FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Wednesday, October 10, 2018

8:00 a.m. to 11:33 a.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh, PharmD, BCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Massimo Cristofanilli, MD, FACP

Associate Director of Translational Research and Precision Medicine

Robert H. Lurie Comprehensive Cancer Center

Chicago, Illinois

Susan Halabi, PhD

Professor of Biostatistics and Bioinformatics

Duke University Medical Center

Durham, North Carolina

Christian S. Hinrichs, MD

Investigator & Lasker Clinical Research Scholar

Experimental Transplantation and Immunology Branch

National Cancer Institute (NCI)

National Institutes of Health (NIH)

Bethesda, Maryland

Heidi D. Klepin, MD, MS

Associate Professor of Internal Medicine

Section of Hematology and Oncology

Wake Forest University Health Sciences

Winston Salem, North Carolina

Grzegorz S. Nowakowski, MD

Associate Professor of Medicine and Oncology

Mayo Clinic Rochester

Rochester, Minnesota

Brian I. Rini, MD, FACP

(Chairperson)

Professor of Medicine, Lerner College of Medicine

Leader, GU Program

Department of Hematology and Oncology

Cleveland Clinic Taussig Cancer Institute

Cleveland, Ohio

Thomas S. Uldrick, MD, MS

Deputy Head, Global Oncology

Associate Member, Vaccine and Infectious Disease Division

Associate Member, Clinical Research Division

Fred Hutchinson Cancer Research Center

Seattle, Washington

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Non-Voting)

Phuong Khanh (P.K.) Morrow, MD, FACP

(Industry Representative)

Executive Medical Director, Amgen Oncology

Therapeutic Area Head, US Medical Organization

Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Andy Chen, MD, PhD

Associate Professor of Medicine

Division of Hematology and Medical Oncology

Oregon Health and Science University

Portland, Oregon

Jerry M. Collins, PhD

Associate Director for Developmental Therapeutics

Division of Cancer Treatment and Diagnosis

NCI, NIH

Bethesda, Maryland

William S. Hancock, PhD

Bradstreet Chair in Bioanalytical Chemistry,

Barnett Institute and Department of Chemistry and Chemical Biology

Northeastern University

Boston, Massachusetts

Randy Hawkins, MD

(Acting Consumer Representative)

Private Practice

Inglewood, California

Adel H. Karara, PhD, FCP

Professor of Pharmaceutical Sciences

University of Maryland Eastern Shore

Princess Anne, Maryland

Eric O. Long, PhD

Head, Molecular and Cellular Immunology

Laboratory of Immunogenetics

National Institute of Allergy and Infectious Diseases, NIH

Rockville, Maryland

Tracy G. Matson

(Patient Representative)

Little Rock, Arkansas

Paul J. Smith, PhD

Associate Professor of Statistics

Director, Mathematical Statistics Program

University of Maryland

College Park, Maryland

Scott A. Waldman, MD, PhD

Chair, Department of Pharmacology and
Experimental Therapeutics
Samuel MV Hamilton Professor
Thomas Jefferson University
Director, GI Malignancies Program
Kimmel Cancer Center
Philadelphia, Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Ann Farrell, MD

Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs (OND), CDER, FDA

Sue Lim, MD

Director of the Scientific Review Staff
Therapeutic Biologics and Biosimilars Staff (TBBS)
OND, CDER, FDA

Nicole Gormley, MD

Deputy Director (Acting)

DHP, OHOP, OND, CDER, FDA

Steven Kozlowski, MD

Director

Office of Biotechnology Products (OBP)

Office of Pharmaceutical Quality (OPQ)

CDER, FDA

Vishal Bhatnagar, MD

Medical Officer Team Leader (Acting)

DHP, OHOP, OND, CDER, FDA

Christopher Downey, PhD

Review Chief

Division of Biotechnology Review and Research IV

OBP, OPQ, CDER, FDA

C O N T E N T S

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. RINI: Good morning, everyone. We're going to go ahead and get started. I'd like to remind everyone to please silence your cell phones or other devices, first, if you haven't already done so and identify the FDA press contact Sandy Walsh.

Sandy, if you're president, please stand. Thank you.

We'll first go around and introduce ourselves. If you'd just state your name, your institution, and your role or expertise, and we'll start with P.K. down on the end.

DR. MORROW: P.K. Morrow, medical oncologist. I'm the industry representative, and I'm employed by Amgen.

DR. WALDMAN: Scott Waldman, Thomas Jefferson University, Department of Pharmacology and Experimental Therapeutics in Philadelphia. I'm a clinical pharmacologist.

DR. HANCOCK: William Hancock, Northeastern University. I'm the analytical guy, HPLC, mass spec.

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

DR. CHEN: Andy Chen, Oregon Health and Science University, and I'm a practicing malignant hematologist and transplant.

DR. Adel Karara, University of Maryland, Eastern Shore, clinical pharmacology.

MR. MATSON: Tracy Matson, patient rep.

DR. HAWKINS: Randy Hawkins, physician in private practice, Charles University.

DR. HENDRICKS: Christian Hendricks, National Cancer Institute. I'm a physician, scientist, oncologist.

DR. NOWAKOWSKI: Greg Nowakowski, Mayo Clinic, Rochester. I'm a medical oncologist specializing in lymphoma.

DR. ULDRICK: Thomas Uldrick, medical oncologist, Fred Hutch Cancer Research Center.

DR. RINI: I'm Brian Rini. I'm a GU medical oncologist at Cleveland Clinic.

DR. TESH: Lauren Tesh, designated federal officer for ODAC.

DR. KLEPIN: Heidi Klepin I'm a geriatric oncologist at Wake Forest School of Medicine.

DR. CRISTOFANILLI: Massimo Cristofannilli, breast medical oncologist, Northwestern University.

DR. HALABI: Susan Halabi, biostatistician, Duke University.

DR. SMITH: Paul Smith, University of Maryland, statistician.

DR. COLLINS: Jerry Collins, National Cancer Institute at NIH. I lead the developmental therapeutics program.

DR. DOWNEY: Chris Downey. I'm a supervisory chemist in the Division of Biotechnology Review and Research, FDA CDER's Office of Biotechnology Products.

DR. KOZLOWSKI: Steven Kozlowski, director of the Office of Biotechnology Products in OPQ CDER.

DR. BHATNAGAR: Vishal Bhatnagar, acting clinical team leader, Division of Hematology Products.

DR. GORMLEY: Nicole Gormley, acting deputy division director, Division of Hematology Products, FDA.

DR. LIM: Sue Lim, director of the scientific review staff, Therapeutic Biologics and Biosimilars, FDA.

DR. FARRELL: Ann Farrell, division director, Division of Hematology Products. U.S. FDA.

DR. RINI: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair person. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in Sunshine Act, we ask that 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 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.

I'll now pass it to Dr. Lauren Tesh, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting; expert witness testimony; contracts; grants; CRADAs; teaching, speaking, writing; patents and royalties; and

primary employment.

Today's agenda involves discussion of biologics license application, BLA 761088 for CT-P10, a proposed biosimilar to Genentech, Inc's rituximab, Rituxan, submitted by Celltrion, Inc. The proposed indications for CT-P10 are treatment of adults with one relapse or refractory low-grade or follicular CD20-positive, B-cell non-Hodgkin's lymphoma as a single agent; 2, previously untreated follicular CD20-positive B-cell NHL in combination with first-line chemotherapy; and in patients achieving a complete or partial response to rituximab product in combination with chemotherapy as a single agent maintenance therapy; and 3, non-progressing, including stable disease low grade CD20-positive B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone chemotherapy.

This is a particular matters meeting which during 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 may have had concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

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 had with the firm at issue. Thank you.

DR. RINI: Thanks, Lauren.

I will now proceed with opening FDA remarks from Dr. Vishal Bhatnagar.

Opening Remarks - Vishal Bhatnagar

DR. BHATNAGAR: Good morning. We're here today to discuss an application for CT-P10, a proposed biosimilar to U.S. Rituxan. This application is being presented at today's advisory committee because, if approved, would represent the first Rituxan biosimilar.

This application was originally submitted on April 28, 2017. A complete response letter was issued in February 2018 due to clinical, product quality, and facilities' deficiencies. The applicant's resubmission was received on May 28th of 2018. The initial approval for U.S. licensed Rituxan occurred in 1997. The applicant is seeking indications for CT-P10 limited to 3 U.S. Rituxan non-Hodgkin's lymphoma indications. The applicant is not seeking the U.S. licensed Rituxan indications for diffuse large B-cell lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangitis, or Pemphigus vulgaris.

Before we discuss the development of CT-P10, I

will provide a brief overview of the development and approval pathway of biosimilar products in the United States. On March 23, 2010, the Affordable Care Act was signed into law. This gave the FDA the authority and responsibility to regulate biosimilar biological products.

The pathway to licensure for a biosimilar product is described in the Biologics Price Competition and Innovation Act of 2009 or the BPCI Act. What the BPCI Act did was create an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA licensed reference product.

The BPCI Act states that a biological product that is demonstrated to be highly similar to an FDA licensed biological product, known as the reference product, may rely for licensure on publicly available information regarding FDA's previous determination that a reference product is safe, pure, and potent, or in other words, safe and effective. This licensure pathway then permits a biosimilar biological product to be licensed under Section 351(k) of the Public Health Service Act or PHS Act, and that is what is meant by an

abbreviated licensure pathway.

Notably, the abbreviated licensure pathway does not mean that a lower approval standard is applied to a biosimilar product than to an originator biological product.

Biosimilar or biosimilarity means that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Note that there are two parts of the statutory definition, and both parts must be met for the product to be licensed as a biosimilar product. The goals of a stand-alone and biosimilar product development differ. The figure on the left depicts a stand-alone development under 351(a) of the Public Health Service Act, and the goal of such a development program is to establish the safety and efficacy of a new product.

The types of data that would support a 351(a) application include analytical data, animal data,

clinical pharmacology data, including data from phase 1 and phase 2 studies, which would include dose finding that would look for a dose to bring forward into phase 3 trials; then there are typically two phase 3 trials that would support the safety and efficacy.

In contrast, on the right-hand side of the slide is the abbreviated licensure pathway for a product that is developed under Section 351(k) of the Public Health Service Act. The goal is not to independently reestablish the efficacy and safety of the reference product. The goal is to demonstrate biosimilarity to a reference product.

351(k) applications also include analytical data, animal data, clinical pharmacology data, and additional clinical studies. However, you'll notice that the size or area of the layers in the pyramid are different, and that's intended to indicate the weight that is generally put on the types of data to support approval of biosimilar products.

The focus here is analytical data. FDA has outlined in the guidance a step-wise approach to generate data in support of a demonstration of

biosimilarity. At each step of data generation, there's an evaluation of residual uncertainty about the demonstration of biosimilarity as the data builds. This concept of the data building on itself is known as the totality-of-evidence approach in evaluating biosimilarity.

Unlike a stand-alone development program, which contains pivotal clinical trials to support safety and efficacy, for biosimilarity, there is no one pivotal trial that supports biosimilarity. We consider and look at the totality of evidence.

In summary, analytical similarity data is the foundation of biosimilar development. Because analytical differences are inherent to biological products, there will be analytical differences observed between the reference product and the biosimilar. The key for the biosimilar applicant is to identify those differences and evaluate whether those differences have clinical impact.

Understanding the relationship between quality attributes and the clinical safety and efficacy profile aids in the ability to determine residual uncertainty

about demonstration of biosimilarity and to predict expected clinical similarity from quality data. The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products after conducting extensive analytical similarity testing.

Comparative clinical studies will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about whether there are clinically meaningful differences between the proposed biosimilar and the reference product. Lastly, the approvability of a biosimilar application is based on the totality of evidence submitted by the applicant.

The applicant for CT-P10 has included the following sources of data to demonstrate that CT-P10 has biosimilarity to U.S. Rituxan. Today's presentations from the applicant and the FDA will focus on this data as a part of the totality of evidence.

With all those points in mind, the FDA has identified three key topics for the advisory committee to consider for today's meeting. The first topic is to discuss whether the evidence supports a demonstration

that CT-P10 is highly similar to U.S. Rituxan notwithstanding minor differences in clinically inactive components.

The applicant used an array of analytical methods to assess the primary, secondary, and higher order structure, physicochemical properties, and biological functions of CT-P10 in comparison to U.S. Rituxan.

The second topic is to discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between CT-P10 and U.S. Rituxan. The applicant conducted comparative clinical studies in advanced follicular lymphoma and low-tumor burden follicular lymphoma to demonstrate that there were no clinically meaningful differences.

The third topic is to discuss whether there is adequate justification to support licensure for all of the proposed indications sought by the applicant. The advisory committees should consider the totality of evidence not withstanding minor differences in clinically inactive compounds.

Finally, the FDA requests the committee to vote

whether the totality of evidence supports licensure of CT-P10 as a biosimilar product to U.S. Rituxan for the indications for which the applicant is seeking licensure. Thank you.

DR. RINI: Thank you.

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

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at

the beginning of your presentation, it will not preclude you from speaking.

We'll now proceed with the applicant's presentations.

Applicant Presentation - Elizabeth Pollitt

DR. POLLITT: Good Morning, Dr. Rini, today's advisory committee, and to the FDA. My name is Elizabeth Pollitt. I'm an independent consultant. And as former vice president to the CMC for regulatory affairs at Celltrion, I was involved in the development of CT-P10.

We're pleased to be here today to present the data that support our application for CT-P10, a Rituxan or rituximab biosimilar. For our agenda this morning, I'll introduce you to the development program, and we'll show you the data that support physicochemical structure and functional similarity. Then Dr. Kudrin will describe results of our comparative clinical, and finally, Dr. Rizzieri will provide his clinical perspective.

We also have experts with us today to help answer questions and representatives from Teva, our U.S.

marketing partner. All external experts have been compensated for their time and travel.

So what is CT-P10? CT-P10 is a proposed biosimilar to Rituxan. Rituxan was first licensed by the FDA more than 20 years ago, and there's considerable experience in more than 4 million patients. It's for intravenous administration is marketed as MabThera in the European Union, and CT-P10 has been approved as a biosimilar to MabThera in the EU. The active substance is rituximab, which is CD20 antibody. And as we've heard, Rituxan is approved for use in multiple oncology and inflammatory indications.

Considering the current intellectual property and exclusivity landscape, Celltrion is seeking approval for CT-P10 for use in three non-Hodgkin's lymphoma indications only. These NHL indications are identical to the respective ones in the Rituxan label and as a single agent in relapsed or refractory low-grade or follicular non Hodgkin's lymphoma; in combination with first-line chemotherapy; and as a single maintenance therapy in previously untreated follicular non-Hodgkin's lymphoma; and as a single agent after first-line CVP

chemotherapy in non-progressing, including stable disease, low-grade, non-Hodgkin's lymphoma

The analytical, nonclinical and clinical studies we'll present today intended solely to satisfy the statutory requirements for licensure of biosimilar and are not intended to encourage use of CT-P10 in any indication outside of the proposed indication.

How does rituximab work? The structure and functions of rituximab are well understood. Rituximab is an anti-chimeric monoclonal antibody, and there are two main regions of the molecule. The Fab region is responsible for binding CD20 on B cells at intermediate stages of differentiation, and the FcyR factor region binds to complement receptors on effector cells.

Together, binding of Fab and FC regions results in activities which lead to B-cell depletion. Binding of rituximab to CD20, found only on B cells, needs to complement dependent cytotoxicity, CDC, and antibody-dependent cellular cytotoxicity, ADCC, which are important modes of B-cell depletion.

Binding of rituximab to CD20 can also result in antibody-dependent cellular phagocytosis, ADCP, and

apoptosis of the B cell through intracellular signaling, which might contribute to B-cell elimination. In oncology indications, rituximab-induced B-cell depletion directly reduces tumor burden.

So how was CT-P10 developed? The development of CT-P10 followed the step-wise approach to established biosimilarity as outlined in FDA guidance. The underlying basis is the product that shown to be highly similar to a reference product in structure and function can be expected to perform like the reference product in the clinical setting, allowing an abbreviated clinical program.

It's important to note that a biosimilar is not like a generic drug in that it's not an exact duplicate of the reference product, and as such, biosimilars have allowable differences. So at each step, the residual uncertainty on biosimilarity was used to identify the studies at the next step to address that uncertainty.

The FDA's input was sought and incorporated into the development program for CT-P10. As we'll see, our data for CT-P10 demonstrates similarity to Rituxan and MabThera. A wide range of orthogonal highly

sensitive methods were used to demonstrate physicochemical structure and functional similarity to both Rituxan and MabThera, and the nonclinical studies included comparative toxicokinetics and toxicology.

Comparative Clinical studies demonstrate similarity in pharmacokinetics and immunogenicity, and clinical studies show no clinically meaningful differences in efficacy or safety with CT-P10 and Rituxan in patients with advanced follicular lymphoma and/or low-tumor burden follicular lymphoma. As you'll see, our data demonstrating similarity support that CT-P10 can be expected to have the same therapeutic effect as Rituxan in the proposed indications.

Starting with the analytic similarity, CT-P10 has the same route of administration, formulation, and strength as Rituxan. It's manufactured in a CHO cell line, and controls are applied to ensure acceptable product quality. The analytical similarity data support that CT-P10 is similar to the reference product in physicochemical structure and all biological functions.

Let me show you how we assessed on analytic similarity. In line with the FDA's advice,

physicochemical and structural attributes and biological functions were ranked according to severity and likelihood of clinical impact based on literature, data, and in-house studies.

Attributes and functions were assigned to three tiers for statistical analysis using the criticality ranking. Those with very high criticality, such as CDC and ADCC assays, were analyzed by equivalence tests, and the confidence intervals with means difference will be depicted by bars within the equivalence acceptance criteria represented by vertical solid lines.

Attributes of functions of high to moderate criticality were analyzed using the quality range approach based on Rituxan variability represented by dashed red lines. Those of low criticality, such as terminal variance, or for qualitative test methods, were officially assessed. To be complete, we conducted comparisons of CT-P10, Rituxan, and MabThera to support comparison of CT-P10 with MabThera in nonclinical studies, and the lots of Rituxan and MabThera used in these similarity studies were sourced from the open market.

The comparative analytical studies address all physicochemical and structural attributes, including primary structure, which are the linear sequence of amino acids post-translational modifications, which includes minor chemical modifications of amino acids; higher order structure, which is a 3-dimensional form that results from folding of the linear chain; protein content, which could impact efficacy and would manifest through PK and clinical studies; purity and impurities, which can include high molecular weight forms or non-assembled forms; charged variants, which may include deamidated forms' terminal variants or charged glycans; and glycosylation, where glycan structures are routed to the amino acid at the molecule as it's produced in the cell, which can impact Fc receptor binding.

Over 25 state-of-the-art orthogonal methods were used to evaluate the physicochemical structure generally using 15 lots of each product. Each method measures multiple attributes, providing a comprehensive assessment of the similarity between CT-P10, Rituxan, and MabThera. All methods were validated or qualified and shown to be suitable for use prior to use.

Minor differences detected were evaluated considering the magnitude and direction of the difference and the nature of the attribute and potential clinical impact. I'll present data from representative lots of the three products, focusing on areas where minor differences were observed. And therefore I won't present the data from every method, but the conclusions on biosimilarity will be shown.

Let's start with primary structure. Methods evaluating primary structure showed high similarity between CT-P10, Rituxan, and MabThera. Here we show peptide mapping data with Rituxan in orange, CT-P10 in blue, and MabThera in gray. Peptide mapping showed an identical profile without missing or additional peaks, demonstrating that CT-P10 is highly similar to Rituxan. Likewise, intact mass analysis showed high similarity between CT-P10, Rituxan, and MabThera.

Analysis of post-translational modifications by LC-MS detected minor differences in the levels of some deamidated arginine, but these were sites outside of the binding regions and didn't impact functional activities. Overall, the levels of post-translational modifications

were low in the three products. Higher order structure methods showed overlapping spectra, the same disulfide bond positions, and same free thiol levels.

Here are data from differential scanning calorimetry with the transition temperatures for the CH2, Fab, and CH3 domain marked with dotted lines. The data show that the thermal stability and confirmation of the three products are highly similar.

The protein concentration target was revised during development to match that of Rituxan, and over 90 percent of CT-P10 lots were within the quality range of Rituxan, showing high similarity. The single outlier is within .04 mg per mL of the quality range of Rituxan and has to be considered in the context of the range of values of Rituxan, as all Rituxan lots are considered equally safe and efficacious.

We looked closely at the purity and impurity profiles. The SEC-HPLC data suggested the CT-P10 has a slightly lower level of high molecular weight forms, but this was not corroborated by other methods and would not be expected to increase risk because CT-P10 has a lower level of these impurities. The higher intact IgG and

lower non-assembled forms are not expected to result in higher risk, as CT-P10 has a lower level of the non-assembled forms.

The differences in non-glycosylated heavy chain in light and heavy chains are very small and don't preclude that CT-P10 is highly similar to Rituxan because they have no impact on functional activities. The same charge variant profile, variants were detected in all three products. IEC-HPLC showed that CT-P10 contains slightly lower levels of acidic peaks, which contained deamidated forms in charge glycans and higher levels of basic peaks, which have N and C terminal variance.

This is not expected to result in higher risk as the charge variant peaks of the three products contain the same variants, and these variants are known to occur on endogenous antibodies or to be removed in vivo. In addition, as all IEC-HPLC peaks are functionally active, the difference has no effect on functional activities.

Analysis of glycosylation showed that the same glycan structures are present in the three products.

The most abundant glycans, afucosylated, and the products have similarly low levels of sialic acids, the same monosaccharides, and similar levels of glycation.

CT-P10 has a slightly higher level of Man5, an afucosylated glycan, which could increase clearance by binding to mannose receptors or have increased binding affinity for Fc gamma receptor 3a and enhanced ADC activity. But the minor difference did not result in increased binding affinity to Fc gamma receptor 3a or increased ADCC, as we'll see in our functional similarity studies.

The difference is very small and is unlikely to result in significant difference in serum clearance as is supported by the clinical data. Therefore, the minor difference in levels of Man5 does not preclude a finding that CT-P10 is highly similar to U.S. licensed Rituxan.

These minor differences, which are showed here in bold, have to be considered in the context of the 1,326 amino acids at the molecule and the potential clinical impact. Based on the supportive studies and scientific knowledge, the data support a conclusion that CT-P10 is highly similar to Rituxan notwithstanding

minor differences in clinically inactive components.

Let's turn to the functional similarity studies, which show the impact of some of these minor differences. The functional activities were evaluated using 14 assays, capturing all key elements and constituents of the known and putative modes of action of rituximab. We looked at CDC of a B-lymphoblast cell line and ADCC and ADCP of a B-lymphocyte non-Hodgkin's lymphoma cell line. We measured binding to CD20 and the apoptosis induced by binding to CD20. We also evaluated binding to complement and Fc receptors.

So let me start by sharing the CDC in ADCC data because these are the most important activities, which were statistically analyzed by equivalence test. As we can see here, the data show highly similar CDC and an assay using WIL2-S target cells, and normal human complement. Statistical analysis demonstrated that CT-P10, Rituxan, and MabThera are equivalent in CDC and could be expected to have the same CDC mediated therapeutic effect in the proposed indications.

ADCC was measured at 3 concentrations in the linear range at the dose response curve using Raji

target cells. These were B-lymphocyte cell lines from a Burkitt's lymphoma patient. A normal donor PBMC, we used the surfactant [ph] cells. CT-P10 and MabThera lots were within the acceptance criteria of Rituxan. Supporting of the products [indiscernible] can be expected to have the same ADCC mediated therapeutic effect in the proposed indications.

As ADCP may contribute to B-cell elimination, ADCP was evaluated using Raji target cells and primary monocyte-derived macrophages. All lots of CT-P10 and MabThera were within the three standard deviation quality range of Rituxan showing high similarity in ADCP.

We measured binding to CD20 using a cell-based ELISA with CHO cells engineered to express CD20. We applied stringent criteria to assess similarity on all CT-P10 lots within the two standard deviation range of Rituxan lots. These data support an expectation that CT-P10 will have similar activity to Rituxan in the proposed indications, as all functional activities are initiated by binding to CD20.

The apoptosis induced by binding CD20 was

evaluated using Raji target cells. As shown, CT-P10, Rituxan, and MabThera induced highly similar levels of apoptosis. High similarity was also demonstrated in binding to complement and Fc receptors. Here's the data for binding to neonatal Fc receptor, FcRN, which can influence PK. CT-P10 and MabThera were within the quality range of Rituxan, supporting that the products will have a similar PK profile, as was confirmed by our clinical studies.

We've shown that CT-P10 has equivalent CDC and ADCC to Rituxan, highly similar ADCP, highly similar CD20 binding and apoptosis, and highly similar binding to complement and Fc receptors. We also have data showing CT-P10, Rituxan, MabThera have comparable functional activities on primary human B cells.

In conclusion, these data support that the minor differences in physicochemical structure have no impact on functional activities. Therefore, CT-P10 is highly similar to Rituxan in all biological and functional activities and can be expected to deliver the same therapeutic effect as Rituxan in the proposed indications. The similarity data also demonstrate that

MabThera and Rituxan are physically, chemically and functionally indistinguishable, supporting the use of MabThera in nonclinical studies.

Moving to the next step of the pyramid, the nonclinical studies fulfill statutory requirements for animal studies, including an assessment of toxicity and form the next step of the pyramid. Overall, the nonclinical assessments showed CT-P10 and MabThera were similar. CT-P10 and MabThera have similar binding to lymphocytes and lymphoid aggregates in several human tissues and have similar pharmacology, toxicokinetics, toxicology, and local tolerance in an 8-week repeat dose toxicology study in cynomologous monkeys. Given the high analytic similarity between MabThera and Rituxan, these data are also relevant for Rituxan.

Now I'll turn the podium over to Dr. Kudrin, who will take you through the clinical data.

Applicant Presentation - Alex Kudrin

DR. KUDRIN: Thank you, Dr. Pollitt.

I'm Alex Kudrin, clinical expert for Celltrion, and I was involved since the foundation in the planning and execution of the CT-P10 clinical development program

and supportive with approval of CT-P10 in European Union and other countries.

In my presentation today, I'll cover clinical similarity data from CT-P10 clinical studies that contribute to the totality of the biosimilarity evidence and allow us to conclude that there are no clinically meaningful differences between CT-P10 and Rituxan in safety, purity, and potency for the proposed indication.

CT-P10 biosimilar development program consists of three comparative clinical studies designed to demonstrate both similarities of clinical pharmacology as well as to show that there were no clinically meaningful differences in efficacy and safety between CT-P10 and Rituxan.

The three comparative studies in this program were designed with input from EMA and FDA, two oncologic studies in treatment-naive patients were CD20 positive for follicular lymphoma, studies 3.3 and 3.4. The choice of low-tumor burden follicular lymphoma patients in pivotal studies CT-P10 3.4 was recommended by FDA as the most sensitive and homogenous study population.

Study CT-P10 3.2 in rheumatoid arthritis

patients provides with PK immunogenicity similarity data. Based on published data, RA patients were known to display higher levels of anti-drug antibodies to Rituxan compared to NHL patients, and the immunogenicity and PK data in these patients contribute to the assessment of clinical similarity.

The focus of discussion of RA data will be around clinical PK and immunogenicity. Safety and immunogenicity were thoroughly evaluated across all conducted studies.

Study 3.3 was a randomized, active-controlled, double-blind study to demonstrate similarity of PK and noninferiority of efficacy for CT-P10 compared to Rituxan for treatment-naive patients with confirmed CD20 positive advanced grade 1 to 3a and Ann Arbor 3 and 4 stage, follicular lymphoma matching with the World Health Organization 2008 classification.

The first 24-week period included 8 cycles of CT-P10 or Rituxan every 3 weeks in combination with cyclophosphamide, vincristine, and prednisone. This study included a subset of patients who participated in primary PK assessment. 140 patients with follicular

lymphoma were enrolled in the study, including to 121 patients who contributed to pharmacokinetic subset.

Following completion of the first 8 cycles of treatment, patients who showed response had the opportunity to enter a maintenance period for continuous monotherapy with CT-P10 or Rituxan for an additional 12 cycles for up to 2 years. The maintenance period generates additional comparative efficacy and safety data, including survival, durability of responses, and disease progression outcomes.

The study is ongoing and the BLA includes primary PK and PD clinical efficacy and safety data. This included median follow-up data of 22.6 months, including monotherapy maintenance period of 10 months or more.

The primary PK endpoints were area under the curve tau and maximum concentration at steady state throughout cycle 4, between weeks 9 and 12. These endpoints are appropriate based on previous NHL studies conducted with rituximab, which indicated that the steady state is reached at the fourth cycle of treatment. This study was agreed with EMA.

The efficacy endpoint was overall response rate during 24 weeks to demonstrate that CT-P10 is noninferior to Rituxan. The assessment of overall response was done using computer tomography imaging at prespecified study visits, and the tumor assessments were reviewed by independent centralized reviewers who were blinded to treatment.

Unconfirmed complete response confirmed by CT imaging but without bone marrow biopsy is a standard component of overall response assessment based on international working group criteria because not all patients were subjected to serial bone marrow biopsies. Throughout the maintenance period were also evaluated progression-free survival, overall survival, and duration of response. Other endpoints evaluated safety and immunogenicity.

Study 3.4 was a randomized, active-controlled, double-blind study designed to demonstrate therapeutic equivalence in objective overall response between CT-P10 and Rituxan in treatment-naive patients with confirmed CD20 positive low-tumor burden follicular lymphoma based on GELF criteria, including the size of the largest

tumor lesion was less than 7 centimeter.

This criteria included patients with grade 1 to 3a and Ann Arbor stage 2 and 4. This study was designed upon recommendation of the FDA because the monotherapy and the use of low-grade and low-tumor burden status reduces the impact of confounding factors and allows to assess if there are any clinically meaningful differences should they exist.

258 patients were randomized. Patients received the rituximab monotherapy treatment weekly for 4 weeks in the induction study period. After completion of the first 4 cycles of treatment, those patients who had their disease under control had an opportunity to enter the maintenance period for continuous monotherapy.

Those patients received either CT-P10 or Rituxan for an additional 6 cycles over one year, administered every 2 months. Subsequently, all patients would receive CT-P10 every 2 months for one additional year.

Once the study's ongoing, currently the available data includes 7 months from the start of induction study period highlighted in the bracket. The

primary efficacy endpoint was objective overall response rate over 7 months to demonstrate that CT-P10 is equivalent to Rituxan. The overall response rate is defined as the proportion of patients with best overall response is complete response, unconfirmed complete response, or partial response.

The best overall response assessment was done up to 7 months prior to the maintenance cycle 3. This primary endpoint is recommended by FDA, and there's an objective imaging-based assessment of the tumor size changes throughout the study. It has been used for two other biosimilar monoclonal antibody products discussed previously at ODAC and approved by FDA in oncology conditions.

The assessment of overall response was done using computer tomography scans at prespecified study visits, and the tumor assessments were reviewed by independent centralized reviewers who were blinded to treatment. The secondary endpoints were PK, additional efficacy, safety, and immunogenicity.

In addition, a randomized double-blind control study CT-P10 3.2 two was carried out in patients with

moderate to severe active rheumatoid arthritis, confirmed by 1987 ACR classification criteria and included patients who failed or were intolerant to one or two anti-TNF agents.

In our subsequent presentation, we'll focus on PK and immunogenicity data from this study. As we would expect, rheumatoid arthritis patients display much higher immunogenicity to Rituxan compared to oncology conditions, and the assessment of PK and immunogenicity in RA patients contributes to overall clinical similarity.

The study included a PK subset of the first 189 patients comparing PK similarity between CT-P10, Rituxan, and MabThera. After 2 consecutive courses of treatment, 48 weeks, patients in the Rituxan group were re-randomized to transition to CT-P10 or Rituxan in order to assess the safety and immunogenicity following the single transition.

The total period of assessment for all patients in the study was 72 weeks of all three courses of treatment. This study had been completed. The primary endpoints were evaluated over 24 weeks. The PK

assessment included area under the serum concentration time curve from zero to time to last quantifiable concentration; AUC from zero to infinity; and maximum serum concentration after the second infusion.

Similar to other studies, we also evaluated immunogenicity and safety to show that CT-P10 is similar to Rituxan. Let's review the comparative PK data from RA and follicular lymphoma studies with demonstrated clinical similarity between CT-P10 and Rituxan for the proposed indications.

In study 3.2, we saw similar mean concentration time profiles establishing PK similarity between CT-P10, Rituxan, and MabThera in patients with rheumatoid arthritis. The main concentration profiles were consistent for 2 intravenous infusions. Looking at the results in the forest plot, we can clearly see that all endpoints are within the predefined equivalence margin of 80 to 125 percent with a similarity shown between CT-P10 and Rituxan.

Moving now to follicular lymphoma studies, study 3.3 in patients with advanced follicular lymphoma show similar mean concentration time profiles throughout

the 3-week cycle 4 establishing PK similarity between CT-P10 and Rituxan. The 90 percent confidence interval or geometric means ratio for AUC tau and Cmax at steady state were entirely contained in the PK similarity margin of 80 to 125 percent consistent with FDA guidance.

Moving next to study 3.4, in this study, PK was assessed descriptively in patients with low-tumor burden follicular lymphoma. The mean maximum concentration Cmax and Ctrough levels of CT-P10 and Rituxan were nearly identical. The concentration time profiles are very closely overlapping at each time point.

Let me now review the comparative clinical efficacy data, which demonstrate clinical similarity between CT-P10 and Rituxan for the proposed indications. Let's review the results of study 3.3 in patients with advanced follicular lymphoma. The study included treatment-naive patients with Ann Arbor 3 and 4 stage, CD20-positive follicular lymphoma. Patients with aggressive high-grade lymphoma or evidence of transformation to diffuse large B-cell lymphoma were excluded.

In this study, the primary endpoint was best overall response assessed during the induction period on background of CTP up to week 24. The normal [indiscernible] ratio of ORR was evaluated using minus 7 percent margin using Marcus 2005 and Federico 2013 studies.

140 patients were randomized in this study, 70 patients to CT-P10 and 70 to Rituxan. Similar proportions of patients completed induction and entered the maintenance period. There were similar proportions of discontinuations between treatment groups. The overall demographics and baseline disease characteristics were generally balanced between CT-P10 and Rituxan.

The only differences between groups noted were a slightly higher proportion of patients with Ann Arbor stage 4 and a high proportion of patients with presence of bone marrow involvement in CT-P10 group compared to Rituxan. These differences were considered to be important in interpreting safety results in study 3.3.

In line with more advanced stages of disease, patients in the study were sicker than patients with

low-tumor burden follicular lymphoma in study 3.4. Overall, the study population was comparable to the population included in Marcus 2005 historical study with Rituxan and CTP combination regimen in patients with follicular lymphoma.

The proportions of patients with complete response, unconfirmed complete response, and partial response achieving and overall response over 8 cycles was similar for both groups. The ITT analysis noninferiority was demonstrated since the lower bound of 95 percent confidence interval of the treatment difference fell on the positive side of the margin of minus 7 percent.

Proportions of patients with complete and partial responses were comparable between treatment groups. The noninferiority has been also confirmed by per protocol and missing data imputation analysis.

We conducted time-to-event analysis, including duration of complete response and partial responses throughout the study and the follow-up period. The follow-up period duration was a median of 22.6 months, including at least 10 months on monotherapy treatment.

Here you see the duration of responses measured from the time of first response until relapse or progression, and this was found to be similar between CT-P10 and Rituxan. In addition, time-to-event for progression-free survival was captured, and this trend was similar with no clinically meaningful differences between treatment groups. And as expected, the event rate for overall survival was low and similar between treatment groups.

This is just to remind you of the methodology of low-tumor burden follicular lymphoma study. This study was agreed with FDA and included treatment-naive patients with low-tumor burden using GELF criteria with the largest tumor lesion of less than 7 centimeters in size.

The primary endpoint was best overall response assessed prior to the maintenance cycle 3. In contrast to study 3.3, as recommended by FDA, this study was designed as an equivalence study with two-sided symmetrical margin in order to demonstrate that there are no clinically meaningful differences between CT-P10 and Rituxan in terms of efficacy.

The equivalence of overall response was assessed using an equivalence margin of plus or minus 17 percent, which was derived the Ardeshna study 2014 in low-tumor burden follicular lymphoma study and was agreed with FDA. 258 patients were randomized in this study, 130 patients to CT-P10 and 128 to Rituxan.

Overall, the proportions of patients with primary endpoint evaluation and reasons for discontinuation were similar between treatment groups. The overall demographics baseline disease characteristics were well balanced between CT-P10 and Rituxan. The majority of patients in this study had overall good performance status. The characteristics of the study population were consistent with those in historical study by Ardeshna in 2014.

The proportion of patients achieving an ORR was similar between groups. In ITT analysis, the 90 percent exact confidence interval for the treatment difference was entirely within the equivalence margin of plus or minus 17 percent, establishing therapeutic equivalence between CT-P10 and Rituxan.

The equivalence has been also confirmed by per

protocol analysis and missing data imputation. Primary analysis of overall response in both follicular lymphoma studies together with time-to-event analysis of secondary endpoints in advanced follicular lymphoma patients support the conclusion that there are no clinically meaningful differences between CT-P10 and Rituxan in terms of efficacy.

Moving now to the clinical safety, follicular lymphoma studies provided comparative safety data that overall support clinical similarity between CT-P10 and Rituxan. It is important to recognize that biosimilar studies are not powered for safety. Whenever possible and in agreement with FDA, we have integrated the safety data sets and presented the data from advanced follicular lymphoma and low-tumor burden follicular lymphoma studies separately due to potential impact of CTP regimen on safety.

In advanced follicular lymphoma patients, disease characteristics and background chemotherapy treatment can influence the safety. Here we present safety data from study 3.3 with separate presentation for CTP induction period and for the monotherapy

maintenance period when the confounding impact of CTP no longer applies.

As expected, greater frequencies of adverse events were reported during the induction period due to impact of CTP regimen. We have found that most subjects who received CT-P10 experienced at least one serious adverse event and discontinued treatment due to an adverse event. However, the number of patients enrolled in study CT-P10 3.3 was relatively small, and there were slight differences at baseline characteristics, particularly those patients with Ann Arbor stage 4 and bone marrow involvement in CT-P10 group compared to Rituxan.

These findings limited the interpretation of the safety results. However, these findings were not implicated in the larger study, CT-P10 3.4, in low-tumor burden follicular lymphoma, which I will cover in a moment.

Here we provide a list of serious adverse events reported by more than one patient in study 3.3. Again, there were few events reported in individual preferred term subgroups, and this did not follow any

specific or reproducible pattern.

We have examined the occurrence of adverse events listed as warnings and precautions, and they took some prescribing information. The proportions of patients with these events was comparable between groups, and there were no cases of progressive multifocal leukoencephalopathy across all CT-P10 studies.

Most frequently reported adverse events in either group included neutropenia, infusion-related reactions, constipation, peripheral neuropathy, and upper respiratory tract infections. The majority of AEs were potentially attributed to CTP therapy. There were slightly more patients with neutropenia and CT-P10 treatment group compared to Rituxan.

This finding was due to the fact that more patients CT-P10 growth had bone marrow involvement at baseline. However, numerical increase in neutropenia did not result in change in incidence of infections, and there were no difference in severe, febrile, or prolonged neutropenia between treatment groups. There were other slight numerical differences in AEs, which

did not follow any specific pattern, and they were likely due to a relatively small size of study 3.3 and impact of CTP regimen.

Here, we see the overall safety profile in patients with low-tumor burden follicular lymphoma. In this study, monotherapy of CT-P10 and Rituxan was used throughout and there was no confounding impact of chemotherapy. Slightly medical differences were observed between treatment groups, but this was less prominent, and overall, the incidence of adverse events was comparable between CT-P10 and Rituxan.

These are all serious adverse events reported by Preferred Term. The proportion of SAEs was comparable between groups. The proportion of patients with adverse events listed in the warnings and precautions in Rituxan USPI were comparable between groups, and there were no reported cases of some events. A similar proportion of patients in each treatment group experienced an adverse event. Infusion-related reactions and upper respiratory infections were the most frequently reported events in both groups.

Taken in totality and reviewing adverse events

across both follicular lymphoma studies, we have noticed variability in incidence of adverse events in study 3.3, which did not follow any specific direction. The high incidence of neutropenia observed in the 3.3 study was not observed in the larger study, 3.4. And in conclusion, the safety results from study 3.4 addressed the concern of potentially clinically meaningful differences between CT-P10 and Rituxan presented by study 3.3

In addition, extensive analytical functional and PK similarity data did not reveal any differences that could explain numerical differences in adverse events in study 3.3. Following detailed analysis and with results from a larger study, 3.4, it is concluded the overall safety results support that there are no clinically meaningful differences between CT-P10 and Rituxan.

Next, let's look at the immunogenicity results using state of art and validated methods. Comparative immunogenicity data from RA follicular lymphoma studies demonstrate clinical similarity between CT-P10 and Rituxan for the proposed indications. In line with FDA

guidance, the objectives were to evaluate the emergence of anti-rituximab, anti-chimeric antibodies, also called ADA, to detect if these antibodies were neutralizing, to determine the titer, and to really evaluate the clinical impact on PK, efficacy, and safety.

In RA study 3.2, the proportion of ADA-positive patients was comparable between CT-P10 and Rituxan with very low incidence of neutralizing antibodies. If present, ADA and NAbs were found with low titer, and this finding was consistent between treatment groups. Most of the patients had negative ADA test results at each time point.

We also show here the immunogenicity results from the single transition data in extension of study 3.2. Newly developed anti-drug antibodies were detected in 2 patients following study drug infusion in the extension period, and the immunogenicity findings were consistent with the results observed before single transition. Of course both follicular lymphoma studies, a low proportion of patients, showed immunogenicity, and these ADA responses were similar between CT-P10 and Rituxan.

In conclusion, the totality of evidence across comparative analytical nonclinical and clinical status provide the necessary data to demonstrate that CT-P10 is biosimilar to Rituxan for the proposed indications. Thank you for your attention, and now Dr. David Rizzieri will share his clinical perspective.

Applicant Presentation - David Rizzieri

DR. RIZZIERI: Good morning. I'm David Rizzieri. I'm chief of the section of hematologic malignancies at Duke Cancer Institute, and I'm here today to offer my clinical perspective on CT-P10.

Rituximab has been one of the key targeted therapies in treating patients with non-Hodgkin's lymphoma. It can be used alone or in combination with different chemotherapy regimens, and the use of Rituximab has changed the natural history of B-cell lymphomas, improving overall response rates, progression-free survival, and overall survival in patients with lymphoma.

Overall, rituximab has been well established to be safe, it's well tolerated, and it has modest and manageable toxicities.

As a hematologist/oncologist treating patients with lymphoma, I want to put the low-tumor burden follicular lymphoma study in context by comparing it with other published lymphoma studies.

You can see here the data from study 3.4. First, the population characteristics, these are treatment-naive patients grade 1 to 3a, stage 2 to 4 disease. They had to have measurable disease of at least 1 and a half centimeter size nodes, and they had to have low-tumor burden by GELF criteria primarily, so no B symptoms, normal LDH, less than 3 nodal sites with largely those being greater than 3 centimeters in size, and the largest lesion being less than 7 centimeters. They had to have no splenomegaly, serious effusions or organ failure.

So the first question I had is who is this patient in our clinic? These look like pretty well patients. And we remember that observation for many patients with low-tumor burden disease remains very appropriate. But unfortunately many of these patients are older, they have lots of comorbidities. One of the biggest things they complained to us about is fatigue,

and that's primarily what I think about in older patients who are otherwise well, but they're just not feeling as well as they did a couple of years ago.

Through the course of this disease, at some point there remains a concern about fatigue or their decrement in their daily activities, is it related to the disease or not, and that's the type of patient that a single agent, rituximab-like therapy remains very appropriate.

So if we think of that type of patient here in study 3.4, we can see historically the rituximab data has a pretty good response rate in the 88 percent range. In study 3.4, CT-P10 had an 86.8 percent response rate and rituximab 83.3 percent response rate, so very comparable. Similarly, we just saw the safety and toxicity. Immunogenicity and exposure also seemed to be quite comparable.

Let's now look at the patients enrolled in the advanced follicular lymphoma study, 3.3. Again, these are treatment-naive patients grade 1 to 3a, advanced stage, stage 3 to 4. They did have to have measurable disease, and the CVP backbone was chosen as the

chemotherapy comparator.

Now, we all have regimens we're used to. We've probably used CVP for decades. It is one of the reasonable regimens, not the only regimen that one could use in this setting, but certainly one that's still very common after 30 years of therapy. So in the context of that is the backbone in combination with chemoimmunotherapy. Historically with rituximab data, we see it again, a very nice, well established response rate, 80 to 90 percent here.

In the 3.3 study, CT-P10 has the 95.7 percent overall response rate and rituximab 90 percent response rate. And of course one of the issues is long-term tolerability, progression-free survival, and overall survival. You can see in the study results they remain quite comparable, as does the safety and toxicity, immunogenicity, and overall exposure.

This provides me with confidence that the results from both the low-tumor burden follicular lymphoma and advanced follicular lymphoma studies are consistent with our experience with rituximab.

The Leukemia Lymphoma Society states the annual

incidence of non-Hodgkin's lymphoma in the U.S. in 2018 is about 75,000 patients with a prevalence in the U.S. of about 650,000 patients, a third of which have follicular lymphoma. So therefore, having another agent in the form of a biosimilar in the lymphoma indications for which Celltrion is seeking licensure is an attractive option for our patients.

Thank you, and I will now turn the lectern over to Dr. Kudrin to take any questions you may have.

DR. RINI: We'll do questions after FDA presentations. So now we'll proceed with FDA.

FDA Presentation - Haoheng Yan

DR. YAN: Good morning. My name is Haoheng Yan. I'm a product quality reviewer from the Office of Biotechnology Products, along with my colleague Dr. Yu-Ting Weng from the Office of Statistics. We'll be presenting FDA's analyses and conclusions based on the assessment of applicant's analytical similarity data to support new licensure of CT-P10 as a biosimilar to U.S. Rituxan, also known as rituximab.

I'll start by summarizing the structure, target cells and the recognized mechanism actions of rituximab.

Rituximab is a chimeric murine/human IgG1 kappa monoclonal antibody expressed in a mammalian cell culture system and target CD20 on human B cells. A schematic structure of IgG1 representing CT-P10 is shown on the right.

As shown in the figure, it consists of 2 light chains and 2 heavy chains linked by disulfide bonds. The Fab region binds to the target CD20, and the Fc region contains N-linked glycosylation and other sites that play important roles in antibody stability, in vivo half-life, and effector functions.

Regarding the mechanisms of action of rituximab, based on scientific literature, our current understanding is that rituximab eliminates CD20 expressing B cells through one or more of the following mechanisms: complement-dependent cytotoxicity, CDC; antibody-dependent cell-mediated cytotoxicity, ADCC; antibody-dependent cellular phagocytosis, ADCP; and apoptosis.

Next, we'll present the applicant's analytical similarity program and data. To assess analytical similarity, the applicant used an array of analytical

methods to compare quality attributes between CT-P10 and U.S. Rituxan to support a demonstration that CT-P10 is highly similar to U.S. Rituxan.

This slide shows the product quality attributes evaluated by the applicant. The attributes can be grouped into eight categories, including primary and higher order structures, glycosylation, biological activity, protein concentration, size and charge variants, and post-translational modifications.

For some attributes, the applicant used orthogonal methods to conduct similarity assessment. In addition, degradation profiles of the products under different conditions were also evaluated.

Fifteen lots each of CT-P10 drug product and U.S. Rituxan were included in the analytical similarity evaluation. The 15 CT-P10 lots were derived from 15 independent drug substance lots, including 12 lots manufactured using the proposed commercial manufacturing process and the lots used in the clinical studies.

The applicant assessed the criticality of quality attributes according to their potential impact on biological activities, pharmacokinetics,

pharmacodynamics, safety, and immunogenicity.

Depending on the criticality of the attributes and the quantitative or qualitative nature of the analytical methods, the applicant evaluated analytical data for each attribute using one of the three following approaches: equivalence testing, quality range comparison, and visual comparison of analytical data. The agency agrees with the applicant's approach. FDA's assessment included independent statistical analysis of the applicant's data.

As we described in an earlier slide, the recognized mechanisms of action of rituximab include CDC, ADCC, ADCP, and apoptosis. The applicant developed 4 cell-based assays to evaluate these 4 attributes. Key features of these assays are shown in this table. Based on the current understanding of the mechanisms of action of rituximab and assays' performance for each of these 4 cell-based assays, data from CDC and ADCC assay were analyzed using statistical equivalence test.

Now, I would like to invite Dr. Weng to present the statistical equivalence analysis of the CDC and ADCC results.

FDA Presentation - Yu-Ting Weng

DR. WENG: Thank you, Dr. Yan.

Good morning. My name is Yu-Ting Weng, the product quality statistical reviewer from the Office of Biostatistics. I will present the result of statistical equivalent testing in the assays for relative activities of CDC and ADCC.

First, I will briefly describe the statistical equivalence test. The null hypothesis is that the main difference between two products is outside of the equivalence margin delta, and the alternative is that the main difference is within the equivalence margin. For these submissions, the equivalence margin delta is 1.5 times the standard deviation of CDC or ADCC over reference product. The reference standard deviation is estimated from CDC or ADCC data for reference product generated by the applicant.

We conclude that the quality attribute passes the equivalence test if 90 percent confidence interval for a mean difference falls within the equivalence margin.

For equivalence testing, the agency focused on

the relative activity of CDC and ADCC. The CDC activities was measured at multiple product concentrations and the relative activities, EC50, were calculated against the applicant's CT-P10 internal reference standard.

In the left figure, the orange and blue dots represent the relative activity results for U.S. Rituxan and CT-P10, respectively. The relative CDC activity data indicates that the means and the data spreads of both products are similar. In addition, because the right figure shows that the 90 percent confidence interval for a mean difference between two products is within the equivalence margin, we conclude that relative CDC activity passes the equivalence test.

The applicant measured the ADCC activities of CT-P10 and U.S. Rituxan at three different concentrations within the linear range of the drug dose-response curve, and the relative activities were calculated for each concentration against the applicant's CT-P10 internal reference standard. The figures here show the result at the level of .01 micrograms per milliliter, which was the concentration

closest to the EC50.

From the results, we conclude that the relative ADCC activity at the level of .01 micrograms per milliliter passes the equivalence test. The analyses also show that relative ADCC activities at the other two concentration levels pass the equivalence test.

In summary, the CT-P10 results for both CDC and ADCC pass equivalence testing. Therefore, the results support a demonstration that CT-P10 is highly similar to U.S. Rituxan. Now, Dr. Yan will continue the discussion for other quality attributes.

FDA Presentation - Haoheng Yan

DR. YAN: Thank you, Dr. Weng.

Among the 4 mechanisms of action, Dr. Weng presented the results from the assays measuring CDC and ADCC activities. I'll continue to present the results from the ADCP and apoptosis assays.

The applicant used a quality range testing to evaluate the results from these two assays. In the ADCP assay, the applicant measured the relative phagocytotic [ph] activity of CT-P10 and U.S. Rituxan at three different concentrations within the linear range

of the drug dose-response curve.

The figure on the left shows the results from one of the three concentrations that is close to the EC50. Here, the orange-dotted lines represent the quality range limits calculated for the U.S. Rituxan lots. The analysis showed similar ADCP activity between the two products.

The results from the other two concentrations led to the same conclusion. On the right side, the figure shows the results from the cell-based apoptosis assay. Apoptotic activity is also similar between the two products.

In addition to the four assays presented so far, the applicant also assessed and compared products' binding to CD20, complement component 1Q neonatal Fc receptor, Fc gamma receptors. These attributes all contribute to the biological activity and function of the product. Data analyses showed similar binding activities between CT-P10 and U.S. Rituxan for each of these attributes.

This slide summarizes the overall analytical similarity assessment based on the data provided by the

applicant. We have presented the assessment on biological activities grouped in the left lower corner. Data analysis showed CT-P10 had the same primary structure as U.S. Rituxan. The two products showed similar higher order structure and protein concentration. However, differences were detected in product glycosylation, charge variants, size variants, and post-translational modifications, which we will discuss further in the following slides.

This slide listed the specific attributes in each category that showed differences between CT-P10 and U.S. Rituxan. These attributes were further studied using orthogonal methods; and when necessary, biological activity assays were used to evaluate their potential impact. In each case, the attributes which had differences were found not to affect product activity, and thus these differences do not preclude a demonstration that CT-P10 is highly similar to U.S. Rituxan.

Now, I will present the results and analyses of these attributes. In the glycosylation assessment, the applicant evaluated their product afucosylation,

galactosylation, sialylation, and high mannose content. The data showed that CT-P10 and U.S. Rituxan have the same N-glycosylation sites, the same glycan species, and similar levels of most glycans, except for high mannose content, which is shown in the figure.

Based on published literature, high mannose forms are known to affect ADCC activity and product rate of clearance from the circulation. Such concerns are mitigated by the following factors. First, the difference is small between the two products. Second, similar ADCC activities were demonstrated between the two products. Last, the impact on PK was further addressed in a comparative PK study, which you will hear in the clinical pharmacology presentation.

Differences were observed in amounts of charge variants between the two products. To elaborate on the differences, the figure on this slide shows a representative ion exchange chromatographic profile of CT-P10. Peak 4 is identified as the main peak; that's the big peak in the middle, while the peaks before the main peak are the acidic peaks, and after the main peak are the basic peaks.

As shown in the bottom two scatter plots, CT-P10 has a lower percentage of acidic peaks but a higher percentage of basic peaks compared to U.S. Rituxan. In both cases, the results for CT-P10 did not meet the quality range criteria. No difference was noted in the main peaks between the two products.

It is known that post-translational modifications of monoclonal antibodies, such as deamidated species or oxidative species, sialylated glycans, and N- and C-terminal variants can lead to change in charge variant. Some of these modifications can affect the biological activity of monoclonal antibody products.

To determine the impact of the charge variants differences observed between the two products, the applicant isolated and characterized fractions containing enriched levels of acidic and basic peaks. This characterization revealed that the same types of product variant are present in both products, albeit in different amounts. More importantly, each isolated fraction showed similar levels of biological activities between the two products. And similar biological

activities were demonstrated for CT-P10 and U.S. Rituxan, despite the observed differences in charge variants. Therefore, we concluded that the differences observed in charge variants do not preclude a demonstration that CT-P10 is highly similar to U.S. Rituxan.

Minor differences were also observed in product size variants, which are shown in the three figures here. For product aggregates, shown on the left, CT-P10 has a lower percentage of aggregates compared to U.S. Rituxan measured by the size exclusion HPLC, but the difference is small and orthogonal methods support the two products have similar levels of aggregates.

The applicant used non-reducing and reducing CE-SDS to assess product purity. The results are presented as percentage of intact IgG shown in the middle and percentage of heavy chain and light chain sum shown on the right, respectively.

For intact IgG in the middle, two of the 15 CT-P10 lots were outside of the quality range defined by U.S. Rituxan, however, these two lots have higher level of intact IgG than the upper limit of the quality range.

For heavy chain and light chain sum shown on the right, CT-P10 showed a lower percentage of heavy chain and light chain sum. Considering all the CT-P10 lots analyzed that showed at least 99 percent purity, this minor difference is unlikely to have clinical impact.

Overall, these differences in size variants do not preclude a demonstration that CT-P10 is highly similar to U.S. Rituxan.

Product deamidation, oxidation, glycation, N- and C-terminal variants were evaluated and compared between the two products as part of the post-translational modification assessment. All of these post-translational modifications were similar between the two products, except for the deamidation at asparagine 365 and 388; 3 and 2 CT-P10 lots showed marginally higher levels of deamidation at asparagine 365 and 388, respectively. Considering the deamidation levels are low in both products and both these asparagine residues are outside of the Fab and Fc functional groups, these minor differences do not preclude a demonstration that CT-P10 is highly similar

to U.S. Rituxan.

In conclusion, the analytical similarity data demonstrate that CT-P10 is highly similar to U.S. Rituxan notwithstanding minor differences in clinically inactive components. The analytical results add to the totality of the evidence to support a demonstration of biosimilarity between CT-P10 and U.S. Rituxan. This concludes the product quality presentation, and I'll invite Dr. Chung, who will discuss the results from the clinical pharmacology data. Thank you.

FDA Presentation - Sang Chung

DR. CHUNG: Good morning. My name is Sang Chung, clinical pharmacology reviewer for this submission. I will summarize the agency's assessment on the clinical pharmacology and clinical immunogenicity data. First, I will summarize the assessment on the clinical pharmacology information.

The core of a clinical pharmacology program is to evaluate pharmacokinetic similarity between CT-P10 and U.S. Rituxan. The applicant conducted the study 3.2 to evaluate PK similarity between CT-P10 and U.S. Rituxan. This study was conducted in patients with

rheumatoid arthritis.

The PK over CT-P10 and U.S. Rituxan was also compared in two other studies that were conducted in patients with advanced follicular lymphoma and low-tumor burden follicular lymphoma. The study designs will be briefly summarized from the clinical pharmacology perspective in the next slide, as the applicant has already provided details of them.

As indicated in the red box, part 1 of the study 3.2 was used to evaluate PK similarity between CT-P10 and U.S. Rituxan. Part 1 of the study 3.2 was a randomized, double-blind, parallel-group study conducted in 129 patients with rheumatoid arthritis. The CT-P10 or U.S. Rituxan was given 2 IV doses of 1000 milligrams separated by 2 weeks and co-administered with methotrexate.

PK samples were collected up to 24 weeks after administration of the first dose, which was adequate to fully characterize the PK profiles. PK endpoints were AUC zero to infinity, AUC zero to last, AUC zero to 14 days, and Cmax.

Study 3.3 was a randomized, double-blind,

parallel-group study in patients with advanced follicular lymphoma. Patients received CT-P10 or U.S. Rituxan 375 milligrams square meter, IV dose every 21 days. In this study, PK samples were collected for the estimation of a trough and maximum concentration following each of dose. Four additional samples were collected in cycles 4 to derive the AUC tau.

Study 3.4 [indiscernible] a similar design in dose and regimen to that of a 3.3, but was conducted in patients with low-tumor follicular lymphoma. Sparse PK samples were collected for the estimation of a Ctrough and Cmax following some doses. The PK data from 3.3 and 3.4 are considered supportive, and thus data from these studies will not be described during my presentation.

This slide shows results from PK similarity study 3.2. The mean concentration time profile for each product is shown in the graph. As you can see from visual inspection, both concentration time profiles appear to be virtually superimposable.

Results of a statistical analysis are summarized in the forest plot. For all PK parameters, the 90 percent confidence intervals for the CT-P10 to

U.S. Rituxan geometric mean ratios were within the predefine acceptance range of 80 to 125 percent. Therefore, it was concluded that PK similarity was demonstrated between CT-P10 and U.S. Rituxan. This result also supports the conclusion that difference noted in high mannose contents between two products, as presented by Dr. Yan as part of the same assessment, did not result in any clinically meaningful difference in PK.

In summary, based on the results from study 3.2, we concluded that PK similarity was demonstrated. The PK study results support a conclusion of no clinically meaningful difference between CT-P10 and U.S. Rituxan. The PK result is added to the totality of the evidence to support a demonstration of biosimilarity between CT-P10 and U.S. Rituxan.

The second part of the presentation is a summary of a clinical immunogenicity assessment. Clinical immunogenicity was assessed in study 3.2. While I previously described the design of study 3.2 from part 1, which was used to evaluate PK similarity, I will now briefly highlight the design as related to the

evaluation of immunogenicity.

Overall, study 3.2 enrolled -- the slide doesn't move.

DR. RINI: We're going to have to power the computer down, so we're going to do our break now. It's 9:30. Why don't we just take a 10-minute break while we fix our technical issues, and then we'll come back and continue. Thanks.

(Whereupon, at 9:29 a.m., a recess was taken.)

DR. RINI: We'll as Dr. Chung to continue his presentation with the clinical immunogenicity assessment.

DR. CHUNG: The second part of the presentation is a summary of a clinical immunogenicity assessment. Clinical immunogenicity was assessed in study 3.2. While I previously described the design of study 3.2 from part 1, which was used to evaluate PK similarity, I'll now briefly highlight the design as it relates to the evaluation of the immunogenicity.

Overall, study 3.2 enrolled 312 patients with rheumatoid arthritis and 2 courses of treatment were administered. The development of anti-drug antibodies

and neutralizing antibodies were mentored for the immunogenicity assessment in this study. Immunogenicity samples were collected at baseline, defined as week zero, week 24, and 48 post-dose, which correspond to each treatment course duration. The study design allowed for a comparative assessment of immunogenicity between CT-P10 and U.S. Rituxan in a sensitive population.

The clinical incidence of anti-drug antibodies and neutralizing antibodies are summarized in the table on this slide. As described in the table, at baseline, following through months with CT-P10 and U.S. Rituxan, there were small numerical differences in the incidence of ADA and neutralizing antibodies between arms at each monitoring time point that is week zero, 24, and 48.

However, it is concluded that these differences are unlikely to result in clinically meaningful differences as the incidence difference between two products is small and shows inconsistent trends among the sampling time points. Furthermore, there was no apparent impact of immunogenicity on PK parameters from study 3.2.

In conclusion, clinically immunogenicity in study 3.2 was assessed using validated assays. Similar immunogenicity results were observed between CT-P10 and U.S. Rituxan in study 3.2. The data supports a demonstration of no clinically meaningful differences in immunogenicity between CT-P10 and U.S. Rituxan.

This concludes the agency's assessment of the clinical pharmacology and immunogenicity data. Thank you for your attention, and I'd like to introduce the next speakers.

FDA Presentation - Rachel Ershler

DR. ERSHLER: Good morning. My name is Rachel Ershler, and along with my colleague Dr. Cindy Gao, we will be presenting the clinical efficacy and safety results. Two clinical studies were used for evaluation of safety and efficacy. The initial submission included data from studies CT-P10 3.3, which was conducted in 140 subjects with advanced follicular lymphoma.

The current submission included a safety update from study 3.3 as well as safety and efficacy data from studies CT-P10 3.4, which was conducted in 258 subjects with low-tumor burden follicular lymphoma.

I will now go into these in more detail. Study CT-P10 3.3 was a randomized, double-blind, active-controlled, parallel-group study in patients with advanced follicular lymphoma. Subjects were randomized 1 to 1 to receive either CT-P10 or U.S. Rituxan in combination with CVP chemotherapy. The primary endpoint was noninferiority based on ORR with a prespecified margin of 7 percent.

Study CT-P10 3.4 is a randomized, double-blind, active-controlled, parallel-group study in patients with low-tumor burden follicular lymphoma. In this study, subjects were randomized 1 to 1 to receive either CT-P10 or U.S. Rituxan. The primary objective was to demonstrate that there are no clinically meaningful differences between the products by using an equivalence test.

This study is currently ongoing, however, analyses of safety and efficacy up to the 7-month assessment were included in this application.

I will now turn it over to my colleague, Dr. Cindy Gao, who will discuss the clinical efficacy findings.

FDA Presentation - Cindy Gao

DR. GAO: Thank you, Dr. Ershler.

Good morning, everyone. My name is Cindy Gao, and I will present FDA's review of clinical efficacy based on study 3.3 and study 3.4. Today, my presentation will follow the regulatory review history, study 3.3 first, followed by study 3.4. Please keep in mind the clinical efficacy will be primarily supported by study 3.4, while study 3.3 provides additional supportive information.

Study 3.3 was designed as a noninferiority study with ORR as the primary endpoint. The planned sample size with 134 patients provided 80 percent of power to demonstrate noninferiority of CT-P10 versus U.S. Rituxan. The noninferiority margin for ORR difference was prespecified as negative 7 percent, which represents half of the effector size of U.S. Rituxan in the study Marcus 2005. Noninferiority is demonstrated if the lower bound of 90 percent confidence interval of ORR difference is greater than the noninferiority margin.

FDA identified the following concerns in

study 3.3. First, FDA considered that equivalence design is generally more appropriate than a noninferiority design to support a demonstration of no clinically meaningful differences for this patient population.

Second, as the study 3.3 is designed to demonstrate noninferiority only, it's likely to be underpowered to demonstrate equivalence of CT-P10 versus U.S. Rituxan. And third, sensitivity of the advanced follicular lymphoma population to detect the differences between the products could be influenced by the presence of concurrent background chemotherapy.

Shown in these slides are our analysis results of ORR assessed by the central review. The lower bound of the 90 percent confidence interval of the ORR difference is negative 1.7 percent and is greater than the prespecified noninferiority margin. Therefore, the results show that CT-P10 is noninferior to U.S. Rituxan. However, as the study is designed to show noninferiority only, inference regarding equivalence will be post hoc and most likely underpowered.

In the resubmission, the applicant included

updated data of duration response with longer follow-up time. The Kaplan-Meier curves of the duration of response are shown in this figure. Please know that these are not meant for comparative inferences as this represents only responders. But of those who responded, duration of response appears to be similar in the two groups.

Following FDA's recommendation, the applicant added a comparative clinical study, 3.4, of CT-P10 or U.S. Rituxan monotherapy in patients with low-tumor burden follicular lymphoma in the resubmission.

In this study, the equivalence margin was used to assess whether there's a clinical meaningful difference between the two products. The equivalence margin for ORR difference was prespecified as negative 70 percent to positive 70 percent, and 70 percent is approximately 23 percent of the effect size of U.S. Rituxan in study Ardeshna 2014. Equivalence is demonstrated if 90 percent of confidence interval of the ORR difference is within the prespecified margins.

This slide shows the primary analysis results of ORR assessed by the central review. The 90 percent

confidence interval is within the prespecified equivalence margins. Therefore, equivalence of CT-P10 versus U.S. Rituxan was demonstrated.

Shown in these slides are the sensitivity analysis results of missing data. In contrast to the primary analysis that assumes the patients with missing response status as nonresponders, this sensitivity analysis assume that various numbers of the patients are responders in either arm.

In all cases, including the most extreme case in the bottom-left corner of the table, 90 percent confidence interval for the ORR difference were with the equivalence margins, showing that robust results were obtained from the sensitivity analysis of missing data.

In summary, FDA's review of clinical efficacy was based on study 3.3 and study 3.4 Study 3.3 was designed to demonstrate noninferiority of CT-P10 versus U.S. Rituxan. The lower bound of 90 percent confidence interval of the ORR difference is greater than the margin. Therefore, noninferiority is demonstrated. However, the study was not designed to demonstrate equivalence, so influence regarding equivalence will be

post hoc.

Study 3.4 was designed to demonstrate the equivalence of CT-P10 versus U.S. Rituxan. The 90 percent confidence interval of the ORR difference was within equivalence margins. Therefore, equivalence was demonstrated. Equivalence was also supported by the robust results from sensitivity analysis of missing data.

This concludes FDA's review of clinical advocacy. Next, Dr. Ershler will continue to present FDA's review of clinical safety.

FDA Presentation - Rachel Ershler

DR. ERSHLER: Thank you. I will now present the clinical safety results. A total of 140 subjects were randomized and treated in study CT-P10 3.3, 70 in each treatment arm. This table depicts the overall safety findings from study 3.3. The majority of subjects in both treatment groups experienced at least one treatment-emergent adverse event.

There were more subjects with grade 3 and higher AEs and at least 1 SAE in the CT-P10 treatment group. However, the trial design was such that the

numbers were small and did not allow for a rigorous assessment of safety comparisons between the two treatment groups. In addition, the differences observed were likely confounded by the use of CVP backbone chemotherapy as well as differences in the baseline occurrence of bone marrow involvement of disease.

This table depicts the summary of treatment-emergent adverse events in the safety population. More subjects in the CT-P10 treatment group experienced neutropenia. However, approximately 64 percent of subjects in the CT-P10 arm had bone marrow involvement at baseline compared to 47 percent in the U.S. Rituxan arm.

The observed difference in the incidence of neutropenia in study 3.3 may be attributable to the difference in bone marrow involvement between the two treatment groups. The remainder of the adverse events were similar in both treatment groups.

This table depicts the serious adverse events by Preferred Term that occurred in at least two subjects and either treatment group. Thirty percent of subjects in the CT-P10 treatment group experienced an SAE

compared to 18.6 percent in the U.S. Rituxan. The most common SAEs were lower respiratory tract infections, pneumonia, and febrile neutropenia. The SAEs not listed in this table were heterogeneous and from a variety of system organ classes.

In study CT-P10 3.4, a total of 258 subjects were randomized and received treatment, 130 in the CT-P10 arm and 128 in the U.S. Rituxan. There were slightly more grade 3 and higher adverse events, serious adverse events, drug discontinuations due to treatment-emergent adverse events, and deaths in the CT-P10 arm. However, the numbers of subjects experiencing these findings were small.

This table illustrates the most common treatment- emergent adverse events that occurred in at least 3 percent of patients in either treatment group. The most common adverse events in both groups were infusion-related reactions, fatigue, diarrhea, upper respiratory tract infection, and nausea. The overall incidence of adverse events was similar in the two treatment groups.

There were no clinically meaningful differences

in the occurrence of adverse events between the two groups. Of note, the difference in the incidence of neutropenia that was seen in study 3.3 was not reproduced in study 3.4.

This table illustrates the serious adverse events that occurred in each treatment arm. There were slightly more SAEs in the CT-P10 treatment arm. However, the numbers were small, and as you can see, several of these were due to extraneous causes such as squamous cell carcinoma of the lung and gastrointestinal surgery.

Major events of special interest that are listed as warnings and precautions in the U.S. Rituxan label include infections, infusion reactions, cardiac adverse reactions, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy or PML. Infections and infusion reactions were observed in both treatment arms with no imbalances. There were a few cardiac disorders in both treatment groups, again, with no imbalances. There were no cases of severe mucocutaneous reactions or PML in either study.

In summary, the safety monitoring in both

clinical studies was adequate. There were no relevant differences in the number of subjects who experienced treatment-emergent adverse events in either study.

In study CT-P10 3.3, there were differences between the two treatment groups that may be significant. In particular, more subjects experienced neutropenia, grade 3 or higher adverse events, and SAEs, and more subjects discontinued treatment due to an adverse event. However, the study design did not allow for a rigorous assessment of the safety comparisons between the two treatment groups, and the differences in neutropenia may have been due to the higher incidence of bone marrow involvement at baseline in subjects in the CT-P10 arm.

These differences were identified as clinical deficiencies in the CR letter. With the current application, the applicant included data from study 3.4, which included a larger patient population, and the results were not confounded by the use of concomitant chemotherapy. The differences in safety findings from this study were not as pronounced. Taken together, the data from the two studies did not suggest meaningful

differences between CT-P10 and U.S. Rituxan.

I will now discuss the overall FDA findings. The analytical data using an array of analytical methods demonstrate that CT-P10 is highly similar to U.S. Rituxan notwithstanding minor differences in clinically inactive components. Pharmacokinetic immunogenicity and clinical efficacy data support a demonstration that there are no clinically meaningful differences between CT-P10 and U.S. Rituxan.

From a clinical perspective, there were concerns that the safety results from study CT-P10 3.3 may not have provided support of a demonstration of no clinically meaningful differences for the targeted oncology populations. However, study CT-P10 3.4 adequately addressed these concerns. Overall, the safety and efficacy data from the clinical studies support the assertion that there are no clinically meaningful differences between the two products.

The analytical data demonstrate that CT-P10 is highly similar to U.S. Rituxan notwithstanding minor differences in clinically inactive components. The data demonstrate no clinically meaningful differences between

CT-P10 and U.S. Rituxan in terms of safety, purity, and potency of the product. The totality of evidence supports that CT-P10 can be licensed as a biosimilar to U.S. Rituxan for the indications being sought.

Based on the applicant and FDA presentations, we request that the advisory committee consider the following discussion points. One, discuss whether the evidence supports a demonstration that CT-P10 is highly similar to U.S. Rituxan notwithstanding minor differences in clinically inactive components; 2) discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between CT-P10 and U.S. Rituxan; 3) discuss whether there's adequate justification to support licensure for the proposed indications being sought by the applicant.

We have the following voting question for the committee. Does the totality of evidence presented support licensure of CT-P10 as a biosimilar to U.S. Rituxan for the following indications. Thank you.

Clarifying Questions to Presenters

DR. RINI: Thank you. We'll now take clarifying questions from the committee to any of the

presenters. If you have a question, just wave at Lauren or I, and we'll write your name down and get to you in turn. Remember to state your name for the record before you speak, and if you can, direct your questions to a specific presenter. Dr. Hancock is going to lead us off.

DR. HANCOCK: Thank you. I'd like to begin by asking some analytical questions, so if I could have the appropriate -- to begin with, it was presented that this is an extremely large protein with many amino acids. So my question is with the characterization of the peptide map by LC-MS.

I assume you used several different protease enzymes. My question is, did you find mass spec evidence for every amino acid present in the protein backbone?

DR. KUDRIN: Thank you very much. I'd like to invite Dr. Pollitt to respond to this.

DR. POLLITT: Thank you for the question. Yes, when we count up peptide mapping, we do get full coverage, and we do use all three enzymes to obtain that coverage. So it does give us confidence that we have

looked at the whole amino acid sequence.

DR. HANCOCK: Right, and no amino acid substitutions.

DR. POLLITT: No, indeed. We don't detect any amino acid substitutions in this product, no.

DR. HANCOCK: If I could switch my questions to the cysteine residues, did you see any trisulfide in your product?

DR. POLLITT: No. We don't see any trisulfides. None were detected, and we do have the same level of free thiols, and the same disulfide bond positions were detected as well.

DR. HANCOCK: Thank you. With the free sulfhydryl, did you see an increased amount on your stability study? Because that could be more reactive then.

DR. POLLITT: We don't see significant changes in free thiols as far as I can remember on stability or in -- we did see -- actually, I don't think we included free thiols in the stability studies. It may have been included in the forced degradation.

DR. HANCOCK: Then if I can move to the size

exclusion assay where you're doing comparisons, did you look at the recovery of material after the size exclusion assay since aggregate material could be bound to the size exclusion column, and therefore distort the results?

DR. POLLITT: Indeed, we understand, but, no, we don't do that as standard. We do validate that method according to ICH criteria. So it is fully validated for robustness as well. But we don't do recovery on that particular assay asset as such. It's rather done as a prevalidation of the assay.

DR. HANCOCK: All right. So in the prevalidation, you would do recovery to make sure that there's not loss of a particularly significant variant.

DR. POLLITT: For the validation includes precision, specificity, accuracy, linearity range, as well as the robustness of these assays, so that's what we would have included. We also include stress samples to show that the assay is capable of detecting what we think we're detecting, and also we use relevant targets and things, in the other assay systems, to make sure that those are working properly.

DR. HANCOCK: Yes. By orthogonal measurements, you could get a sense of whether there's loss of [indiscernible]. It's always a concern in these types of assays.

My final comment, with the increase in the Man5 structure, did you try the reverse transcription qPCR assay to get a quantitation of the glycosyltransferases in your cell line?

DR. POLLITT: No. We don't look at those specifically, but rather we look at what the impact of the high mannose is on the activity. So we do artificial samples at artificially high levels of afucosylated glycans. That doesn't necessarily mean just the high mannos, but these are also G-zero as well.

We create these artificial samples in the lab to look at what the impact is of those afucosylated glycans on assay gamma receptor 3a binding affinity an ADDC. And as you can see, the samples -- these are the highly afucosylated samples. We can see the -- relationship [mic fades.] But when we look at the actual data from our similarity -- it includes all 15 lots of each product. You can see there is no

specific impact at the level -- [mic fades] in the product.

DR. HANCOCK: Yes. I can see your data. It was I think more in terms of understanding your cell line, and this could be a development project where the glycosyltransferases would help you control the glycosylation preps in future development work.

Thank you for your responses.

DR. RINI: Thank you. Dr. Hawkins?

DR. HAWKINS: Randy Hawkins, consumer representative. We appropriately reference the Biological Price Competition and Innovation Act of 2009. My question probably is the applicant.

What is a primary goal of this act, specifically the price competition portion? And if CT-P10 is approved, what would be the benefit to the consumer?

DR. KUDRIN: Thank you very much. We have our team representative, Adam George.

DR. GEORGE: So I'd actually like to have my colleague Deb Blake address this.

MS. BLAKE: Good morning. Deborah Blake, Teva

Pharmaceuticals. goal of biosimilars is to increase access and to decrease costs. So the reason we're bringing forth CT-P10 to you today is because our goal is to decrease the cost of biologics, specifically of that of rituximab.

DR. RINI: Dr. Karara?

DR. KARARA: My question relates to the Ctrough values that you obtained, the rituximab trough values. The literature shows that patients on rituximab who respond have higher values, Ctrough values, compared to patients who do not respond. Typically, patients who respond have values greater than 25 micrograms per mL, compared to the patients who don't respond has median values maybe in the single digits, maybe about 6 micrograms per mL.

So my question with regards to your study 3.3 and 3.4, you didn't measure trough values after dosing. Have you looked at the patient who did not respond or the group of patients that had a partial response, their exposure, the trough values versus the patient who responded?

DR. KUDRIN: Right. Thank you very much. We

have done extensive analysis of PK, whilst of course these data were considered by DA [ph] supportive. That is the analysis we have done, lots of different analyses of secondary PK parameters, which showed a similar pattern between CT-P10 and Rituxan.

We haven't done a correlation analysis in terms of exposure efficacy relationship between overall response and Ctrough levels. But when we examine Ctrough levels -- and I'd like to show you the data off the sparse PK in 3.4 from core presentation. You can see overlap in PK. Even that was a sparse evaluation of PK, so obviously this was not assessed by 80 to 125 criteria. PK was superimposable.

When we take into account equivalence results data from the overall response assessment based on imaging, it's quite an astringent, two-side symmetrical margin we use. And together with that sort of PK observed in the low-tumor burden follicular lymphoma class, overall response assessment -- may I have overall response data from the 3.4 study, with emphasis on complete response, the histogram from core presentation?

Even when we take the complete response

proportions there, it gives us confidence that there are no really difference between products in terms of efficacy, and there are no PK concerns which could have led to any concerns in efficacy.

DR. KARARA: Well, the literature seems to suggest that the levels of -- if you go back to this slide that you showed, the levels are about 19 micrograms per mL across the two groups. The literature seems to suggest for successful therapy, maintaining a level of about 25 microgram per mL. Even in the patients that have a higher tumor burden, they would require even higher exposure than in patients with lower tumor burden they had in their study.

DR. KUDRIN: Thank you. We're aware that there were publications by Berinstein, and then subsequent publications have actually been questioning whether there is a valid threshold which can be used for therapeutic monitoring in patients with lymphoma.

I'll show you where that -- over years, this was a debate where therapeutic monitoring of rituximab should be used in patients with lymphoma. For example, Ternon's paper published modeling and indicated that

potentially gamma receptor [indiscernible] should be looked at.

Nevertheless, over years, therapeutic monitoring didn't gain momentum in oncology because different assays use different types of bi-analytical assays and readouts. So we relied on our validated, using state-of-art methodology. And based on our data, PK was similar, and obviously efficacy support this using centralized reading.

DR. KARARA: Yes, I agree the PK similarity is very convincing. My question was related to have you examined the patients who did not respond, their trough levels versus the ones that responded? Have you looked at that group?

DR. KUDRIN: No, we didn't.

DR. RINI: Dr. Halabi?

DR. HALABI: Susan Halabi. I have some questions that I would appreciate some clarification on. Study CT-P10 3.4 had three stratification variables: region, stage, and age. The primary analysis that you presented was based on the exact binomial test, so one question I have is whether an analysis based on the

logistic regression and looking at adjusting for these factors, whether the 90 percent confidence interval fell within the region of plus and minus 17.

I would appreciate clarification on that, and I have a few other questions after that.

DR. KUDRIN: Thank you very much. Dr. Sang Joon Lee, statistician.

DR. LEE: Sang Joon Lee, statistician at Celltrion, [indiscernible] SVP. Yes, we investigated the adjusted logistic regression by the stratification factors. As you can see in the picture, the 90 percent confidence interval also shows therapeutic equivalence within equivalence margin of plus/minus 17 percent.

DR. HALABI: Thank you. The other questions were related to the per protocol analysis, so if we can have that slide again, because I wanted to make sure that the 90 percent confidence interval falls entirely within plus and minus 17. Thank you.

DR. LEE: In this slide, you see a per protocol population [indiscernible]. As we can see here, lower bound is minus 4.56 percent and upper bound is 11.56 percent. And the confidence interval, the upper

bound is within the equivalence margin, plus/minus 17 percent.

DR. HALABI: Thank you.

DR. RINI: Dr. Long?

DR. LONG: I have questions about the ADCC assay and the CP assay described on pages 57 to 160 of the Celltrion proposal.

DR. KUDRIN: Dr. Pollitt will address this question.

DR. LONG: Okay. You use two ADCC assays. One was with peripheral blood mononuclear cells, and the targets of the tumor cell Raji with or without the CD20 antibody. It's described as an assay done with an effective target ratio of 16 to 1, but the time of incubation is not given.

DR. POLLITT: The time of the incubation for that, which we consider to be the classical ADCC assay, is 4 hours.

DR. LONG: Okay. The second essay is using a reporter, in this case, the effector to target ratio is 2, principally because it's a unique -- there's only one effector cell. What was the length of this essay?

DR. POLLITT: I think it's actually longer, but I would need to check the exact time on that. I think the important thing is that we've looked at ADCC using two different assay systems, both the sensitive reporter assay system, which actually measures signaling from the assay gamma receptor 3a and also the classic assay, which actually gives us cells there, and showing that we actually have equivalent in the case of the classical assay and highly similar in the case of the reporter assay activity.

These are the standard assays. The reporter assay, by the way, is available. It's a kit that you can buy.

DR. LONG: Okay. So the ADCP assay measures phagocytosis by macrophages. In this case, the ratio of the macrophages to the target is not given. And again, what is the time?

DR. POLLITT: Absolutely. What we do is we look to make sure that our assay are suitably sensitive to detect a difference. When we're developing the assays, we look at different effector target ratios, and what we look for is the most sensitive, at which point

the assay is most sensitive. And we then use that effector to target ratio for all of the studies.

Again, the phagocytosis is actually longer; that's in several days. And obviously, we know that we've got phagocytosis because we've got the double labeling. Again, the important thing is that this is a validated assay and that it does show high similarity between the two products in this activity.

DR. LONG: It's expressed as the percent, phagocytosis, but it doesn't say whether it's the percent of macrophages that have phagocytosis or the percent of target cells that have been phagocytosis. Do you have figure 81? Maybe that will help.

DR. POLLITT: It's relative percent. So all of our assays against an in-house reference standard, we use that because obviously we can't get 45 samples on a plate. So we use that to take out assay to assay variability. The in-house reference standard is being used. It's the same reference standard in all of the assays. And as I say, it's just there to remove some of the variability of the system. So it's all relative percentage to the internal reference standard

DR. LONG: Because the phagocytosis doesn't reach even 30 percent, so what does that 30 percent? I mean, it looks like it's not very efficient.

DR. POLLITT: In the dose-response curves for phagocytosis, yes, that's correct. It's relatively low, and as I say, we have optimized that system through E to T [ph] ratios to try to get the highest signal that we can.

So when you're talking about the 30 percent you're talking about there in the dose-response curves, it's actually the absolute cell death. That is not a relative number. But all of the assays and the similarity data are based on the relative number.

DR. LONG: Okay. Thank you.

DR. RINI: Dr. Klepin?

DR. KLEPIN: Thank you. I have two questions. The first relates to safety data. In study 3.3, there were some safety signals, particularly the neutropenia, that was discussed, and some of the explanation around why there may have been differences observed related to the small sample size, so the differences in bone marrow involvement that were not taken care of at

randomization.

Can you show us any data that would support the hypothesis that those patients with bone marrow involvement were the ones driving the neutropenia?

DR. KUDRIN: Thank you very much. I'd like to show you the analysis post hoc, which were done to address the issue of difference in terms of neutropenia. And we also did an analysis for serious adverse events.

Here you can see that this is actually on the right showing you what imbalance, what occurred at the baseline, which is not necessarily surprising not just given the small size of the study, but the fact that even with stratification criteria, we did not have bone marrow stratification at baseline.

You can see that once the neutropenia imbalance has occurred, it clearly was not prominent in the maintenance period, but also the fact that there were no grade 3 neutropenia differences and also serious neutropenia and prolonged neutropenia.

So when we look at the analysis of patients by bone marrow involvement, this is the presentation of patients who had bone marrow involvement, and you can

see how this is presented here. So there are more patients with bone marrow involvement with neutropenia.

May I have also analysis of neutropenia and infections, please? When we look at how -- this also could be helpful to give you insight in terms of serious adverse events by bone marrow involvement, which shows slight imbalance in positive patients. Similarly, Ann Arbor stage 4 were more prominent in CT-P10 group. And in that subanalysis, we have seen also imbalance, which actually clearly shows that more patients with stage 4 will have serious adverse events and adverse events due to discontinuation.

So then we questioned -- obviously, we were concerned about it and we wanted to know whether this neutropenia difference was clinically impactful. So when we look at the infection distribution in patients with and without neutropenia, you can see that actually this wasn't -- the difference in the neutropenia group, there was no really adverse difference in terms of infections in neutropenia versus non-neutropenia groups. And similarly, there was a really marked increase in terms of study-related infections.

DR. KLEPIN: Thanks. The second question relates to study 3.2, which was used for the immunogenicity data. In the eligibility criteria, there is an upper age limit on that of 75 as a cutoff. And I'm curious if there was a scientific rationale for that.

DR. KUDRIN: I would have to come back to you on the eligibility criteria reasoning for the upper cutoff.

Dr. Strand, would you be able to comment on this?

DR. STRAND: Vibeke Strand, Division of Immunology and Rheumatology at Stanford University. The rheumatoid arthritis study was designed to be comparable to the original Cohen study that actually validated the use of rituximab in rheumatoid arthritis. So they specifically made the criteria that they would meet the 1987 diagnostic criteria for rheumatoid arthritis, and they copied the same advanced age of 75, although now newer trials used the 2010 criteria and also use a higher age limit.

DR. KUDRIN: This is to address

[indiscernible].

DR. RINI: Thank you. Dr. Uldrick?

DR. ULDRICK: I have two questions related to the study design for 3.3 and 3.4. My first question is for the FDA. I was wondering if you could comment on the preference of an equivalent study design over a noninferior study design, and what concerns, if any, we should have in interpreting the noninferiority findings in 3.3.

DR. GAO: Cindy Gao, statistical reviewer, FDA. FDA performed a sample size calculation in several scenarios, with the assumption in this study population they would need a much larger sample size demonstrate equivalence. So FDA preferred low-tumor burden follicular lymphoma study population. Because the study 3.3 was designed as a noninferiority study, emphasis regarding equivalence would be post hoc.

DR. SRIDHARA: This is Raji Sridhara again from FDA. I want to clarify that for the biosimilar, we do ask for equivalence. At the beginning, many of the studies were being designed as noninferiority studies, so you do see some of them having a noninferiority

hypothesis.

The problem with noninferiority hypothesis is if they show noninferiority, then they could go ahead and show superiority. So there is a possibility that it can be superior, whereas the idea in biosimilar is that they are equal and neither superior nor inferior.

DR. ULDRICK: Thank you. My second question is for the sponsor. The results in both studies were actually quite similar, but I was curious as to the assumptions that went into the differences in the margins for noninferiority versus equivalence, the 7 percent versus 17 percent.

DR. KUDRIN: Okay. We have statistician here, Dr. Sang Joon Lee. Thank you.

DR. LEE: The concept of defining margin is same, however, to find the mentioned corresponding study, the margin comes out different number. For 3.3 study, the matching study, which is responding to design to our study, is Marcus 2005. And as you can see here -- I have to use statistical terminology a little bit. But when we define margin, we use to terms, M1 and M2. M1 is effect size and M2 is the retention rate.

So if I speak in an easy way, first to show effect size from the historical data, we estimate what is the effectiveness of reference drug? Here, Marcus [indiscernible] study, as we can see here, risk difference turns out to be 24.3 percent. That can be an estimate. However, to be more conservative, we use 95 confidence interval, even lower bound. Therefore, 14.5 percent turns out to be effect size, which is a very conservative estimate of Rituxan.

Now, to show assay sensitivity, which is [indiscernible], in fact, the old history, therefore, to use the retention rate 50 percent, here it comes out to be 7.5 percent. Even the more conservative way -- let me go back to the previous screen. I didn't complete that part yet. So the 7 percent margin comes out to be 50 percent, 52 percent of retention rate. Therefore, in 3.3, 7 percent is considered to be noninferiority margin.

Now, let's move on to 3.4 study, where it comes up to be plus/minus 17 percent. Let's show the primary reserve first. Before moving on to the margin, let me show you the reserve first. As we can see here, the

predefined margin was plus/minus 17 percent. However, the reserve is very tight. We can meet the 11 percent margin as well.

Now, let me explain why we define margin of plus/minus 70 percent. There was only one study addressed in 2014 using low-tumor burden follicular lymphoma with a maintenance period with randomized controlled study. In here, the same concept just as I explained in 3.3 study here: estimated difference, which is the effect size, Rituxan is 82 percent. Using Emmon [ph], which is the 90 percent confidence interval or lower bound, it came out to be 75.3 percent.

Now in general, we use a retention rate of 50 percent to define equivalence margin, but we had a discussion with FDA to show clinically meaningful difference with our [indiscernible] margin, we tightened the margin using 77 percent retention rate of effectiveness of Rituxan. It comes out to be plus/minus 70 percent. It was agreed with FDA as well. Thank you.

DR. RINI: Dr. Nowakowski?

DR. NOWAKOWSKI: I have two questions to ask sponsor. One is the follow-up question on the incidence

of neutropenia. Can you clarify if you allow growth factor support in this study? And if you did, what was the incidence of growth factor support using both arms?

DR. KUDRIN: Right. Thank you. We used in the protocol a discretion of investigators to use those. I don't have data by hand, and if I may come back to you after the break or after we're all here and we have chance to, if you want to see this data.

DR. NOWAKOWSKI: Thank you. The second question is about your global strategy and approval strategy. You discussed very nicely how the approval of a biosimilar can improve patient access to anti-CD20 therapy. You are seeking the approval in low-grade, in follicular lymphoma and low-grade lymphoma. You are not seeking approval in diffuse large [indiscernible] B-cell lymphoma, which is kind of an elephant in the room.

I'm not sure if you're at liberty of discussing it, but could you explain your strategy of not pursuing diffuse large B-cell cell lymphoma at this point?

DR. KUDRIN: Thank you. So we are currently focusing on three proposed indications for intellectual property and exclusivity landscape reasons, but we have

two representatives who can add something on this.

DR. GEORGE: Adam George, Teva Pharmaceuticals. Dr. Kudrin is correct. We are seeking the three proposed indolent, non-Hodgkin's lymphoma indications because of the current patent and exclusivity landscape with Rituxan in the United States.

DR. RINI: Thank you. Dr. Cristofanilli?

DR. CRISTOFANILLI: Yes. My question is in regard, again, to equivalence for 3.3. Obviously, as was explained, there was not enough power to show equivalence, and this is obviously the goal for a biosimilar to show that there is equivalence even in advanced setting, in aggressive setting.

So considering that this is not about possible, when are you going to have the post doc analysis? Because from a practical perspective, the moment that you have an FDA approval, you will let oncologists use this agent in both indication that you're looking for. For the most aggressive, you have only 70 patients treated with this combination with the safety data we already know.

So do you think this was an appropriate

strategy? Do you plan to have this post doc analysis done soon? How do you support the claim of [indiscernible] equivalence between the two in the most aggressive in combination with chemotherapy?

DR. KUDRIN: Thank you. I would like to explain to you the nature of this global strategy and how this is being done in sequential order. We had obviously conducted this global program for support and approval also in the European Union. And the European Medicines Agency differs in terms of their perspective on what study's required for demonstration of biosimilarity.

So [indiscernible] tried to set up therapeutic equivalence study, which we didn't discuss in detail today, but that study showed in a very robust manner the equivalence. Plus, with the analytical data we had, conducted obviously before clinical program, we didn't have residual differences, which would have prompted us to design another equivalent study.

EMA wanted to see a small supportive in advanced follicular lymphoma, while the agency had reservation about advanced follicular lymphoma study and

wished to see low-tumor burden follicular lymphoma, which we executed.

So this study is a two-sided equivalence margin study, and obviously with all totality of the evidence, we don't see the need for doing additional analysis or even gaining any additional benefit out of advanced follicular lymphoma study because low-tumor burden follicular lymphoma study is large enough and supports in totality with the rest of the data demonstration of similarity.

DR. RINI: Thank you. Just to clarify, we're not planning on taking another break, so if you want to answer Dr. Nowakowski's growth factor question, you can do so maybe after the open public hearing.

DR. KUDRIN: Okay.

DR. RINI: You have a little bit of time.

Are there any other questions to any of the presenters, many of our clinical pharmacology colleagues or otherwise? Sure. Dr. Hinrichs?

DR. HINRICHS: I have a question for the FDA, and that is about consistency and approvals and this expedited approval process, where instead of having the

square-shaped development process, you have the triangle with a small number of clinical studies at the top.

So we're really looking at one study that showed equivalence and then one study that showed noninferiority. How does that compare to other approvals and other use of this pathway?

DR. FARRELL: The approval is really based on the totality derived initially from the analytical similarity. So we wouldn't even be getting to a position about design of a clinical trial until we have some confidence that the product is likely to be similar to the reference product. So it's a building on that foundation.

DR. HINRICHS: That wasn't quite my question. I understand that there's a building on the foundation. My question is, in approval of other biosimilars, have they been approved on the basis of -- well, the combination of all that information, but from a clinical standpoint, one equivalent study?

DR. LIM: Sue Lim, therapeutic biologics and biosimilars staff. As Dr. Farrell noted, the role of the clinical studies is to address any additional

residual uncertainties. So we take a product-specific approach and look at the totality of the data and determine whether one or more additional clinical studies are needed.

In this particular case, Celltrion described the regulatory history and how they designed an equivalent study in RA and EMA's request. So I would say there's no one size fits all, and there isn't a required number of clinical studies for a particular product. We look at it from a sponsor-specific perspective, as well as the perspective of what we know about the reference product.

DR. FARRELL: You're also thinking about mechanism of action when you're developing these products. So if you have a similar mechanism of action in another disease, you may not be requiring two trials. You may say if we've proven that we're equivalent and we know the mechanism of action is the same, we'd go with one trial.

DR. KOZLOWSKI: Steve Kozlowski, FDA. There may even be situations where we don't have a clinical trial at all; we simply have pharmacokinetics or

pharmacodynamics. And in fact, for filgrastim, that's a possibility. I think also, in many cases, companies do multiple clinical trials for their own reasons, either as mentioned, other regulatory regions or their own calculations, whereas a regulatory agency may only need enough clinical data, again, with totality of the evidence to get some verification. Because ultimately, if the products are functionally and structurally highly similar, there is only a limited amount of uncertainty left.

DR. HINRICHS: Thank you.

DR. RINI: Dr. Chen?

DR. CHEN: On that topic, with the biosimilar rituximab, if it is approved in low-grade B-cell lymphoma, there's going to be a tremendous temptation out in the community to use it in the non-labeled, off-label situations. Based on what you have said, you would not necessarily require a study in aggressive or diffuse large B-cell cell lymphoma or CLL. And given the data that you have here, at what point would the FDA extrapolate approvals to wider --

DR. GORMLEY: This is Nicole Gormley, FDA. So

I think, again, as was mentioned by Dr. Lim, we generally consider this based on a case-by-case basis. Right now, they're seeking approval for the three NHL indications, and off-label use is obviously encouraged but not within the purview of an application being sought right now.

In general, if future indications are being sought, it would be a discussion with the agency and the company about the data that is available to support those other indications and the confidence and a separate evaluation of the ability to extrapolate to other indications.

DR. FARRELL: We're also not making a determination about interchangeability at this time with the reference product.

DR. RINI: Okay. Thank you. Are there any other questions to FDA or to the applicant?

(No response.)

Open Public Hearing

DR. RINI: Okay. We'll start our open public hearing part of this meeting.

Both FDA and the public believe in a

transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it's important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

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

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

this committee in their consideration of the issues at hand. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today for this open public hearing is to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only when recognized by myself, and thank you for your cooperation.

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

DR. KOELLER: Good morning. To Dr. Rini and Dr. Tesh, the ODAC members, FDA attendees, I'd like to thank you for this opportunity to speak to you. I'm speaking on behalf of BLA 761088 CT-P10, a biosimilar for Genentech's Rituxan. From a disclosure standpoint, my travel has been covered by Celltrion. They provide no other compensation to me. I'm speaking here on my own behalf.

My name is Jim Koeller. I'm a full professor of pharmacy, medicine, and oncology out of the

University of Texas at Austin and the Health Science Center in San Antonio, Texas. I've been involved in oncology, cancer care, cancer economics for 39 years. I've been in this a long time.

I'm actually speaking here on behalf of this product, and I support CT-P10 as a biosimilar to Rituxan. From the data presented today from Celltrion, this product appears to be highly similar to Rituxan, thus meeting the FDA requirements for biosimilarity.

In addition, they did provide, in addition to the base biologic data, three separate clinical trials, including over 750 patients looking at rheumatoid arthritis in one trial, and two trials in lymphoma, evaluating both pharmacokinetics, efficacy and toxicity, and immunogenicity, and at least from my interpretation of the data, showing noninferiority/equivalence to Rituxan.

Again, from the totality of evidence, also, you must keep in mind that this drug has been approved and used in the EU for over a year and a half now, and it's approved in multiple other countries, so this is not an unused product. We always have to keep that in mind in

the U.S.

As mentioned earlier, Rituxan is a very common drug used in clinical practice. We use this on a daily basis at the University of Texas. And again, this has been a proprietary drug of Genentech now for 21 years. They basically have held a monopoly on this agent, able to raise prices at will, which they have actually done.

I've been involved in cancer drug care cancer economics now for my entire career. I can speak with some authority that the benefit of competition leads to lower drug prices. Seeing that the biologic agents have had a major impact on pharmacy budgets, most budgets in health centers run in the hundreds of millions of dollars, and the biologic agents, including mostly cancer drugs, are a big part of that. So anytime we can see competition to bring down that price, it's extremely helpful to us.

But this high cost of the biologics has not gone unnoticed to the patient. I can tell you from personal experience that the rise in copayments has impacted the patients, at least in the southern Texas area, significantly. And actually -- I created a new

term called "financial toxicity" -- financial toxicity has led to patients making decisions for drug care versus just common the common cost of living. And I can tell you, in our region, we've had numerous patients who have not been able to afford these drugs.

So as a pharmacist, my primary role is always providing safe and effective drugs for the patients we care for. Biosimilars seem to be providing this as highly similar to the originator. They appear to then offer a less expensive alternative for these agents. And again, any mechanism to bring down the cost or limit the increase in costs of these agencies is really welcomed in the outpatient setting and in the community setting.

So in summary, I look forward to being able to offer CT-P10 as an alternative to Rituxan, hopefully in the near future. Thank you for your time.

DR. RINI: Thank you. Speaker number 2?

DR. OSKOUEI: Hello. My name is Sonya Oskouei. I'm the director of pharmacy program development for biosimilars with Premier. I'll start by saying I have no connection to Celltrion and was not supported by them

to attend today's meeting, or have any relevant financial or sponsor relationships.

So the Premier Healthcare Alliance thanks the FDA Oncologic Drugs Advisory Committee for the opportunity to provide comments today. Premier is a leading healthcare improvement company and unite an alliance of more than 4,000 health systems and hospitals across the country, including approximately 165,000 providers and other organizations who transform healthcare. In my role, I have the unique role of leading the National Biosimilar Strategy for our organization on behalf of our healthcare members.

My comments today are intended to highlight the importance of biosimilars in the U.S. market and their potential impact on patient care. Premier views the accessibility of biosimilars as a key element in decreasing the cost of healthcare for the creation of a more competitive marketplace.

It's no secret that our nation continues to experience increases in drug prices for a range of products that are vital to patient care. Biologics, which are of course widely used in oncology practice,

are the most expensive drug category in the U.S. They can range from $1000 to $50,000 per individual or episodic treatment. In fact, according to the American Journal of Health System Pharmacy, the top five drugs based on expenditures in 2017 and nonfederal hospitals, were all biologics, accounting for over $5 billion healthcare costs.

The types of conditions often treated by biologics are chronic and severe conditions that of course can impact patients for a lifetime, both clinically and financially. The introduction of biosimilars not only has the potential to reduce drug spending on biologic drugs by $54 billion over the next 10 years, but more importantly help patients with chronic illnesses access critical therapies and enhance patient outcomes.

To date, there have been certain policy considerations and market dynamics inhibiting biosimilar success within health systems, and the FDA continues to work with a variety of stakeholders on a broader approach to adjust these challenges, including the release of the Biosimilars Action Plan.

However, as the committee reviews the application before it today, Premier urges the committee to put aside any policy considerations and barriers to adoption of biosimilars and instead focus on the scientific integrity of the data to determine if the biosimilar applicant sufficiently demonstrates that it is highly similar and has no clinically meaningful differences from an existing FDA-approved reference product

Furthermore, as the committee reviews the application, we encourage the committee to provide clear detailed and transparent feedback regarding the scientific merit of the application to really maximize scientific and regulatory clarity for biosimilar manufacturers and further encourage the development and introduction of biosimilars in the market.

Lastly, we recognize the importance of gathering real-world evidence to monitor for ongoing safety and efficacy of both biologics and biosimilars, and Premier welcomes the opportunity to support ongoing safety surveillance for biologics and biosimilars through our comprehensive electronic healthcare database

that contains data for over 200 million unique patients.

This post-approval activity coupled with pharmacovigilance warranted for these products will serve as a key strategy to enhance market acceptance of biosimilars and will further influence the development of biosimilar treatment options for patients.

So in conclusion, we urge ODAC to, aside of any policy considerations, evaluate the application based on scientific integrity and data, and provide that clear, transparent, and detailed feedback regarding the scientific merit of the application. Again, I thank you for the opportunity to provide these comments.

DR. RINI: Thank you. Speaker number 3?

DR. PATEL: Hi. Good morning, FDA team and ODAC members. My Name is Dr. Kashyap Patel. I'm a practicing medical oncologist in the Carolinas in the suburban as well as rural locations. Celltrion has taken care of my travel. I don't have any other financial disclosures to make.

Apart from practicing oncology, I'm also a board member for the Community Oncology Alliance and secretary for the same group. I'm also trustee for the

Association of Community Cancer Centers. I'm also sitting on the CAC advisory committee for the J11 MAC Region, the Palmetto GBA Medical Contractors. And we are also one of the alternate payment sites chosen by CMMI under the title of Oncology Care Model.

I want to share our own experience of incorporating biosimilars in our practice with the supportive care arena. We have seen a distinct improvement in the access and affordability. Looking at the totality of evidence of CT-P10, as well as scientific data and the impact on the society, I would strongly like to support the approval of biosimilar CT-P10 with the everlasting [indiscernible] challenge of drug prices and a case study of [indiscernible] practice, which I was president of the ASCO Quality Care Symposium

I do feel there's definitely a place for bringing competition in a biologic arena, and I really want to make a strong case as a community practitioner as well as having a seat on several national organizations that additional biosimilars in the arena will definitely improve the access and affordability.

Thank you very much.

DR. RINI: Thank you. Speaker number 4?

DR. KOONTZ: Good morning, Chairman Rini, Dr. Tesh, ODAC members, and representatives from the FDA. I appreciate the privilege of coming before you today to provide comments on BLA 761088 for CT-P10, a proposed biosimilar for Genentech's rituximab submitted by Celltrion, Incorporated. Before I begin, I want to acknowledge that Celltrion supported my travel to participate in today's meeting, but they are not compensating me for my time. I have no financial ties to Celltrion, and I'm speaking here today on my own behalf.

My name is Suzanna Koontz, and I am the principal of Koontz Oncology Consulting in Houston, Texas. Prior to starting my consulting firm, I was the clinical pharmacy specialist for the Children's Cancer Hospital at the University of Texas MD Anderson Cancer Center, where I was a member of several teams caring for pediatric and adolescent cancer patients.

As an oncology pharmacist, I appreciate the complexities in ensuring the availability of medications

that are safe and effective. This morning we heard the totality of the evidence, including data from clinical trials involving over 600 patients observed for up to two years, suggest that the proposed biosimilar CT-P10 is highly similar to the originator rituximab despite minor differences in clinically inactive compounds.

CT-P10 has been approved in Europe for more than a year and a half, where it was the first biosimilar utilized for a potentially curative intent in cancer patients. Today it's available in almost 50 countries around the globe.

As an oncology pharmacist, I'm all too familiar with the rising costs of cancer therapies. In fact, in oncology, we now recognize financial toxicity as a leading cause for patients' concerns with cancer therapy along with more traditional adverse events such as nausea and vomiting and alopecia.

A recent report in ASCO's Journal of Oncology Practice characterized the spending on anti-neoplastic agents in the United States between 2011 and 2016. During this period, anti-neoplastic expenditures rose from 7 percent of total U.S. drug expenditures to

9.4 percent, with older biologics representing the largest expenditure in hospitals and clinics, and at the top of this list was rituximab with an average annual expenditure in the United States of around $3.5 billion.

As an oncology pharmacists, I'm committed to cancer patients having access to life-saving medications. The approvals of biosimilars are expected to drive innovation, which in turn should drive down the costs of drugs. Such has been the case in Europe, where biosimilars have been priced approximately 30 percent less than the reference products.

If that same pricing model were applied here in the United States, rituximab biosimilars such as CT-P10 have the potential to produce slightly more than $1 billion in savings annually. And any savings could climb in the coming years, as we may see an increasing need for Rituxan biosimilars due to both the increasing incidence of lymphoma and patients living longer past the time of their diagnosis.

The ever-increasing costs of cancer care are unsustainable and continue to limit patients from receiving optimal treatments in optimal circumstances.

The value of biosimilars such a CT-P10 is they allow greater access to potentially curative treatments at a reduced financial burden to the healthcare system and patients alike. Thank you for your time and attention.

DR. RINI: Thank you. Speaker number 5?

DR. FUHR: Good morning, and thank you for having me. I'm Joe Fuhr. I'm a professor emeritus of economics at Widener University, and I'm a health economist, and I've published over 10 articles on the economics of biosimilars. Celltrion's supported my travel but not my time. I have no financial ties to Celltrion, and I'm speaking on my own behalf.

Biosimilar competition has the potential to decrease price of expensive biologics. These lower prices will increase access and decrease healthcare costs. The biosimilar market has some similarities to the generic market, but it's generally quite different. There are greater barriers to entry, especially research and development. Competition has been slow to develop in the U.S. market. Biosimilars in the EU have been around longer, and the market has developed and resulted in savings and increased access.

There are many barriers to entry that make biosimilar entry more difficult than generics. Biosimilars are much more costly to develop and the process takes much longer than generics. Biosimilar development is expected to cost between $100 million and $200 million and take between 8 to 10 years. Once a biosimilar is approved, uncertainty over patent rights have caused delay and entry in the U.S.

The current patent system needs to be changed. It is too complex, which leads to uncertainty. Between 2011 and 2014, over 90 percent of initial generic entrants faced patent disputes. Biosimilars seemed to follow the same pattern. There has already been a Supreme Court decision concerning patent [indiscernible] and the 180-day entry requirement. There is also an antitrust case between Pfizer and Johnson and Johnson concerning biosimilars.

Generic drugs have saved over a trillion dollars in healthcare costs over a 10 year period. Price of biosimilars are not expected to decrease as much as generics. However, the savings to consumers and society could be much greater in the case of biosimilars

because of the higher price of biologics.

It's important to note that the primary public policy objective is to increase consumer welfare. The market share of biosimilars is not a fully informative metric. The relevant welfare benchmark is not the price of biosimilars relative to the reference product, but the comparison price before the competition occurs. The increase in the quantity due to lower prices will increase access.

There's an ironic relationship between biosimilars, generics, and originator companies. There would be nothing to copy without the originators. There is the possibility for even greater innovation as innovators and firms want to develop new drugs to replace the biologics that are now subject to competition. The biosimilar market decreases the price of older drugs, and this frees money in the budget to allow for higher price, newer drugs. Consumers benefit from both.

In conclusion, there's a tradeoff between competition with lower prices and innovation. Public policy must balance the dual objectives of fostering

innovation and increasing competition. Biosimilars can decrease prices. Competition will lead to lower prices and increase access if the biosimilar experiment succeeds. Biosimilars are the great experiment. If biosimilar competition does not work, the result could be price controls. This could decrease the incentive to innovate and lead to fewer drugs being developed, which will hurt consumers. Thank you for your time and attention.

DR. RINI: Thank you. The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will turn its attention to the task at hand, that is careful consideration of the data before the committee as well as public comments.

Before we get to the discussion around the questions and the vote, of note I've been overruled about not giving you a second break.

(Laugher.)

DR. RINI: It's a little after 11. We'll take a break until 11:15 and then come back to finish up. Thank you.

(Whereupon, at 11:02 a.m., a recess was taken.)

DR. RINI: Before we proceed to the questions and the discussion, the applicant has some responses I think to a couple of things that came up prior to the break.

DR. KUDRIN: Regarding analytical data, Dr. Pollitt has an answer.

DR. POLLITT: To clarify for Dr. Long that the ADCP is read after 3 hours, and it's the macrophage differentiation that we allowed to go for several days.

DR. KUDRIN: And Dr. Nowakowski requested some information about user of filgrastim. I can confirm we checked that in study 3.4, low-tumor burden follicular lymphoma, there were no patients using filgrastim at all. And in study 3.3, we had 24 patients, which is 34.3 percent in CT-P10 group versus 16 patients, 22.9 percent, in the Rituxan. This imbalance was exactly in line with the imbalance of neutropenia observed in study 3.3.

Questions to the Committee and Discussion

DR. RINI: Thank you. We'll now proceed with 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 the specific request of the panel.

I'm going to read the questions out. If you have any question about the questions, about the wording, please ask me and I'll clarify. The first question, please discuss whether the evidence supports the demonstration that CT-P10 is highly similar to U.S. licensed Rituxan notwithstanding minor differences in clinically inactive components.

The floor is open to discuss this question. Dr. Hancock?

DR. HANCOCK: While there are some minor differences as stated here, and I think no one analytical test will answer all the questions about a particular difference, there has been a large battery of analytical tests run, which are orthogonal. So one test may not give the whole result, but then the other tests will fill in the missing gaps.

So with that background, I am comfortable about the analytical characterization and the demonstration of a high degree of similarity.

DR. RINI: Thank you. Anybody else want to comment from clinical pharmacology about minor differences? At the end I can't see.

DR. WALDMAN: In close agreement with what Dr. Hancock said, the analysis with multiple orthogonal approaches demonstrated that the physicochemical characteristics of this agent are highly similar notwithstanding some minor differences in some of those characteristics. That similarity translated to its biological activity in vitro assays, as well as its pharmacokinetic characteristics. And that translated into noninferiority in the 3.3 study and equivalence in the 3.4 study.

So the totality of the evidence, taking everything into consideration, would support the suggestion that this agent is biosimilar compared to the innovator product.

DR. RINI: Dr. Collins?

DR. COLLINS: Jerry Collins. I thought the discussion about the analytical piece was really excellent. I liked the drilling down to details. And in addition to its role in biosimilars, we're still

learning a lot about this whole field. So when a product is first developed, like it is in our program, at an early stage, the whole process is going to be transferred to somebody else to actually market it.

There has to be some -- it's a lower standard of bioequivalence, but we still need to know -- we still have to be similar to it as the product moves. Then further, after a company has been successful, they build a new plant somewhere thousands of miles away. And the product that's produced there, it's not automatic that everything will just work fine.

So getting this on the record, hearing about the issues and hearing them discuss, that was, for me, one of the highlights of the meeting.

DR. RINI: Thank you. Other comments about this particular question? Dr. Smith?

DR. SMITH: Well, I was pleased to hear that there was some explanation about why some feature of the product was not clinically relevant. Really, that wasn't made clear in the materials until the briefings today, where it was actually explained that certain parts of the molecule have to do with binding, and

binding is a critical feature.

It would be a little bit better -- I know that you cannot define highly similar, but obviously those words were chosen because it was felt that -- it's an undefinable concept. But what makes something appear to be highly similar ought to be more than here's a bunch of numbers, and we think it's highly similar. There should be a better explanation. And today, there was presented a better explanation in terms of the molecular biology, but that really didn't appear in the briefing materials.

DR. RINI: Thank you. Other comments?

(No response.)

DR. RINI: I think to summarize what we've heard from our experts is that there's, I think, relative consensus that this product is highly similar across the multiplicity of assays to the best of the ability to define that.

If we could turn to question 2, please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between CT-P10 and U.S. licensed Rituxan. The floor is open to discuss

this question regarding the clinically meaningful differences or lack thereof. Dr. Chen?

DR. CHEN: I thought the two clinical trials shown, the 3.3 and 3.4, particularly the 3.4 equivalence study did show that there were no, -- that they're clinically equivalent in efficacy and toxicity. The slight signal difference in the 3.3 study I think was adequately explained by the neutropenia and the bone marrow involvement.

DR. RINI: Thank you. Dr. Halabi?

DR. HALABI: I was also pleased with the sponsor presentation, and I put more weight on CT-P10 3.4, since this was designed originally as an equivalence drug. So it was properly designed and properly conducted. I thought the rationale for choosing the noninferiority or the equivalence margins were well justified, and the analysis based on ITT and per protocol seemed adequate. Thank you.

DR. RINI: Thank you. Dr. Nowakowski?

DR. NOWAKOWSKI: I also agree with the statement. I think those two studies are complimentary with frequently used Rituximab and in combination with

chemotherapy, which was the 3.3 study. But to isolate the single agent, the 3.4 study was quite convincing in terms of demonstrating that there are no meaningful clinical differences between those two.

DR. RINI: Thank you. Dr. Hawkins?

DR. HAWKINS: I didn't think to ask earlier, but just curious, after a year use of the product in Europe, where there are more adverse events that we didn't see here we wonder about, but were there -- are there more adverse events with a year of the use of this product in Europe.

DR. RINI: You're asking about the adverse event profile of the European product.

DR. HAWKINS: Yes.

DR. RINI: I don't know.

DR. KUDRIN: Thank you very much. We brought here an expert from Germany who is using the CT-P10 now in hundreds of patients in Germany, specifically in follicular lymphoma. Dr. Christian Buske.

DR. BUSKE: Yes. Thank you very much. My name is Christian Buske. I'm from Ulm University Hospital. In my function as a medical director at the university

hospital but also as a member of the steering committee and upcoming president of the German Lymphoma Alliance, which is one of the largest clinical study groups for lymphoma, we oversee quite a lot of patients treated with biosimilars because this constantly changes our experience quite a lot. From what we know is that there is no difference with the biosimilar CT-P10 in the labeled indications, so that we feel really confident to use this biosimilar.

I'm also the coordinator of the working party of the ESMO guidelines for hematological malignancies, and I'm also responsible for the official guidelines for indolent lymphoma in Germany, Switzerland, and Austria. And we are very sensitive to this issue, and we think twice and three times what we are writing, and there are clearcut position papers from all societies which implement these experiences which we have.

So saying that there is indeed biosimilarity and that we do not see any toxicity signal.

DR. RINI: Thank you. Other comments from the committee? Other discussion around this particular question?

(No response.)

DR. RINI: I think just to summarize what we've heard is I think the committee is comfortable that there are not clinically meaningful differences given what we've heard about efficacy and toxicity, as well as the statistical design, as mentioned.

If we could turn to question 3, please discuss whether there is adequate justification to support licensure for the proposed indication sought by the applicant. So the floor is open for discussion around this question, around the proposed indication, specifically.

Dr. Nowakowski?:

DR. NOWAKOWSKI: I think as a lymphoma physician, all three proposed indications are consistent with our use in clinical practice, although there are some new CD20 antibodies entering this space as well, but rituximab is still used for all those three indications. So based on the totality of evidence, which we have seen here, I think the use in follicular lymphoma, which is mentioned here in low-grade C20-positive non-Hodgkin's lymphoma, is supported by

this.

DR. RINI: Okay. Thank you. Other comments around the indications?

(No response.)

DR. RINI: If there's no further discussion on these questions, we'll now begin the voting process. We will be using an electronic voting system for this meeting. Once we begin to vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in, and the vote will then be displayed on the screen. A designated federal officer will read the vote from the screen into the record, and next, we will go around the room, and each individual who voted will state their name and what they voted into the record. And please also state the reason why you voted as you did in any discussion around your vote if you wish to.

The vote is, does the totality of the evidence support licensure of CT-P10 as a biosimilar product to U.S. licensed Rituxan for the following indications: treatment of adult patients with relapsed refractory low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma as a single agent; previously untreated follicular CD20 positive B-cell NHL in combination with first-line chemotherapy and in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy; a single agent maintenance therapy and non-progressing, including stable disease; and low grade CD20 positive B-cell NHL as a single agent after first-line CVP chemotherapy.

Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or wish to change, press the corresponding button again before the vote is closed. Please vote now.

(Voting.)

DR. TESH: For the record, the voting results

are 16 yeses; zero, no; zero abstentions; and zero no voting.

DR. RINI: Thank you. Now that the vote is complete, we're go around the table and have everyone who voted state their name, their vote, and if you'd like, and please do, state the reason why you voted as you did into the record.

We can start with P.K. even though she didn't vote. Any comments?

(Dr. Morrow gestures no.)

DR. RINI: Okay. So we'll go to Dr. Waldman then.

DR. WALDMAN: Scott Waldman. I voted yes. I thought the totality of the analytical, clinical, pharmacological, and clinical evidence supported biosimilarity.

DR. HANCOCK: William Hancock. I voted yes, and I think Scott just nicely summarized my reasons for voting yes.

DR. LONG: I'm Eric Long. I voted yes. The evidence was quite strong that the product is equivalent.

DR. CHEN: Andy Chen. I also voted yes.

DR. KARARA: Adel Karara. I voted yes because of the compelling PK similarity data that has been provided.

MS. MATSON: Tracy Matson. I also voted yes.

DR. HAWKINS: Randy Hawkins, yes. And I hope that the healthcare system and consumers will be a beneficiary of the price reduction, promised

DR. HINRICHS: Christian Hinrichs. I voted yes. I believe the analytical data, the PK data, the immunogenicity data, and the clinical data were all consistent with equivalency.

DR. NOWAKOWSKI: Grzegorz Nowakowski. I voted yes. I believe the totality of evidence strongly supported the biosimilarity of those products. Also, I'm a lymphoma physician. I do believe that this approval could improve patient access to anti-C20 therapy, which remains a cornerstone of our treatment in B-cell lymphomas.

We also had a lot of exchanges with our European colleagues and colleagues from other countries, which actually commented on improved access to anti-C20

therapy after biosimilar products were approved there.

DR. ULDRICK: Tom Uldrick. I also voted yes. The totality of the evidence supports licensure. Anti-CD20 therapies really transform B-cell lymphoma therapy, and the sponsors convincingly demonstrated that CT-P10 is highly similar to U.S. Rituxan, with the exception of minor components with no biologic activity. The clinical PK efficacy and safety data is consistent with equivalence.

DR. RINI: Brian Rini. I voted yes for the same reasons as outlined. I thought the preclinical analytics were fairly consistent. I think the clinical data supports efficacy in terms of at least response rate. There were some concerns about safety, and I think that's probably just what you get when you have a lower number of patients treated in this type of development program, that you get some imbalances in baseline characteristics that, to me, seem to explain some of the differences observed.

DR. KLEPIN: Heidi Klepin. I voted yes, based on the totality of the data. And I would just echo what Dr. Rini just said.

DR. CRISTOFANILLI: Massimo Cristofanilli. I voted yes; obviously the totality of data. I didn't see any major signals of safety, and I think, I hope, that in the future that can be applied to other applications where rituximab is used.

DR. HALABI: Susan Halabi. I voted yes based on the totality of the data from analytical studies to nonclinical/clinical pharmacology, and clinical efficacy and safety. And I congratulate the sponsor for doing a rigorous job from the pyramid down, all the way to the top.

DR. SMITH: Paul Smith. I voted yes. I felt that the discrepancies that were located or identified at the early stages of the analysis were completely overwhelmed by the good clinical results.

DR. COLLINS: Jerry Collins. I also voted yes based on totality, though I'd prefer that all these things only had one clinical trial. In this case, it really sealed the deal and will given higher confidence in this product.

Adjournment

DR. RINI: Thank you. We'll now adjourn the

meeting. Panel members, please leave your name badge on the table so they can be recycled. Please take all your personal belongings with you, and any meeting materials that you need to leave on the table will be disposed of. Thank you for your time.

(Whereupon, at 11:33 a.m., the meeting was adjourned.)