarios, that CT-P13 might be worse than EU Remicade, but that that upper right-hand cell is probably so implausible that it's very unlikely to happen.

I guess my question for anyone at FDA really is, is the opposite similarly concerning to people at the agency, namely that there are actually a number of other cells on this where CT-P13 might actually be better and that some of the scenarios are more plausible, and in fact, those confidence intervals do not include zero? I think that would be similarly problematic because we're looking for a biosimilar, not a bio-better.

Does the FDA worry about some of these scenarios where, in fact, it could be better? Because we only talked about one of them where it could be worse, but I guess I'm equally concerned about the alternative.

DR. LEVIN: This is Greg Levin. I can start and then maybe turn it over to my clinical colleagues to see if they have anything to add.

When we were doing our tipping point analyses, we were considering both sides of the equation. I presented the upper region for brevity. But yes, there are more plausible scenarios under which the results would tip in the

direction of superiority using a plus or minus 12 percent margin.

For example, the second from the top left going down that left column, the 0.06 where it's minus 0.01 to positive 0.13, I still think that that scenario is unlikely because it still requires the assumption of a reasonably large difference between the response rates among the dropouts on the two arms, about a 15- to 20-percentage point difference in the response rates, which is unlikely given the fact that you had similar proportions of dropout, similar reasons for dropout, and similar baseline characteristics among the people who dropped out. That's the first comment.

Second comment is -- I'll allow clinical colleagues to follow up on this -- we have discussed the possibility of relaxing the upper bound of the similarity margin, particularly for products where there are no issues with dose-related safety concerns.

I'll let others follow up on that. I didn't present that here, but something like a minus

12 percent, plus 15 percent margin, we have entertained that possibility. And under that scenario, you would have equally implausible assumptions required to tip the results.

DR. NIKOLOV: And maybe I can add to that. Remicade and many of the TNF inhibitors are essentially dosed to saturation. We don't really expect that, based on what we know about the molecule and its potency, it would act any differently or certainly better than the reference product.

DR. CURTIS: But I guess just to follow up, you would find a 17-percent sort of worse response in one arm compared to the other so implausible that you're not worried about it, even though the study had a 25 percent dropout rate?

DR. LEVIN: No. I think it's possible that that assumption could hold true. It's more possible than a 70-percentage point, which was what I focused on in my talk. So you're right. It's possible. But like I said, I think there is -- personally, I have a greater concern with a

loss of efficacy than a gain of efficacy if we're going to talk about -- if we're going to talk about clinically meaningful, that would be more concerning to me.

That's my personal response. I understand the statute says "no clinically meaningful differences" and you have to talk about both sides of the equation. But when we're talking about choosing margins, not just based on clinical relevance but also based on feasibility, as we have done here, we have entertained the idea of relaxing the upper bound of the similarity margin, which I didn't discuss here, but we've discussed it.

DR. CURTIS: Would that relaxation apply to only clinical endpoints or certain considerations or features but not others, or would you then perhaps entertain one side of the hypothesis testing rather than two-sided? I guess how far might that thinking take you?

DR. LEVIN: I think it would be setting-specific, and I think that's as far as I can comment on that.

DR. CAPLAN: I'm going to now briefly summarize the discussion around the question of whether the committee agrees that CT-P13 is highly similar to the reference product.

There were issues raised about whether analytic differences translates to clinical differences and additional data provided in the form of purification of impurities and the effect of that on Fc receptors and ADCC.

There was the point made that with all these additional assays, it would have been nice to have access to the actual results and also a countering concern for retention of trade secrets, and then some questions about missing data and how plausible the missing data would have to be in order for the results to be different.

Does anyone else have any other comments which I neglected to mention in the summary?

(No response.)

DR. CAPLAN: Okay. Then we will move to our second question of whether the committee agrees that there are no clinically meaningful differences

between CT-P13 and US-licensed Remicade, specifically as studied in the conditions of use, meaning rheumatoid arthritis and ankylosing spondylitis.

Yes? Dr. Brittain?

DR. BRITTAIN: Erica Brittain. I think, overall, at the big picture level for the RA result, the fact that ignoring the missing data issue, we have certainty that 80 percent of the benefit which retained is a really important result.

With that said, to me, I don't like -- as I said earlier, I don't really like the rationale of the margin of 0.12, which the whole tipping point analysis was predicated on.

That 0.12 is saying, as long as we have retained 50 percent of the benefit, that's good enough. And for something where MDs and patients are going to perceive as being essentially the same product, which I think what they will perceive as if it's called biosimilar, that feels like -- it doesn't feel like a stringent enough standard.

Again, the positive here is in this case, they did better than that. They retained, at least in the point estimate, they retained -- I mean not the point estimate. Ignoring the missing the data, we're confident they retained at least 80 percent of the benefit.

That said, I totally understand the feasibility issue, so maybe what I'm concerned about isn't really practical to address. But overall, I feel pretty good because of that 80 percent benefit. The tipping analysis -- I mean the effect of the missing data, I don't know -- I don't feel as confident about because it's all based on that only retaining 50 percent of the benefit. But still overall, I feel pretty good.

DR. CAPLAN: Dr. Gobburu?

DR. GOBBURU: I'd like to opine on that topic, too. We often get lost in these confidence intervals, but we should not ignore the point estimate also, which is more interpretable.

We're talking about -- for a test to be successful statistically, with a 50 percent margin

to preserve the M2, you really have to be slightly better than the reference to meet that criteria. It's not the same as saying the biosimilar product is -- could be half as efficacious as the reference is totally wrong.

You can see that in the numbers presented that the point estimate is 60 for the biosimilar. I don't remember the one for the reference, which was 58 or something like that. You got to be numerically superior, numerically, to meet the non-inferiority margin. We cannot ignore that.

This is a misunderstanding by a lot of people even in the generic world. They think that it is 80 to 125, so the generic could be 20 percent less compared to the reference, which is also false because if you have to meet the bioclinical standard, your mean, the point estimate, cannot be more than 5 to 6 percent different from the reference.

DR. CAPLAN: Yes. Go ahead.

DR. BRITTAIN: I agree that the results -- I was talking more about the standard in which the

whole design was predicated on, the 0.12. I don't think that's a -- I don't really agree with that standard.

But the results, because of the particular confidence interval, that they achieved is better than that. The only concern then is about the missing data because the missing data tipping point analysis that they've done is all predicated on only showing that it's within 50 percent retention of benefit. So it's not as strong as it would be --

DR. GOBBURU: I mean, the reason for my comments are -- I know you're an expert in statistics. It's not for you, but it's for the benefit of everybody else so we can have a lively discussion. I agree with the EU inference too.

DR. CAPLAN: Dr. Horonjeff?

DR. HORONJEFF: Jennifer Horonjeff. I'm here representing the consumer. I am encouraged as a whole about kind of what I'm seeing. I appreciate what Dr. Strand presented about looking at health-related quality of life using the

Short Form 36. So that's encouraging to see that it looks as though what we're talking about here is having similar effects to the patient themselves.

I was also encouraged by looking at the data on the adverse effects of looking at these two comparisons in RA and in ankylosing spondylitis. However, just thinking about the numbers quoted in here that Remicade has been used in over 4.2 million consumers at this point, of course, our sample size that we're looking in just these adverse events is small in comparison to that. Of course, that would take a lot of time to actually see enough patients come through to see the same sorts of events occur.

But just as a consumer myself, being somebody who has been changed even just on a generic and having a severe systemic reaction to just the minor differences that we see in different generic forms, it gives me pause to make a blanket statement, that this is actually the same sort of drug with the same clinical presentation to each patient.

Although the totality of the evidence, I am encouraged that they do look very clinically similar, it's something -- just as the consumer and what many of our patient and caregiver advocates here today were talking about, that people and the consumers, the patients, are very sensitive to these types of drugs. It's something that is just kind of on my radar for how they actually react to the medications.

DR. CAPLAN: Ms. Aronson?

MS. ARONSON: Diane Aronson, patient representative. In relationship to clinically meaningful differences, has there been any discussion with the sponsor to the FDA about any REMS, risk management strategies, in relationship to switching? This is the clinically meaningful differences. I'm just wondering about whether physicians or pharmacists will be educated about this.

DR. NIKOLOV: This is Nikolay Nikolov. Just to clarify, by switching, you mean the single transition that the applicant provided data for or

switching multiple switches?

Again, from our standpoint, the single transition is different from multiple switches, but I'll get to that. The primary comparison that we are evaluating for determination of no clinically meaningful differences is actually the randomized controlled data during the blinded period. And this transition is additional safety data that reassures us that if this product gets on the market, patients who are previously exposed to Remicade would not suffer some major immune-mediated reactions. That's in addition to the biosimilarity assessments for safety for these products.

Switching, in our eyes, in our views, is different from the single transition. When we talk about switching, we're moving towards discussion of interchangeability, which is not really the subject of this application.

DR. CAPLAN: I have a question also for the FDA just around understanding the regulatory stipulations. In order to meet the -- or in order

to be named by the same product, is it necessary to be interchangeable or is it biosimilar? What's the standard for keeping the name or being called by the same name?

DR. CHRISTL: This is Leah Christl from FDA. FDA has issued a draft guidance with regard to naming of biological products, which would include biosimilar and interchangeable products and has proposed a unique identifier for all biological products. It would be in the form of a suffix.

When you think about the Zarxio biosimilar that was approved, that was licensed with the name filgrastim-sndz to distinguish that product. Biosimilar and interchangeable products in addition to standalone biological products would have that unique identifier. And that's FDA's draft policy position that they've put out into the public. That would be for both, again, biosimilars and interchangeable products.

Getting to the education piece of things, again, it was said in the context of the single transition that we're looking at, that there's no

expectation that biosimilar products would be limited in labeling to treatment-naïve patients only.

Again, the clinical folks are looking in certain populations where there would be a concern to add to the safety evidence, but that does not go towards interchangeability. And there is an expectation that if switching or alternating was thought to need to be evaluated in order to demonstrate interchangeability, that that would be an evaluation of multiple switches in an appropriate population.

DR. CAPLAN: Dr. Becker?

DR. BECKER: Hi. Mara Becker. On that note, just to clarify, especially from some of the questions from the audience, if this was approved, it would be also approved for, at least, a one-time switch. And if that's the case, do you guys put any type of mandate as far as notification of the patient, or the provider, or the prescriber, so that people know? There's obviously a lot of questions and concerns, and I'm curious about that.

DR. CHRISTL: Right. I think people need to be careful when we're talking about switching or substitution or things like that. What's stated in the BPCI Act is that an interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the product.

As a general matter, state laws and state boards of pharmacy oversee pharmacy level substitution. There are a number of activities that are going on in the states right now of looking at legislation around substitution of biosimilar products.

What we're talking about here, in terms of evaluating the single transition, again, the labeling for the product wouldn't be limited to use of the biosimilar in a treatment-naïve patient population. But we expect that biosimilars will be prescribed and that they wouldn't be open to that pharmacy-level substitution.

A prescriber can make an appropriate decision for their patient, either a

treatment-naïve patient or a patient that's already on existing therapy. If they wanted to prescribe the biosimilar product for their patient for whatever reason, they have the option of doing so. And they should look at the labeling, what the biosimilar is approved for in terms of are there differences in indications, things like that, and look at that information.

When we talk about substitution, that's really pharmacy-level substitution that we're talking about, not a prescriber decision about changing their patient.

DR. BECKER: Totally understood. But is there anything that we can do or you guys can do? Do you have power to help mitigate that?

It's a lot of fear, it sounds like, as far as the unknown switching of meds, unknown to the patient, unknown to the provider. And I don't know what kind of influence you or we may have at the state level or the pharmacy level to help minimize that.

DR. CHRISTL: Right. Again, that's a

general matter overseen by state law and state boards of pharmacy. We're certainly aware of legislative efforts in various states, and there's publicly available information about that.

There are a number of organizations that are involved in terms of the pharmaceutical associations, sponsor companies that are involved working with state legislators, whether there would be notification, recordkeeping, things like that. But that's really occurring more at the states than at our level. We are aware of the conversations, and we are seeing more and more states address this specifically.

DR. CAPLAN: Dr. Wolpaw?

DR. WOLPAW: Thank you. Yes. I'm Terry Wolpaw. I would like to ask about how no clinically meaningful differences will translate in to some clinical decision-making as we move into biosimilars. I'm interested not so much in those patients who respond but what about those who don't.

As a clinician, let me sort of play this out

and ask your help. At the moment, if I have a patient on Remicade, I don't put them on Remicade again if they don't respond. I'm interested now, if this biosimilar is available, do we now have to assume that if there is clinically meaningful difference, that we would not go to one or the other alternative? Could you help me understand the clinical decision-making that this new possibility might bring forward for us?

DR. NIKOLOV: This is Nikolay Nikolov. The same rationale for us determining that the products are highly similar with no clinically meaningful differences would mean that if it works -- if Remicade works in that patient, it would be expected that the proposed biosimilar would also work in that patient.

The opposite is also true. If Remicade does not work in that patient, we wouldn't have reason to believe that the proposed biosimilar would work. Again, that would be on a case-by-case basis. Maybe physicians can try it. But we don't really have the expectation that the product would

work -- well, the biosimilar would work when the Remicade doesn't.

DR. CAPLAN: Dr. Curtis? Jeff Curtis?

DR. CURTIS: Can the FDA give us some insights into their thoughts about what kind of pharmacovigilance or REMS might be required for people who will end up switching likely multiple times back and forth?

We have data here for a one-time switch, but it's probably unlikely that people will have this one-time transition, and then it will never happen again because they'll always be on a biosimilar. And down the road, there may be other infliximab biosimilars.

So even though that's not the data in front of us and understanding that no one is seeking interchangeability at this moment, I think the reality is we all know that this is going to happen, and where might that data come from in the future to study pharmacovigilance, even for a product that isn't seeking interchangeability?

DR. KOZLOWSKI: Dr. Christl mentioned this

before. We're interested in good pharmacovigilance for all biological products, not just biosimilars. Dr. Christl also mentioned that there is a draft guidance with the current thinking of the FDA on naming, and that draft guidance also includes a discussion of pharmacovigilance and the importance of both passive and active pharmacovigilance for these products, for all biological products.

We would hope that there are ways of tracking all biological products in the market place.

DR. CHRISTL: This is Leah Christl again. In terms of the switching data and where that would come in, again, the standard for interchangeability discusses the evaluation of the impact of switching or alternating on safety and efficacy as compared to patients receiving the reference product without such alternation or switch.

If a product was seeking licensures as an interchangeable product, it would be the expectation of the agency that there was data or information that would go towards addressing that

particular standard.

DR. CAPLAN: We have a follow-up question by Dr. Horonjeff.

DR. HORONJEFF: Yes. Following up to what Dr. Wolpaw was saying, but also just the idea of going back and forth between thinking about switching between either the biosimilar and the medication itself, how does this play out in an insurance coverage standpoint?

If the FDA is saying that they are the same in terms of being similar, then if a physician actually wants to try the other medication, be it the biosimilar or the Remicade itself, how does that happen? Will they get denied because of it? Of course, this may be a very small percentage of patients but are they now not getting the coverage that they need?

DR. CHRISTL: The agency can't really speak to payer decisions. Again, the expectation is that a prescriber -- again, that the product is not intended to be limited in labeling from the biosimilar standpoint to a certain patient

population in the context of treatment-naïve or not treatment-naïve. But it would be a prescriber decision. But we can't really speak to payer decisions that would factor into that.

DR. CAPLAN: Dr. Ranganath?

DR. RANGANATH: Okay. I'm sorry for belaboring this point over and over again, and take that as you will. Interchangeability, I understand, is not the indication that we're looking for here. But in real-world scenarios, patients are going to switch from one insurance provider to another where this is going to happen. I wonder if we need to recommend to have some type of data for us to evaluate for future products so that we can make the best decisions.

DR. KOZLOWSKI: Steve Kozlowski, FDA. So physicians make treatment choices all the time. They switch from one TNF antagonist to another. As long as they're involved in the decision, then I don't see why switching to a biosimilar is different than switching to another anti-TNF.

I mean, all the other considerations you

brought up, payers and things, again, which we're not going to comment on, may factor into things. But interchangeability is a standard that says it gets substituted without necessarily involving the physician. Biosimilar does not say that. That's not the FDA recommendation for biosimilarity, nor is it in the statute.

DR. CAPLAN: Dr. Siegel?

DR. SIEGEL: I promise this will be the last Fc receptor question I'll ask.

(Laughter.)

I'm curious maybe based on the one previous experience. There's this difference that it's now public. We've been talking about it. But when it comes to putting things on the label, will that kind of data go in?

DR. KOZLOWSKI: Steve Kozlowski. I won't comment on the label, but a way of thinking about this difference is, there's a lot of stacked probabilities. You have likely mechanisms of action, clearly blocking soluble TNF and directly blocking membrane TNF. The reverse signaling seems

to have a lot of data about it, and then you have some of these Fc functions, and it only seems to impact NK cells. And then when you look at it, it only seems to impact the NK cells that have targets that express very, very high levels of membrane TNF.

So I think if you look at each of these things individually, you say, that's a problem. But if you start stacking those probabilities, you say, what is really the likelihood that that's going to matter to the patient?

If you add on top of that the distributions overlap and there will be a quality control to make sure that they overlap, then the actual uncertainty associated with that decision seems to be really reduced.

When you look at any one thing, look, there's differences in Fc R gamma 3a binding or whatever, that's an issue. But if you start stacking all those things, I think it leads to potentially a different way of looking at it.

DR. SIEGEL: I'm with you on the data

analysis. One quick question just on what we're discussing. I think maybe some of the other panel members are confused.

I know it's not a policy forum, but if this is approved as a biosimilar, you're saying that despite the fact that it's not equivalent, interchangeable, some states will substitute without a physician or a patient's knowledge. I just want to -- it was unclear to me from what you said.

DR. CHRISTL: No, it is not our expectation that the state discussions around substitution decisions would substitute biosimilars rather than permit substitution of products that FDA had licensed as interchangeable, that there would be a look.

FDA has a public resource called the Purple Book that would list products of whether they were biosimilar or interchangeable, and folks can look at that and see what the approval is. But it is the expectation that prescribers and pharmacists would also look at the FDA decision as to whether

or not something was deemed as interchangeable, and only the interchangeable products would be substituted.

DR. SIEGEL: That's the key phrase that I wanted because it was a little unclear to me. Thank you.

DR. CAPLAN: Comment by Dr. Long.

DR. LONG: Yes. I think the emphasis on the difference in the ADCC is somewhat exaggerated here. There's no data saying that ADCC is useful, is good, that more or less ADCC is going to have real impact. In fact, one of the drugs that's used, certolizumab, has no Fc fragment. There's no ADCC at all with that drug, and it is used for treatment of IBD.

So now we're worried about a biosimilar that has a little bit less ADCC activity than Remicade. It is a difference. I don't know what it will do, but I think it's important to realize that ADCC per se is not necessary.

DR. CAPLAN: Okay. I'm going to summarize as best I can that free-flowing discussion, which

included concerns about the latitude that were allowable under the FDA's definition of acceptable confidence bands, concerns about switching to generics on the part of the patients.

There were also comments about retaining the unique nomenclature for biosimilars and comments made about draft guidance documents, which has been issued, addressing that concept.

There were a number of questions and concerns about switching, whether the switching would be mandated, whether it would be allowable under biosimilars versus interchangeable and comments made about where the control for that switching was occurring and the policies at the state level that govern switching.

Were there any other comments that folks wanted to make?

(No response)

DR. CAPLAN: Okay. Hearing none, the chair will move on to the third discussion item, which is whether the committee agrees there is a sufficient scientific justification to extrapolate data from

comparative clinical studies of CT-P13 in RA and AS to support a determination of biosimilarity of CT-P13 for the following additional indications for which US-licensed Remicade is licensed: psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, adult and pediatric ulcerative colitis.

If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant, and the floor is open to the panelists. A question by Dr. Brittain?

DR. BRITTAIN: Yes. The issue that came up in the previous discussion period about the trial, is it a randomized -- I really do not have a good understanding about the ongoing trial in IBD. I think there's a randomized trial. Could we get some more clarification about the design of that trial and its status?

DR. CAPLAN: I think we're asking just for the last slide, which may have been a switch-over. Was that the switch-over trial maybe?

DR. KUDRIN: To remind that extrapolation is not dependent to randomized controlled study. But this is the Crohn's disease study we're currently running. This is a non-inferiority study, which is comparing Crohn's disease activity index at week 6. And it's enrolled 220 patients, and the study is done under IND, so we have some U.S. sites.

Basically, we're looking at also at the transition of patients in a single manner, so a single transition from CT-P13 and Remicade in a randomized manner at week 30 and looking also at safety and immunogenicity, and pharmacokinetic profile up to one year. The results of the study will be available throughout the final quarter of this year.

DR. CAPLAN: Dr. Miller?

DR. MILLER: Yes. It seems like IBD is really the issue here. A couple of the consumer representatives mentioned a small Irish study that showed lack of efficacy and inflammatory bowel disease. Could anybody comment on that Irish study?

DR. KUDRIN: May I comment on this study? This case study, this is not a real study; it's a case report which was published and reported -- may I have this slide, please?

So this was published in one of the congresses last year. First of all, I would like to remind that as Hospira and Pfizer and Celltrion, we have a rigorous pharmacovigilance system in place collecting all historical data from any case reports and also reports from healthcare practitioners, patients, and consumers.

Hospira and Pfizer received certain reports of suspected lack of efficacy from the pharmacy, from the named hospital in Ireland. These cases were very carefully reviewed in context to what we know about lack of efficacy with Remicade, and we have access to a risk management plan of the reference product in Europe where we know that up to 25 percent of lack of efficacy is normal with infliximab given that patients have primary and secondary TNF non-response.

So this is completely in line with what we

have observed with only few cases of lack of efficacy reported with Remsima. Of note, when we tried to examine these cases, we couldn't identify further details. But in some cases, clearly, there was evidence of primary or secondary non-response and prior exposure to biologics, which might have explained the lack of efficacy.

DR. CAPLAN: Dr. Fuss?

DR. FUSS: So I had brought this up previously. Part of the discussion, we're also looking at the pediatric population. Of note, there is limited studies in the pediatric population. In the two studies that were -- we've heard more as a case-reports, there's a total of 64-patients split between both UC and Crohn's between two studies.

There is definitive differences in the efficacy of the biosimilar in pediatric UC. In one study, there was evidence of attaining a response and remission rate. Another study, we had no significant remission rates achieved.

There was also of concern, evidence of

dropout due to AE-type events. So it remains unknown, at least in my mind, whether there is efficacy in peds UC, is there a safety issue in pediatric UC population.

This latter issue also translates to some of the other studies that were mentioned in this packet. All the studies are not randomized controlled trials. They are dissimilar in the trials in that some are looking at a switch-over; some are using naïve patients.

My concern remains an ADA-type response in patients who had seen Remicade before, will this affect its efficacy. And that still remains partially answered and partially still unknown in that there is more data that still needs to be found.

There is, at least what appears to be, a response and some achievement of remission but these studies are not across the board. Again, additional studies, such as the one that is presently being studied, will give us some answers. But again, it's not going to give us the answers in

pediatrics specifically, which may need a separate study at least to look at these parameters.

DR. GOBBURU: Gobburu. It's a comment. The way I'm thinking about this is on the following lines. The key question for this product is whether the biosimilar product is highly similar to the reference product. That comes from a battery of tests and comparisons. The question is not whether the biosimilar is efficacious and safe for every indication that the reference product was approved for, meaning -- I need to clarify the comment because it could be misinterpreted.

What I mean is, I don't have to prove time and again that the same highly similar -- if that's deemed as highly similar -- for me to prove that for every indication, I need additional registration trials to claim the efficacy and safety.

The question here is not whether, quotes, "the reference product or the biosimilar product are efficacious in every indication or not, but if they are highly similar, that it is very reasonable

to assume that this efficacy and safety is somehow not going to be different in a different set of patients."

I have fundamentally answered the question that both from any in vitro comparison, as well as from a pharmacokinetic point of view, as well as from a clinical point of view that they're highly similar, that I don't have to replicate that evidence in every which population that there is. That's my thinking.

For those reasons -- you can see where I'm going with this. For those reasons, because we have discussed in the past and at least I have opined, there is high similarity between the two products that it is scientifically justified to, quotes, "extrapolate."

I don't even know why we use that word. Maybe we have to use some other word which is more comfortable. "Extrapolate" implies no data. This is not the case; you have data, and you have safety data from even the reference product postmarketing. We cannot ignore all that in making a decision

about this new biosimilar.

DR. CAPLAN: Dr. Jeff Curtis?

DR. CURTIS: I had a question and follow-up to your comments about the Irish study just to make sure I understood that we're talking about the same thing. This is the one by Murphy, et al., published in 2015.

I think maybe I misheard you say it was a case report, but in the one that I was aware of, it's actually a cohort study of consecutive patients with IBD treated with the biosimilar and all of them have IBD. And then there's a comparator group, also a cohort of people, and showed significantly higher rates of hospitalization, surgery, steroid use, and those were statistically significant.

Are we talking about the same thing? Because that's not what I would call a case report or even a case series? It's a small cohort study.

DR. KUDRIN: Well, certainly. It could be called study or case report. Certainly, there are a lot of question marks about how this was designed

in the first place and also how this historical comparator was obtained. But as I said, we received some of these reports, and we carefully examined them because they came through adverse events reporting as well.

As I said, some of the information from this report informed us that a lot of different factors in the history of these patients wasn't accounted for to explain lack of efficacy. And as I said, exposure to prior biological treatments, including other biological anti-TNF agents was the case.

It is important to note that this product is appropriate for patients who showed prior response to infliximab but obviously would be most appropriate because we're not claiming interchangeability status for patients who are deemed needing infliximab.

For that reason, if there is evidence of primary non-response or secondary non-response, of course, this product won't show any efficacy.

DR. CAPLAN: Dr. Mager?

DR. MAGER: I just wanted to follow up on

some points that I was asking for clarification of in terms of pharmacokinetics.

Before I do that, I'll state right from the beginning that I do believe that we have sufficient scientific justification for extrapolation to the other conditions that the original product is approved for.

Having said that, there's a point, again, in the FDA's presentation that there were no notable differences in the PK across the diseases, and I'm not sure that I agree with that. I think there are some studies to suggest that there are differences in the pharmacokinetics across different diseases. However, I would say that that's not a requirement for declaring the product a biosimilar.

There can be differences between diseases, but if they're biosimilar, they'll both change the same in all of the diseases. I don't think -- number one, I don't necessarily agree that there are no notable differences across diseases, but having said that, I don't think it's an issue. I think that they can be biosimilar, and they will

be similarly different in each of those diseases. I just wanted to clarify that point.

I completely agree that we have sufficient scientific justification for the extrapolation and that the PK similarity is real. I don't think we want to state that there necessarily have to be similar across diseases.

DR. NIKOLOV: This is Nikolay Nikolov. I think this is a very important point that you brought up. Even though there might be differences in different aspects of efficacy, or safety, or immunogenicity or exposure PK across different indications, the point here is, are there any differences structurally in the molecule that we would expect to result in differences between the reference product and the biosimilar in all those indications?

DR. CAPLAN: Dr. Solga?

DR. SOLGA: I'm going to agree with Dr. Gobburu, maybe restating it similar in a slightly different way. I think there's scientific justification. The analytics make sense to me. I

believe there's a biological plausibility and intellectual consistency to the 351 pathway in the data that's been presented so far.

I also don't know what's behind the other door. I read and re-read the 76 pages of public comment last night, and a lot of the letters said, we support biosimilars, but we want a clinical trial for each and every indication. Oh, by the way, we support biosimilars.

Where does that go? There's no sense doing a poorly designed clinical study. If you're going to be doing a clinical study for an indication, it might as well be a large, randomized controlled trial.

When you look at IBD, Crohn's is different than UC. Adults are different than pediatrics. Induction is different than maintenance and remission. That's eight randomized controlled trials that need to be large. That's no longer a biosimilar pathway. That's a 351(a) pathway. It just doesn't make sense.

Then, oh, by the way, if we had that right

now in front of us, it doesn't get rid of the residual uncertainty. Randomized controlled trials aren't always right. There is an over-reliance on them in many of these letters, in many of these statements, which is why usually when we think about a new drug approval process, we require two large randomized controlled trials. Now, we're talking about 16 trials.

Either you sign on to the BPCI 351(k) pathway and hang your hat on it or you don't. I'm aiming for the former. I'm not sure I'm right about that. My major residual uncertainty at this point is the BPCI stands for Biological Price Competition.

I have no idea what benefit, in terms of access or price, this is actually going to make for the consumer, the patient, the payer, and society at large. At this point, it's complete speculation. So I'm going to have to accept some risk for a possible benefit that biosimilars will maybe increase access, but I don't know.

DR. CAPLAN: Thank you.

DR. NIKOLOV: And maybe I can --

DR. CAPLAN: Yes, go ahead.

DR. NIKOLOV: This is Nikolay Nikolov. I really appreciate this comment. It sounds like what we have been discussing today has been absorbed and understood by the committee, because these are really, really critical points to consider with respect to the importance of clinical data in the biosimilars pathway development.

We agree that clinicians, prescribers, and patients may not feel comfortable if there is no clinical data in specific indications. However, the clinical data would only provide reassurance for something that we know already would be true, that the drug works and is similarly safe.

So we have a lot more sensitive pieces of information before that, which includes the analytical similarity, the PK similarity. In addition, we have reassurance in the clinical efficacy, at least in one indication, to tell us that the drug or the biosimilar would behave similarly in every other indication.

Any additional clinical data should be designed to address residual uncertainty. It's not just to give us comfort as prescribers and patients. And we acknowledge this, and we certainly understand this. But again, from a scientific perspective, we would need to better justify requiring additional clinical studies from a biosimilar sponsor.

With respect to the price competition, we have no control and we don't really take this into consideration when we discuss this. We're discussing purely the science behind our decision.

DR. CAPLAN: Dr. Horonjeff?

DR. HORONJEFF: Jennifer Horonjeff, consumer representative. I know I'm aware we're talking about extrapolation here. But kind of in light of what everybody is sort of talking about and not having some of the clinical data, and specifically in IBD -- and yet the sponsor is doing a study it sounds like just in terms of wanting to show good faith to the stakeholder that they're doing this to be able to have more data, and you say that should

be prepared by the end of the year, I guess my question is, of course, I want access as quickly as possible for these consumers, but is there any harm in waiting and getting that data, and seeing that so that we can have some sort of information to give to the consumers?

Another question regarding that actual study, I know that you put up some of the endpoints you're looking at. But again, being the consumer, in terms of outcomes that are actually meaningful to the consumer themselves, are you collecting the same sort of health-related quality of life outcomes that were seen in the RA and AS studies, or is it purely what you had previously displayed on the screen?

DR. KOZLOWSKI: Steve Kozlowski, FDA. I understand the idea of more data would create comfort and weight. But I think, as we heard from Dr. Solga, if you needed a trial in every indication and a meaningful trial, that that would really make this pathway extremely cumbersome, much more cumbersome than just developing the product

independently.

Even though that information is comforting, I think the danger is if you start always relying on that comfort, then you really hinder the core idea of this pathway, which is that you're leveraging, as Dr. Nikolov said, many pieces of information.

When you develop a new drug, you know nothing about what it's going to do. Here, you know the molecule matches structurally in so many ways. Granted, there may be some differences, but it's a huge difference. One of the public commenters mentioned the TeGenero product which caused horrible side effects right away. I mean that's incredibly unlikely for a biosimilar which matches structure because you know so much about it already.

There are some uncertainties. You reduce them with PK. You reduce them with a clinical trial in some cases. But you're really filling in and confirming. You're not re-proving.

There was mention in the public commenter's

also about safety and efficacy, we want safety and efficacy, not biosimilarity. And Dr. Christl covered this in her opening talk. We of course want biosimilars to be safe and effective. The question is what set of data do you use to show that?

Clinical trials are wonderful things but they have their weaknesses as we heard. And the view is that if you really have different pieces of information, the structural information, the matching of PK, which is probably more sensitive than clinical endpoints, and confirmation in a clinical endpoint when necessary, that that data together is very, very powerful. You just have to see how to connect it as opposed to treat them as separate silos.

So again, we understand that it makes them uncomfortable, but for the pathway in general, if you always need this extra comfort, then you're not really using this idea of totality of evidence.

DR. CAPLAN: We're going to go to Mary Maloney on the phone.

DR. MALONEY: Mary Maloney. It's clear to me that we, as physicians and scientists, live and die on evidence. We're being asked to move to live and die by extrapolation. That, in fact, may be very good for our system and good for patients and good for everything. But it does, in fact, increase risk.

I understand that we are here to talk about evidence and are we ready to move forward on this. But if we say we don't need a study for every indication and we're doing this to increase access, streamline getting drug to market, and to increase the cost -- I'm sorry -- to decrease the cost of innovation, then in fact, we as a group and we as a society do need to expect control of price. And if that isn't why we're here and talking about it, then we all really do need to go home because that seems, to me, to be the crux of the issue.

So yes, we need to protect our patients. We are asking patients to be part of this, and it needs to benefit society. And I just have to say that because, otherwise, I think we're being

hypocritical.

DR. CAPLAN: Ms. Aronson? Dr. Bergfeld?

DR. BERGFELD: I hate to follow Mary Maloney, a dermatologist. I'm Wilma Bergfeld; I'm also a dermatologist.

I want to laud all of the presenters, both on the FDA side and on the industry side. This has been a wonderful presentation and a wonderful discussion. I've sat on the FDA committee since the 1970s, and this has been really an elevated discussion for me.

I believe that this biosimilar is a very new concept, and I love the analytical methods. And I think this will be the future of how we look at drugs and how we look at them for use in patients. So I want to thank all of you for the discussion and all the points that have been brought forward. But I would agree that they have proved the question, both the FDA and Celltrion, that this is a biosimilar drug.

DR. CAPLAN: So I'm going to go ahead and summarize the discussion to this point so that we

have time to vote, and then also follow-up that vote with a discussion/justification by each of the panel members.

It seems, to me, that there is, in general, a fair amount of consensus around the idea of whether there's sufficient justification to extrapolate the data with the majority of the folks that voiced their opinion in favor of extrapolating the data to the additional indications, with the caveat being concerns around IBD and pediatrics as distinct from the other indications, also couched within the context of a small cohort study, which may have some methodologic issues; and then finally, repeatedly, the concern about whether an additional approval of this product would lead to societal benefits in terms of costs and efficacy.

Are there additional comments that folks wanted to add to that summary? Dr. Curtis?

DR. CURTIS: I just had one point of clarification sort of related to Jennifer's comment. So if the FDA, for this or any future biosimilar, chose not to grant all the indications

that were being sought, is there anything that would preclude the FDA from revisiting that with an updated set of data for those indications that weren't granted the first time and to give them those indications at a later point in time with whatever additional data, be it preclinical or clinical data, in the future?

DR. CHRISTL: This is Leah Christl from the FDA. So there's a couple of things that I would say around this. First, the FDA has articulated in guidance that a biosimilar applicant does not need to seek licensure for all the conditions of use for which the reference product is licensed. So they have that option on their side for whatever business decision or issues around patents or anything like that for a biosimilar.

But certainly, as with any application review, if a sponsor seeks licensure for certain indications and the agency makes a determination that the data package does not support licensure for everything that's being asked for, then the FDA, in their scientific judgment, wouldn't approve

the product for everything.

Certainly, as with any other type of application, a sponsor could come back with updated data and information to address those continued issues, and FDA would certainly engage with the sponsor on those.

DR. NIKOLOV: This is Nikolay Nikolov. One more additional comment with respect to the inflammatory bowel disease ongoing study that has been a point of discussion quite a lot today, I just want to get back or take a step back, back to the basics that the clinical study, as designed, uses clinical endpoints that are not sensitive enough to detect any differences that we may have been concerned with, not that we have any concerns from analytical perspective, but for example, the differences in ADCC.

So if a clinical study is important for inflammatory bowel disease indication, that should be sensitive enough to tell us whether products are similar or different that would address this uncertainty. From that standpoint, we would not

ask for this study and we would not consider it necessary. I just wanted to make this point clear.

DR. CAPLAN: We're going to go ahead and swing around the table now. We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start to flash and 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 their vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all the questions have been answered or discussed. There is only a single

vote.

The vote question is as follows, does the committee agree that, based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which the US-licensed Remicade is currently licensed, and CT-P13 is eligible for licensure: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, adult CD, pediatric CD, and adult UC?

Are there any questions about the wording of the question? Dr. Solga?

DR. SOLGA: Are we going to vote for each one individually?

DR. CAPLAN: No.

DR. SOLGA: Okay.

DR. CAPLAN: We're going to vote for the question as it's stated, and then if you have an issue with one of the indications, then you can indicate that as such following when we go around to discuss your vote.

Dr. Cramer?

DR. CRAMER: Can I just ask the FDA why it was posed this way as one yes or no and not separate questions?

DR. NIKOLOV: We have no reason to single out one individual indication. That's really the rationale.

DR. CAPLAN: Seeing no more questions concerning the wording of the question itself, we will now begin the voting process. Press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly.

After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. CAPLAN: We're just waiting for the vote of the folks that are on the phone.

LCDR BEGANSKY: The result is 21 yes, 3 no, zero abstain.

DR. CAPLAN: Seeing that everyone has voted, the vote is now 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. We'll start with Mara Becker. Dr. Becker, please.

DR. BECKER: Hi. I'm Mara Becker. I voted yes. I felt that through the definition, as it was stated for Section 351(k), that I felt that CT-P13 met those criteria for biosimilarity. As a pediatric rheumatologist, I'm forced to use infliximab for many non-FDA indicated conditions, and I feel that the more options we have to have therapies that can be effective in patients, the better.

DR. CAPLAN: Yes?

DR. SOLGA: I'm Dr. Solga. I voted yes. I understand the FDA does not get involved in pricing. However, I am still frustrated that I feel like I have accepted some uncertainty. It's what we do as physicians. We accept uncertainty and we manage it. But I've accepted uncertainty

with a completely unknown and speculative benefit.

If this matures and this product comes to market, and in six months, it's priced at 2 percent less than Remicade, I'm going to feel angry, embarrassed, and manipulated, and I think there's some risk of that.

If the public at large disagrees with the vote, I think it's reasonable a disagreement would exist, then I would suggest this is a matter of law. Really, it's about 351(k) and the BPCI. I believe that the applicant has provided enough information to meet the definition of the totality of evidence.

I don't think there's a strong scientific disagreement on that. I think it's more of philosophical question of whether folks feel like that is sufficient. And for people who disagree, I would suggest contacting your representative to get law repealed.

DR. CAPLAN: Dr. Fuss?

DR. FUSS: My vote was actually a no but a qualifying no in that I think this pathway to

licensure of biosimilar is a wonderful pathway. It will give much benefit to the patients. It will, as what has been proposed, hopefully bring down the pricing of these biologics.

My concern more so is safety, not just efficacy. We've seen that this drug can be efficacious in a broad spectrum of diseases. I think that it will be efficacious in IBD. My concern is just long-term safety and the ability for this drug to remain efficacious without causing safety problems for the patient population.

The study that has been proposed by the sponsor, I think, is going to address a lot of my concerns. My concerns really aren't reliant on the in vitro studies, specifically the ADCC. I think they've tried their best to look at the in vitro analysis of this drug, and it seems very similar.

ADCC still remains unknown. If it plays a role -- it probably doesn't. It probably plays, if anything, a minor role. So I think, as far as the study addressing ADCC, it's less problematic for me. What I'm looking for is just what happens at

week 30 and what happens at week 54 in these IBD patients. Maybe I do need the safety data to be less concerned but I think we still need it. I don't know if we need to go and do multiple trials given we have seen this similarity.

So do I think it should be approved for other indications? Yes. Qualifying that that I would wait to see what happens with the IBD type studies.

DR. CAPLAN: Please state your full name before you describe your vote. Thank you. And could you state your full name.

DR. FUSS: Ivan Fuss.

DR. CAPLAN: Thank you.

DR. GOBBURU: Jogarao Gobburu. I voted yes. The reason I voted yes, I will be brief so we can get on. I have stated my reasons all along. It is fairly straightforward thinking. The goal here is to build on the experience of the innovator product. That's the way the law is in place, to have an abbreviated program such that you can bridge the efficacy and safety from that. Maybe I

like the word "bridge" than "extrapolate."

The systematic assessment of the battery of endpoints, all the way from physicochemical characteristics to the clinical, which is the least sensitive actually, has been the primary reason for me to support this approval. Thank you.

DR. CRAMER: Steve Cramer. I voted yes, even though I have some concerns about the analytics and some concerns about the binding being a little different in some of the SPR studies. I think on average, the company has done an amazing job of putting a package together.

I'm a little concerned the bar has been now raised too high and that future biosimilar applicants may feel like they have to invest unbelievable amounts of money to get a biosimilar through the process, which may raise the price. So I just want to make that comment. But I voted yes based on the ensemble data.

DR. SCHIEL: John Schiel. I also voted yes for approving biosimilarity. I think that the total package showed a very large number of

different analytical techniques that covered the wide variety of critical quality attributes of the product.

I will mention again that some of the specific data sets that were in the briefing materials such as mass spectrometry were mentioned, sequence coverage was mentioned, certain PTMs, et cetera, but there wasn't an explicit presentation of some of that data, CSTS, some of the carboxypepdidase treatment et cetera.

Some of these individual data sets could have been presented in a briefing package. That being said, the methods were indicated as all being qualified and/or validated in the FDA briefing package.

So it is clear from the totality of evidence, including the preclinical and clinical studies, that combined with the analytical studies that were presented, it does seem that biosimilarity, according to the FDA definition, was indeed met.

DR. SHWAYDER: Tor Shwayder. I voted yes.

I urge the company to collect ongoing pediatric safety data. Many patient insurance companies hide behind the FDA age guidelines to cut their cost by denying biologics to my pediatric patients; so please, collect the data to show its safety in the under-18 population.

DR. BERGFELD: Wilma Bergfeld. I voted yes.

MS. ARONSON: Diane Aronson. I voted yes with the totality of evidence on highly similar and a real hope that this is going to make a difference to patients with cost.

DR. HORONJEFF: Jennifer Horonjeff, consumer representative, and I voted no, but again, I will also qualify that that I do believe that this was an excellent application. And I just wanted to note some of the patient concerns because, again, I'm here representing all the consumers, and we heard very much from several people in the audience today and through other letters and literature that I had been reading prior to this meeting just about the concerns of the patient.

I think it takes into -- makes us take into

account what we need to be thinking about maybe going forward on applications and how to possibly get the patient involved earlier so that they're able to maybe understand -- as some of the FDA have described, maybe understanding PK is more important than the outcomes that we're talking about with the patients. But if they don't know these things, their gut feel is that we aren't listening to their concerns about what the medication or the differences in the two may be. That's just something to think about as we kind of go forward.

I think, too, that over time, patients may have more confidence about biosimilars. But where this is very new and we don't understand, it might be something that just kind of to think about. Going forward, this might not be as much of a concern when we see this put into an actual model.

DR. JONAS: Beth Jonas. I voted yes. And it's not just the patients that are uncomfortable with this new pathway. I think many of us around the table are uncomfortable with this new pathway. I think the discussion was really nice to sort of

talk about that.

Having said that, if this is the metric that we're now measuring, I think the sponsor has done an excellent job of presenting data that supports biosimilarity. I just hope that with this that we are able to realize the potential benefits, both in terms of access and cost.

DR. MILLER: Donald Miller. I voted yes. Extrapolation and this kind of pathway always involves some uncertainty, but I feel like the package was very strong and the experience outside of the U.S. also supports, so this is the right decision.

DR. RANGANATH: Veena Ranganath. I voted yes. I do believe that CT-P13 meets the requirement as described about the licensure pathway under 351 of the PHS Act. I do believe that this is a biosimilar to the reference product.

My understanding based on the discussion today is that the minor differences that we're seeing that were in these clinically inactive components wouldn't impact our patients. Of

course, I would like to see post-approval studies that can confirm this point on safety, and efficacy in other conditions, as well as different dosing regimens.

Perhaps because this is one of the first products of this kind that's come for these specific indications. Maybe 10 years from now, 15 years from now, we'll be a lot more comfortable in making decisions probably the way that this -- the 351 was supposed to be used. But I feel that we need, as physicians and probably as consumers and patients, need a little more data.

DR. CAPLAN: Liron Caplan. I do believe that totality of the evidence supports the contention that the CT-P13 product should receive licensure, but I think that the comments, which were made both in the open discussion, as well as around the panel about providing patients with another option, missed the point here.

This is not about providing patients with another option. The point here is that this is similar. The idea is that this medication should

be used in the same clinical scenario as one in which a medication exists. So the real purpose of this and the reason behind this pathway is to provide access and to reduce cost.

If there isn't a rather substantial difference in cost between this agent and one which has been on the market for nearly 20 years, I would never prescribe it, and that would be my opinion. But I do believe it meets the regulatory threshold for approval, and I do commend the sponsors on their submission.

DR. WOLPAW: I'm Terry Wolpaw, and I voted yes. I voted yes for two reasons. One is a professional responsibility to my patients and the other is civic professionalism.

I do feel that the evidence has been very effectively presented, and I do feel that the totality of the evidence is that this is both highly similar with no clinically meaningful differences.

I also agree that the reason to do this is to provide access and hopefully at a reduced price.

And I think that is also a civic responsibility.

DR. CAPLAN: Dr. Maloney, if you could identify yourself and explain your vote?

DR. MALONEY: Hi. Dr. Mary Maloney. I voted yes because I believe all of the things that have already said around the table, this was a very well done presentation.

I've been dramatically impressed with the expertise around the table by all the panel members who have clearly asked deep questions that have made me feel much better about the risk that I think we all feel we're taking as we move into the arena of moving from evidence to extrapolation, not that there isn't evidence in extrapolation but it is a different pathway.

For all of these reasons and because we have the responsibility to take a risk to provide new products that are biosimilars, to reduce the cost of bringing drug to market, and to reduce the cost to patients, we really need to go ahead and take this risk. And I think that this is probably something we're all going to watch very carefully.

But I do think this is a product that I can feel comfortable that we haven't overextended our risk.

Thanks for everyone for all of the wonderful input today.

DR. CAPLAN: Dr. Tchetgen?

DR. TCHETGEN TCHETGEN: Dr. Eric Tchetgen Tchetgen. I voted yes for -- and I agree with everything that has been said by the panel. I thought the presentation was very good. It was really very well done. The evidence is compelling. The analytics were on point.

I do agree that there is some residual uncertainty, but I feel like the evidence that has been put forth outweighed the uncertainty by several folds. And so I voted yes.

DR. CAPLAN: Dr. Curtis?

DR. CURTIS: Jeff Curtis. I voted no, and I would note, though, that it's somewhat predicated on the fact that we were asked to vote for all the indications as a blanket. I think that I had great comfort with the very robust data package that the sponsor put together. At the end of all the

presentations, I felt very confident that licensure as a biosimilar was very well supported by the data as well as extrapolation to most of the indications.

For me, though, I have the biggest residual uncertainties in some of the information that might or might not be meaningful in an IBD population. I think several people around the table raised some questions about the possibility for some analytic differences that might exist, and if those were clinically meaningful, that they might be more likely to affect people with IBD.

I think that that left some open questions. And for people with rheumatic diseases or psoriasis, I think the clinical and the other data was supportive and reassuring, but we didn't have clinical data as part of the totality of evidence to help really augment some of these analytic differences that might be relevant for IBD.

I certainly take Dr. Solga's point that it's unreasonable to ask for different large scale studies in every single disease like the various

combinations he pointed out in IBD. On the other hand, the sponsor is doing that trial, so I guess I feel like it seems quite possible, in fact even likely, that by the end of the year, that that will in fact enhance the totality of evidence, even for IBD, that some of these perhaps small analytic differences are clinically irrelevant.

On the other hand, that study does exist, so if we didn't know about it, then I might have thought differently, but the fact that it will be reported out; and in the unlikely event that it was a negative trial and in particular the immunogenicity issues.

I guess the sticking point for me was understanding immunogenicity in a Crohn's population, I wasn't certain that in fact RA patients on methotrexate nor ank spon patients that have lower rates of immunogenicity in general is necessarily the most sensitive diseases to an IBD population on no background D-mart [indiscernible]. So, again, that left just an open question about the antidrug antibody issues. But hopefully, that

will be resolved with the study forthcoming by the end of this year.

DR. FEAGINS: I'm Linda Feagins, and I voted yes. And I voted yes because per the guidance set out by the FDA for this abbreviated biosimilar pathway, the sponsor, in presenting their data for CT-P13, met the criteria and they presented compelling scientific data for justification for extrapolation to all the indications.

Lastly, I agree the biggest reason to do this all is in hopes that we're going to be able to reduce cost of these medications to our patients.

DR. CAPLAN: Dr. Brittain?

DR. BRITTAIN: Yes. Erica Brittain. I voted yes. It was a somewhat uncomfortable yes largely for the reasons that Dr. Curtis so eloquently described. I agree with a lot of what he said. But I still felt that based on the standards that the company was asked to meet, they met them. I do remain somewhat uneasy particularly about the IBD.

I think it was important for me that the one

clinical trial, the one major clinical trial, the one in RA did have a very convincing result that the great majority of the benefit of the reference drug was retained, and that was an important point to me.

DR. CAPLAN: Dr. Long?

DR. LONG: Eric Long. I voted yes. As a scientist, I was impressed by the presentation, and I think it meets the standards. I understand the concerns about safety but at the same time, I think we have to realize that any new drug would have an even greater probability of safety issues.

DR. MOREIRA: I'm Antonio Moreira, and I voted yes even though certainly I saw some differences in the analytical package that are always a question mark.

When I looked at the totality of evidence and all the information provided by the sponsor and the assurance of good in-process controls and also the information on the impurities that were shared later, I think that scientifically, I'm comfortable with looking at that totality of evidence and

voting yes for the biosimilarity.

I think as we have also, over the years, become more comfortable with companies, sponsors making changes in their manufacturing processes, I think we will, with time, all of us, become more comfortable as well with the concept of biosimilarity and the approach that we are taking for these kinds of products.

This has been a great panel. I wanted to also commend the sponsor for the presentations and thank all my panel members, co-members on the panel. I'd learned a lot and the fact that 10 hours after we started, we are here still all together and probably -- I don't know. Time flew by for me, so I think this has been a very stimulating discussion, and I appreciate all the comments I've heard.

DR. CAPLAN: Dr. Mager?

DR. MAGER: Don Mager. I voted yes. I have little more to add than to the yeses that have already gone around. The data were compelling. There were sufficient scientific evidence to

support the indication that this was a biosimilar. So the totality of the data was sufficient. The presentations were outstanding and the FDA review was compelling. So I have nothing further to add.

DR. SIEGEL: Dr. Siegel. I guess I'll have the last word. I'll be very brief. I'm Richard Siegel. I voted yes, I guess I would say a qualified yes.

First of all, I wanted to underscore my appreciation for both the FDA and the sponsor presentations. Not only were the presentations great but the presenters. The associates knew the data underneath that we spend a lot of time probing.

My qualification really comes from a lot of the same concerns with the extrapolation to other disease areas and the fact that some data still outstanding. I guess my request would be that certainly that data, if it's not statutorily required, should be given to the FDA as a stipulation with the approval. And that because these are biologics and some things are beyond just

molecular characterization in terms of understanding the structure/function relationships, we just will have to vigilant.

But I agree with Dr. Solga. You sort of have to be all in or not all in with allowing any extrapolation because if you're not all in, then it's just essentially back to the original pathway. I appreciate all the discussion today. Thank you.

DR. CAPLAN: I'd like to end by asking the FDA whether they have any additional comments that they'd like to make.

DR. NIKOLOV: Well, this is Nikolay Nikolov. I certainly would like to thank the Arthritis Advisory Committee for your dedication and for the really, really, very productive discussion that we had today. We were certainly excited to have you, and we appreciate your input. We hope the weather doesn't really impact or affect your return, but we'll be happy to see you again.

Adjournment

DR. CAPLAN: And I'll personally say that I appreciated the interdisciplinary nature of this

panel and how gratifying it was to spend a day with all of you.

Panel members, please take all personal belongings with you as the room will be cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that they may be recycled. We will now adjourn the meeting. Thank you.

(Whereupon, at 5:13 p.m., the meeting was adjourned.)