FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Morning Session

Thursday, July 13, 2017

8:00 a.m. to 11:54 a.m.

FDA White Oak Campus

White Oak Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Jay R. Fajiculay, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Grzegorz S. Nowakowski, MD

Associate Professor of Medicine and Oncology

Mayo Clinic Rochester

Rochester, Minnesota

Courtney J. Preusse, MA

(Consumer Representative)

Senior Research Administrator and CLIA

Operations Director

Clinical Research Division

Fred Hutchinson Cancer Research Center

Seattle, Washington

Gregory J. Riely, MD, PhD

(morning session only)

Associate Attending Physician

Memorial Sloan-Kettering Cancer Center

Associate Professor

Weill Cornell Medical College

New York, New York

Bruce. J. Roth, MD

(Chairperson)

Professor of Medicine

Division of Oncology

Washington University School of Medicine

St. Louis, Missouri

Thomas S. Uldrick, MD, MS

Clinical Director

HIV & AIDS Malignancy Branch

Center for Cancer Research

National Cancer Institute

Bethesda, Maryland

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Gary Gordon, MD, PhD

Vice President, Oncology Development

Abbvie

North Chicago, Illinois

TEMPORARY MEMBERS (Voting)

Deborah K. Armstrong, MD

Professor of Oncology

Johns Hopkins Kimmel Cancer Center

Johns Hopkins University School of Medicine

Professor of Gynecology and Obstetrics

Johns Hopkins School of Medicine

Baltimore, Maryland

Cynthia Chauhan

(Patient Representative)

Wichita, Kansas

Shein-Chung Chow, PhD

Professor, Biostatistics and Bioinformatics

Duke University School of Medicine

Durham, North Carolina

Bernard F. Cole, PhD

Professor

Department of Mathematics and Statistics

University of Vermont

Burlington, Vermont

Craig W. Hendrix, MD

Wellcome Professor and Director

Division of Clinical Pharmacology

Departments of Medicine and Pharmacology and

Molecular Sciences

Johns Hopkins University School of Medicine

Baltimore, Maryland

Adel H. Karara, PhD, FCP
Professor of Pharmaceutical Sciences
School of Pharmacy
University of Maryland Eastern Shore
Princess Anne, Maryland

Donald E. Mager, PharmD, PhD
Professor of Pharmaceutical Sciences
Department of Pharmaceutical Sciences
School of Pharmacy and Pharmaceutical Sciences
University of Buffalo, State University of New York
Buffalo, New York

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

Diane Reidy-Lagunes, MD

(morning session only)

Associate Deputy Physician in Chief of Clinical Operations

Memorial Sloan-Kettering Cancer Center

Weill Cornell Medical College

New York, New York

John E. Schiel, PhD

Research Chemist

Institute for Bioscience and Biotechnology Research

National Institute of Standards and Technology

Rockville, Maryland

Deborah Schrag, MD, MPH

(morning session only)

Chief, Population Sciences

Dana Farber Cancer Institute

Professor of Medicine

Harvard Medical School

Boston, Massachusetts

Scott A. Waldman, MD, PhD, FCP, FAHA
Director, Gastrointestinal Cancer Program of the
Sidney Kimmel Cancer Center
Samuel M.V. Hamilton Professor of Medicine
Chair, Department of Pharmacology and
Experimental Therapeutics
Thomas Jefferson University
Philadelphia, Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Leah Christl, PhD
Associate Director for Therapeutic Biologics
OND Therapeutic Biologics and Biosimilars
Staff (TBBS)
OND, CDER, FDA

Patricia Keegan, MD
(morning session only)
Director
Division of Oncology Products 2 (DOP2)
OHOP, OND, CDER, FDA

Steven Kozlowski, MD

Director

Office of Biotechnology Products (OBP)

Office of Pharmaceutical Quality (OPQ)

CDER, FDA

Steven Lemery, MD

(morning session only)

Associate Director

DOP2, OHOP, OND, 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. ROTH: Let's go ahead and get started.

Good morning. I'd first like to remind everyone to please silent your cell phones, smart phones, and any other device you have if you have not already done so. I'd also like to identify the FDA press contact, Angela Stark, over here on the side. If you have any issues, then please address them to her.

I think we'll first go around the table and introduce ourselves. A lot different staff than yesterday, so we'll start at this end, start with Dr. Gordon.

DR. GORDON: Gary Gordon, industry representative, vice president for Oncology Development at AbbVie.

MR. MOREIRA: Antonio Moreira, vice provost and professor of chemical, biochemical, and environmental engineering at the University of

Maryland, Baltimore County.

MR. SCHIEL: John Schiel of NIST. I coordinate a biopharmaceutical reference material program in analytical characterization.

DR. SCHRAG: I'm Deb Schrag. I'm a professor of medicine at Dana-Farber Cancer Institute, and gastrointestinal oncologist.

DR. REIDY: I'm Diane Reidy. I'm also a gastrointestinal oncologist from Memorial Sloan-Kettering Cancer Center.

DR. HENDRIX: Craig Hendrix, clinical pharmacology, Johns Hopkins.

DR. COLE: Bernard Cole, biostatistics, University of Vermont.

MS. CHAUHAN: Cynthia Chauhan, patient representative.

MS. PREUSSE: Courtney Preusse, Fred Hutchinson, CLIA operations director, and consumer representative.

DR. NOWAKOWSKI: Grze Nowakowski, oncologist, Mayo Clinic.

DR. ULDRICK: Thomas Uldrick, medical

oncologist, Center for Cancer Research NCI.

DR. ROTH: Bruce Roth, I'm a GU medical oncologist from Washington University in St. Louis, and chair of the committee.

DR. FAJICULAY: Jay Fajiculay, designated federal officer for the Oncology Drug Advisory Meeting today, FDA.

DR. RIELY: Greg Riely, medical oncologist, Memorial Sloan-Kettering Cancer Center.

DR. WALDMAN: Scott Waldman, clinical pharmacologist, Thomas Jefferson University, Philadelphia.

DR. ARMSTRONG: Deb Armstrong, medical oncologist, Johns Hopkins in Baltimore.

DR. KARARA: Adel Karara, professor at the University of Maryland Eastern Shore.

DR. CHOW: Shein Chow, professor of Biostatistics and Bioinformatics at Duke University School of Medicine.

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

MS. FUCHS: Chana Fuchs, Office of Biotechnology, FDA.

DR. LEMERY: Steve Lemery, associate director DOP2, and acting team leader for this application.

DR. KEEGAN: Patricia Keegan, division director at Division of Oncology Products 2.

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

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

DR. ROTH: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chairperson. We

look forward to a productive meeting.

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

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

Now, I'll pass it on to Dr. Jay Fajiculay who is acting as our DFO for both the morning and afternoon sessions, and will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. FAJICULAY: The Food and Drug Administration is convening today's meeting of the 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 U.S.C., Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this Committee are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a 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 U.S.C., Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves Biologics License Application 761028 for ABP 215, a proposed biosimilar to Genentech/Roche's Avastin, orbevacizumab, submitted by Amgen Inc.

The proposed indications for this product are 1) for the first- or-second line treatment of

patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorourcil-based chemotherapy;

2) in combination fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line ABP 215-containing regimen;

3) for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel;

4) for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent;

5) for the treatment of metastatic renal cell carcinoma in combination with interferon alfa; and

6) in combination with paclitaxel and cisplatin or paclitaxel and topotecan for the treatment of persistent, recurrent, or metastatic

carcinoma of the cervix.

This will be a particular matters meeting, in which specific matters related to Amgen's BLA will be discussed. Based on the agenda of today's meeting and all financial interests reported by the committee members and temporary voting members, conflicts of interest waivers have been issued in accordance with 18 U.S.C., Section 208(b)(3) to Drs. Gregory Riely, Bruce Roth, Debora Schrag, and Adel Karara.

Dr. Karara's waiver involves his stock, the holdings in four potentially competing firms. His current aggregate value of his stock holdings is between $25,001 and $50,000.

Dr. Schrag's waiver involves her ownership of stock in a healthcare sector fund. The current aggregate value of the fund is between $50,000 and $150,000.

Dr. Roth's waiver involves his employer's current study involving a potentially competing firm, which is anticipated to be between $0 and $50,000 in total funding.

Dr. Riely's waiver involves his employer's current 10 studies. One is with the party to the matter, and the other nine are with potentially competing firms. The total funding for these studies ranges between zero and $3.2 million dollars.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waivers documents, which as posted at the FDA's website at www.FDA.gov/advisorycommittee/committeemeetingmaterials/drugs/default.htm Copies of the waiver may also be obtained by submitting a written request to the agencies Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857, or requests may be sent via fax to 301-827-9267.

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

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Gary Gordon is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Gordon's role at this meeting is to represent industry in general and not any particular company. Dr. Gordon is employed by AbbVie.

We would like to remind members and temporary voting members that if discussions involve any other products of firms, not already on the agenda for which an FDA participant has a potential 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 made with the firm at issue. Thank you.

DR. ROTH: Thank you, Jay.

We will proceed with an overview of the regulatory framework and FDA's guidance for the

development approval of biosimilar products in the U.S., and we will hear from Dr. Sue Lim.

Presentation – Sue Lim

DR. LIM: Good morning. I'm going to present an overview of the regulatory framework, and FDA's guidance for the development and approval of biosimilar products in the United States.

Please keep in mind that this is not intended to be a product specific discussion, but rather a general overview that will provide everyone with some pertinent background, go over some definitions and terminology, and go over some of the general requirements in terms of the approval pathway for biosimilars in the U.S.

The second portion of my presentation will focus on the development of biosimilars, specifically discussing FDA's approach to the development of biosimilars and go over some key development concepts.

On March 23, 2010, President Obama passed into law the Affordable Care Act, which gave FDA the authority 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 Act states that a biological product that is demonstrated to be highly similar to an already licensed FDA-licensed biological product, known as the reference product, may relay of licensure on, among other things, publicly available information regarding FDA's previous determination that the reference product is safe, pure, and potent.

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

abbreviated licensure pathway.

A few words more about the abbreviated licensure pathway, and I'll start by saying what is isn't. The abbreviated licensure pathway does not mean that there is a lower approval standard applied to the approval of biosimilar or interchangeable products, compared to the original biological products.

The abbreviation comes from the applicant's ability to rely on FDA's previous finding regarding the safety, purity, and potency of the reference product to support approval of the biosimilar product. This is what potentially allows for a shorter and less costly drug development program, and what is meant by the abbreviation.

You will hear today that, in fact, the data package required for approval of a biosimilar product or an interchangeable product is actually very extensive. Biosimilar applicants must submit extensive comparative analytical data, non-clinical data, and in certain cases, additional clinical study data to support a demonstration of

biosimilarity with the reference product.

As a result of all of this information, once a biosimilar interchangeable product has been approved by FDA, patients and healthcare providers can be assured about the safety and effectiveness of an FDA approved biosimilar or interchangeable product just as they would for the reference product that the biosimilar was compared to.

I'd like to turn to some terminology and definitions, as described in the BPCI Act.

The BPCI Act states that biosimilar or biosimilarity means that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and they are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Please note that both parts of this standard must be met for biosimilarity to be demonstrated.

The reference product is the single biological product licensed under Section 351(a) of

the Public Health Service Act, against which a biological product is evaluated in an application submitted under Section 351(k) of the PHS Act.

An application submitted under Section 315(a) of the PHS Act is known as a stand-alone application, in that it contains all of the necessary information and data to demonstrate that the proposed product is safe, pure, and potent.

In contrast, an application submitted under Section 351(k) of the PHS Act needs to demonstrate that the proposed product is biosimilar to the reference product.

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

The sponsors developing the products under discussion at the advisory committees today are not looking to seek licensure of the respective

products, as proposed interchangeable products. But, the BPCI Act does describe an interchangeable or interchangeability in the following way: it means that the biological product is biosimilar to the reference product; that it can be expected to produce the same clinical result as the reference product in any given patient; and that for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

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

The Act describes the general requirements in terms of what a 351(k) application must include for a biosimilar/biological product. There must be

information demonstrating that the biological product is biosimilar to a reference product. That the biosimilar product utilizes the same mechanism or mechanisms of action for the proposed conditions of use, but only to the extent the mechanisms are known for the reference product.

The conditions of use that the biosimilar product is seeking licensure for must have been previously approved for the reference product. The biosimilar has the same route of administration, dosage form, and strength as the reference product, and is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent.

Thus, the manufacturing standards for a biosimilar product are the same as for reference biological products.

The PHS Act also describes the types of information that can be used to support biosimilarity. In general, there is data from analytical studies demonstrating that the

biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components.

There are animal studies, including an assessment of toxicity, and a clinical study or studies including the assessment of immunogenicity and pharmacokinetic or pharmacodynamics that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed, and for which licensure is sought for the biosimilar product.

The Act states that FDA may determine in its discretion that an element described above is unnecessary in a 351(k) application to support a demonstration of biosimilarity.

I'd like to say a few words here about the use of a non-US license comparator product. I had described earlier that the PHS Act defines the reference product for a 351(k) application as the single biological product licensed under Section 351(a) against which a biological product

is evaluated.

However, FDA has taken the regulatory position that data from animal studies and certain clinical studies, comparing a proposed biosimilar product with a non-US licensed product, may be used to support a demonstration of biosimilarity to a U.S. licensed reference product.

However, it is up to the sponsor to provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity, and establish an acceptable scientific bridge to the U.S.-licensed reference product.

In general, we describe in guidance the types of bridging data needed to support this approach, and this generally includes two data elements. The first is direct physical chemical comparison of all three products, so three comparisons in the pair-wise comparisons described on this slide.

The proposed biosimilar to the U.S. reference product, a comparison between the

proposed biosimilar and non-US license compared product, and the U.S. reference product to the non-US licensed comparator product.

There's also likely going to be a three-way bridging clinical PK and/or PD study, and all three pair-wise comparisons should meet the prespecified acceptance criteria for analytical and PK and/or PD similarity.

Again, please note that a sponsor should justify the extent of comparative data needed to establish a scientific bridge to the U.S.-licensed reference product.

I'd now like to focus on FDA's approach to the development of biosimilars. FDA has published a number of both draft and final guidances in several key scientific areas, which describe our current thinking in terms of the development of biosimilars and how to support a licensing application.

Much of our thinking is described in the guidance and can be distilled to several key development concepts, which I will describe over

the next few slides.

The first key concept is that the goal of stand-alone development is different from biosimilar development. You'll see here on the left a depiction of stand-alone drug development. This is along the 351(k) pathway described in the Public Health Service Act, and the goal of stand-alone development is to establish safety and efficacy of a new product.

The data elements are shown in the figure, and begin with analytical or a chemistry manufacturing control data, non-clinical data, dose finding clinical pharmacology data, and typically phase 1, 2, and 3 clinical safety and efficacy data to support the product.

We see here on the right-hand side that the data elements supporting a biosimilar application are similar with the analytical, non-clinical, clinical pharmacology in additional clinical studies, but the weight and the focus of the data is different than in stand-alone development. This is because the goal of the biosimilar development

program differs from that of a stand-alone development program.

The goal is not to independently establish that the biosimilar product is safe and effective, but rather it is to demonstrate biosimilarity or interchangeability to a reference product. As such, there is more of a focus on the analytical data, and additional clinical studies only form a small piece of the overall data package and is intended to address residual uncertainties.

The second key concept is the idea of step-wise evidence development. FDA has outlined in guidance a step-wise approach to the generation of data in support of a demonstration of biosimilarity, and there is an evaluation of residual uncertainty at each step.

FDA uses a totality of the evidence approach in evaluating biosimilarity. It really is looking at all of the comparative data shown in the pyramid to the right in total, rather than a single phase 3 clinical trial outcome. As such, there is no one pivotal study within a biosimilar development

program that demonstrates biosimilarity.

In keeping with that, there's really no one size fits all assessment. In the application of the step-wise approach to data generation and the evaluation of residual uncertainty, one stops at each step of data generation and asks what differences have been observed and what is the potential impact of those differences.

By asking that question, you can determine what studies or data will address the residual uncertainty, and that would be the next step to take.

The third key concept is that analytical similarity data really is the foundation of all biosimilar development programs. Biosimilar applicants must extensively characterize their product and the reference product through structural and functional characterization.

It begins with a characterization of protein structure. Beginning with primary structure, and going through secondary, tertiary, and going up to quaternary structure characterization.

Biosimilar applicants will observe differences between their product and the reference product, and this is really due to the inherent variability in naturally-sourced and biological products that are manufactured through recombinant technology.

The differences themselves are not necessarily concerning, but it's really the identification of these differences and the evaluation of the impact of those differences that is critical.

Note that in addition to differences between the proposed biosimilar and the reference product, so-called inter lot variability, there's also going to be intra or lot-to-lot variability. This is the differences between lots of the biosimilar itself, and this is an issue that is, again, inherent to biological products and is not a biosimilar specific issue.

There is lot-to-lot variability within all biological products including the reference product. Both inter lot, the protein heterogeneity

described, and the intra lot variability all need to be evaluated as part of the analytical similarity evaluation that biosimilar applicants perform.

In discussing the components of an analytical similarity exercise, we talked about how there is extensive structural and functional characterization in a comparative fashion, and I've included here not an all-inclusive list of some of the attributes that are included in an application. This includes a comparative assessment of attributes including immuno-acid sequence, folding, subunit interactions, and so forth.

In addition to structural characterization, if a molecule is known to have multiple biological activities, each of these mechanisms of actions or activities should be demonstrated to be highly similar between the proposed biosimilar product and the reference product to support functional similarity.

The key is really understanding the molecule and its function, identifying the critical quality

attributes that define the function, and having a really good understanding of the connection.

In terms of generating the analytical similarity data itself, biosimilar applicants must characterize reference product quality characteristic and product variability by characterizing multiple lots of the reference product. They then generate their own manufacturing process for their proposed biosimilar product.

Ideally, it should be designed to produce a biosimilar product that has minimal to no difference in product quality characteristics, compared to the reference product. However, if differences are identified, as mentioned previously, the key is to evaluate the impact of those differences and to identify what studies or data will address the residual uncertainty stemming from these differences.

Again, understanding the relationship between quality attributes and the clinical safety and efficacy profile, aids in our ability to

determine residual uncertainty about biosimilarity and to predict the expected clinical similarity form the quality data.

FDA has taken the position that statistical analyses of analytical similarity data can be used to support a demonstration that the proposed biosimilar product is highly similar to the reference product. This is not intended to be a pass/fail system, but is really intended to add rigor and some objectivity to the assessment of analytical similarity.

In this approach, quality attributes are ranked based on criticality with regard to their potential impact on activity, PK and PD, safety, immunogenicity, and other factors, and from there the data are then analyzed by various testing methods taking into consideration various factors, such as amenability to the testing approach.

Looking at the role of animal data to support a demonstration of biosimilarity, animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to

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

FDA takes a risk-based approach to the need for animal studies, and the key question is really whether animal studies will answer the question or address the residual uncertainty coming out of the analytical similarity exercise.

In some cases a comparison of PK and PD in an animal model may be useful, but it really depends on the relevance of the animal model and whether it can answer the question at hand, and this would be prior to initiating clinical studies.

The fourth key concept relates to clinical studies, and again, we see the familiar pyramid starting with analytical studies as the foundation of a biosimilar development program, and reaching at the very end additional clinical studies.

The nature and scope of clinical studies really does depend on the extent of residual uncertainty about the biosimilarity of the two products after conducting structural and functional analytical characterization, and rare relevant animal studies.

In terms of clinical data as a scientific matter, FDA expects that an adequate clinical pharmacokinetic and pharmacodynamic, if relevant, comparison between the proposed biosimilar product and the reference product be conducted.

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

Again, the role of a comparative clinical study is really only to address any remaining residual uncertainty about the biosimilarity of the product after structural and functional characterization animal testing, human PK and PD data in the immunogenicity assessment.

FDA has taken the position that

pharmacokinetic and/or pharmacodynamic data is generally considered the most sensitive clinical study or assay in which to assess for potential differences between products.

In terms of PK, applicants must demonstrate PK similarity of their product with the reference product in an adequately sensitive population to detect differences, should they exist.

If there is a relevant PD endpoints, similar PD using a PD measure that reflects the mechanism of action or reflects the biological effects of the drug, can be very valuable information to support similarity.

PK and PD similarity data in total supports a demonstration of biosimilarity with the assumption that similar exposure and pharmacodynamics response, if applicable, will provide similar efficacy and safety where an exposure response relationship exists.

Again, a comparative clinical study is necessary only when there is remaining residual uncertainty and is intended to support a

demonstration of whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product.

An applicant should consider the population, endpoints, sample size, and study duration in that these factors should be adequately sensitive to detect differences between products, should they exist.

Typically, FDA asks for an equivalence design for the comparative clinical study, but other designs may be justified depending on product specific and program specific considerations. For all clinical studies conducted for a biosimilar development program, an assessment of safety and immunogenicity should be included.

The last key concept I'll describe today is that of extrapolation. The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation. However, the applicant must provide sufficient scientific

justification for extrapolation in their 351(k) application.

Please note that differences between the conditions of use, such as indications, do not necessarily preclude extrapolation. However, it is up to the applicant to address factors that we've described in guidance that can support extrapolation, and these include describing the mechanism of action in each condition of use, the pharmacokinetics and biodistribution in different patient populations, the immunogenicity in difference patient populations, and differences in expected toxicities in each condition of use and patient population.

To describe extrapolation a little further, let's take as an example standalone drug development. We all recognize the data elements that were described earlier in this presentation that support the approval of a standalone drug. These typically include a phase 3 clinical trial to support the sought indication at the time of approval.

For every subsequent indication that a standalone sponsor or applicant is seeking, the general expectation is that a clinical trial will accompany that indication to demonstrate safety and efficacy.

In considering extrapolation for a biosimilar development program, however, there is a body of comparative data including the analytical similarity assessment, animal data, PK similarity, and PD similarity if relevant, there's a comparative immunogenicity assessment, and if needed there's additional clinical data through the conduct of a comparative clinical study in one or more conditions of use for which the reference product is licensed.

So there's this extensive comparative data that's in the 351(k) application, and that is taken along with FDA's previous finding that the reference product is safe, pure, and potent and that whole body of information is extrapolated to the other indications that were previously approved for the reference product, considering the factors

that I described previously -- namely the mechanism of action, PK, immunogenicity, and known toxicities.

Please note that extrapolation is not from the studied indication for the biosimilar to other non-studied indications that the applicant is seeking. It really is the extrapolation of both the comparative data in the application along with the FDA's previous finding -- along with the sponsor's justification for extrapolation that supports this approach.

In summary, the development of a biosimilar product is different from standalone development, in that the developmental goals are different. The goal of biosimilarity is not to reestablish safety and efficacy, but to demonstrate that the biosimilar product is highly similar to the reference product and that there are no clinically meaningful differences.

We discussed that the analytical similarity data and analytical comparisons are the foundation of a biosimilar development program, and are used

to determine whether the products are highly similar.

Clinical PK and/or PD is generally considered the most sensitive endpoint for detecting differences, if present, between products. There's also an assessment of comparative immunogenicity, and comparative clinical data are collected if there are residual uncertainties about the demonstration of no clinically meaningful differences.

The approval of a proposed biosimilar product is based on an integration of various information. It really is the totality of the evidence approach that was described. It's the information provided by the biosimilar sponsor to provide an overall assessment that the proposed product is biosimilar to the reference product.

As a result, FDA's high standard for approval of biosimilar interchangeable products means that patients and healthcare professionals can be confident of the safety and effectiveness of a biosimilar or interchangeable product just as

they would for the reference product. And with that I will conclude. Thank you for your attention.

DR. ROTH: Thank you, Dr. Lim.

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

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation it will not preclude you from speaking.

We'll now proceed with the applicant's presentation, and begin with Dr. Markus.

Applicant Presentation - Richard Markus

DR. MARKUS: Good morning. I'm Richard Markus. I'm vice president of the Development for Amgen's Biosimilars Division. I have the pleasure of representing the Amgen team that created and evaluated ABP 215; that's the scientific, manufacturing, and development teams.

I'd like to thank the FDA and the members of the advisory committee for the opportunity to present our data today. It's an important day for Amgen and also for patients, as this is the first advisory committee hearing for a biosimilar to bevacizumab, and the first for an oncology therapeutic antibody.

Our presentation today will follow this agenda. I will provide some background on the

development program for APB 215. We designed the program according to FDA guidance, and with many agency meetings. Simon Hotchin, head of regulatory affairs for Amgen biosimilars, has an extensive background in regulatory sciences, chemistry, manufacturing, and control. He will share our development process and data from manufacturing and testing ABP 215.

Importantly, Mr. Hotchin will discuss the comprehensive analytical comparisons that show the product to be highly similar to the reference product in both structure and function.

I will then share the results of the non-clinical and clinical development program, which confirms there are no clinically meaningful differences between ABP 215, and bevacizumab. I will also highlight the considerations for extrapolation to all indications.

Finally, Lisa Bollinger, vice president of Regulatory Affairs and Safety at Amgen, will conclude the presentation.

Amgen is a biotechnology pioneer with more

than 35 years of experience developing and manufacturing complex biologics, including therapeutic antibodies. In addition to the pipeline of innovative medicines, Amgen has a broad pipeline of biosimilars in development.

The Amgen biosimilars and innovative medicines are created by the same scientists and in the same laboratories, and we use the same manufacturing network and quality systems to produce our biosimilars with reliable high quality.

I would now like to briefly orient to ABP 215, which was developed as a biosimilar to bevacizumab. Let's start with the understanding of the mechanism of action of both products bevacizumab and ABP 215, which limit tumor growth by binding and inhibiting VEGF, or vascular endothelial grown factor, and this is illustrated in the following video.

(Video played.)

DR. MARKUS: The video illustrated the fundamental understanding of the mechanism of action across all uses of these products. That's

the binding and neutralization of VEGF.

I will now move on to the development of ABP 215 as a biosimilar. We followed the four major steps of drug development to provide the totality of evidence, as Dr. Lim described. These data were provided in the briefing book, and it will be highlighted in our presentation.

Finally, a key part to the biosimilar pathway allows a biosimilar to be approved in all indications that the reference product's approved. This is called extrapolation of indications; it's applied with a different approach for biosimilars than innovative products.

For an innovative molecule, extrapolation is generally thought of as understanding the clinical risks and benefits in one population, and applying them to a similar population.

However, for biosimilars, extrapolation refers to the expectation of similar clinical performance in each condition of use for the two highly similar products, the reference product and the biosimilar. Comprehensive similarity is the

foundation for biosimilar extrapolation.

The FDA has issued guidance outlining the elements of the scientific justification to support biosimilar extrapolation, and these have been submitted in detail in the marketing application, and will be discussed at a higher level today.

We will show that ABP 215, and the reference product are expected to have the same clinical performance in any condition of use. ABP 215 is expected to perform comparably in all the indications of use. Hence, Amgen is seeking approval for all the indications not protected by regulatory exclusivity. The proposed indications are shown here.

I now would like to introduce Mr. Hotchin, who will review the analytical similarity of ABP 215.

Applicant Presentation - Simon Hotchin

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

similarity data supporting the approval of ABP 215, as a biosimilar to bevacizumab.

First, I will provide a background on Amgen's approach to ABP 215 product and process design. I will then discuss our approach to assess any analytical similarity before reviewing the data and conclusions.

Let's begin by discussing the development of the ABP 215 cell line manufacturing process and formulation. This background is important because these factors can influence the degree of similarity achieved between a biosimilar and its reference product.

At every step of the ABP 215 development, we were guided by a desire to maximize the similarity of the products. In creating the ABP 215 cell line, we screened a large number of clones before establishing the cell bank. This set the foundation to ensure that ABP 215 would match the critical attributes of the reference product.

With the cell line in place, we then focused on developing the manufacturing process. The

process was designed to consistently deliver a similar product, and changes were minimized during development to reduce the potential for shifts in product quality.

Finally, we developed 100 mg and 400 mg vial presentations that matched the formulation and strength of the reference product.

I will now turn to our approach to assessing analytical similarity. An important first step in designing the assessment was to identify the structural attributes and functional activities that drive the safety and efficacy profile of bevacizumab.

We did this based on a thorough review of the literature and a comprehensive characterization of the reference product. Bevacizumab and ABP 215 are humanized monoclonal antibodies of the IgG1 isotype. Both products have the same mechanism of action in all indications, binding and neutralization of VEGF.

The area of the antibody that binds to all isoforms of VEGF is located in the fragment

antigen-binding or Fab domain, indicated by the circles. Therefore, it was critical to assess the structural similarity of the Fab domain, and similar binding and neutralization of VEGF.

The orange circles indicate the binding domain located in the Fragment crystallizable or Fc region of the molecule. Fc-mediated effector functions do not occur for these products. We nonetheless compared in vitro binding of the Fc domains to confirm similar higher order structure.

Another consideration was the similarity assessment criteria. Amgen engaged with the FDA on this topic throughout the development of ABP 215, ultimately implementing the statistical approach recommended by the agency.

Under this approach, each similarity attribute was evaluated based on the relevance of the attribute to clinical outcomes. For attributes with a highest risk to clinical outcomes, a demonstration of statistical equivalence was required.

The panel on the right shows an example of a

passing outcome, where the confidence interval for the difference in means is fully contained within the equivalence acceptance criteria or EAC set at plus or minus 1.5 times the standard deviation of the reference product dataset.

Two attributes were evaluated using this criteria, and correspond to the primary mechanism of action binding and neutralization of VEGF.

For attributes with relatively lower risk to clinical outcomes, we compared individual results to a quality range established as the mean plus or minus 3 times the standard deviation.

The right panel shows an example of a passing outcome, where at least 90 percent of the lots fall within the U.S. quality range, noted by the dashed lines. Each dot represents the result for an individual lot. The remainder of the attributes were assessed qualitatively. These include attributes of the lowest risk to clinical outcomes and those that do not deliver quantitative results.

Amgen's ABP 215 program was intended to

support global approval, and so we met with the FDA early in development to discuss the reference product requirements for our planned studies. Based on agency advice, we designed our analytical and PK similarity studies to include three pair-wise comparisons to establish the similarity of ABP 215 to the U.S. licensed reference product, and to establish the scientific bridge between the U.S. licensed reference product and bevacizumab procured in the EU.

This scientific bridge confirms that the bevacizumab products purchased in different regions are comparable. The analytical data along with the results of the three-armed PK similarity study, which we will present shortly, established a scientific bridge between the U.S. and the EU bevacizumab. We therefore, performed the lung cancer study as a two-armed study using EU source bevacizumab.

As seen here, the analytical assessment was comprehensive, and actually pretty difficult to fit on a slide, but it included approximately 100

attributes/assay combinations evaluating similarity between ABP 215 and bevacizumab. On the following slides I will summarize the results.

I'll start with the evaluation of structural and purity attributes. Throughout this section, a checkmark indicates that the predefined assessment criteria were met. I will discuss the small number of minor differences observed.

Importantly, sensitive modern analytical techniques will identify differences between a biosimilar and its reference product. The question is whether these differences have the potential to be clinically meaningful?

The primary structure analysis included assays to assess amino acid sequence and glycosylation. Shown on the right, are the results of the reduced peptide mapping analysis. In this method the protein is enzymatically digested, and the resulting mixture of peptides analyzed by HPLC.

The similar profile of the peptide peaks supports the conclusion that the products have the same amino acid sequence. The glycosylation

profile was similar between the products, but we did observe some minor quantitative differences.

Specifically, ABP 215 had a slightly higher level of glycosylation, and high-mannose. However, significant differences in glycans could be relevant to Fc mediated-binding and PK; however, the differences we observed were small, Fc medicated effector functions do not occur for these products. As you will see shortly these was no impact to PK.

We also assessed higher order structure, and particles and aggregates. For higher order structure we assessed the similarity of the secondary and tertiary structure; no differences were observed.

As an example here are the results of the near UV circular dichroism assessment. This method provides information on the overall three-dimensional confirmation of the protein, and the overlapping spectra indicate that the products have similar higher order structure. We used a variety of methods to assess aggregates, as well as

particles of different size ranges and morphologies. No differences were observed.

Shown here are the results of microflow imaging of proteinaceous particles greater than or equal to 5 microns. As you can see, all results met the assessment criteria, noted by the dashed line.

Let's now turn to product-related substances and impurities. The main product-related substances and impurities for ABP 215 are size variance and charge variance. We assessed these attributes using highly sensitive techniques, confirming the presence of the same species in both products.

With respect to size variance including low, medium, and a high molecular weight variance the levels are low in both products and on average lower in ABP 215 than in the reference product. Since size variance are typically viewed as impurities, having slightly lower levels in ABP 215 is not considered clinically meaningful.

Focusing on the charge variance, on the

right are the results of the cation and exchange chromatography analysis. This method separates proteins according to their surface charge, which can be influenced by the presence of variants such as deamination and c-terminal lysine.

As you can see, the overall peak profiles were similar, although there were differences in the acidic and basic peak areas. We therefore, performed additional characterization to identify the charge variance driving these differences.

Based on the characterization, we determined that the differences observed in the basic peak resulted from higher levels of c-terminal lysine and proline amidation.

The differences in the acidic peak were the result of quantitative differences in two deaminated species and N-terminal glutamic acid cyclization. Levels of these species were slightly lower in ABP 215.

These charge variants are all present in the reference product, and have also been observed in endogenous proteins and other monoclonal antibody

drugs without noted concerns for PK safety or immunogenicity. They are not within the regions of the molecule responsible for VEGF binding, and no impact to functional activity was observed.

All of the general pharmaceutical properties of the formulation were similar. Notably, the protein concentration results are within the assessment criteria and support a conclusion that ABP 215 and the reference product have the same strength.

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

The similarity assessment for functional activities was comprehensive. We extensively assessed the mechanism of action mediated by the binding and neutralization of VEGF. We also conducted Fc mediated characterization, as this informs the overall structural similarity of the

antibodies.

I will focus on the critical function activities today, but importantly all assessments of VEGF binding and neutralization demonstrated similarity.

Binding to VEGF is critical to the mechanism of action because it prevents downstream signaling. Shown here, the results clearly demonstrate the similarity of VEGF biding between ABP 215 and the reference product. We also assessed the results of this assay by the statistical methodology recommended by the FDA.

On the bottom, the confidence interval for the difference in means for the three pair-wise comparisons is contained within the EAC demonstrating equivalence, which establishes similarity and supports the scientific bridge.

To add some context, variability of plus and minus 10 percent is very good for this type of assay, which provides additional confidence that ABP 215 is similar to the reference product and tightly controlled.

In addition to assessing binding to VEGF, we evaluated the ability to inhibit VEGF-induced proliferation in a primary cell line expressing VEGF receptors. The data clearly established similarity, and as shown again, equivalence was also demonstrated in each of the three pair-wise comparisons.

Here is the overall outcome of the analytical similarity assessment with results meeting the similarity criteria in green, and those where minor differences were observed in orange. Similarity was demonstrated in the overwhelming majority of the attributes.

As expected, a small number of minor differences were observed, but these were not considered clinically meaningful based on the outcomes of the additional characterization and functional testing performed.

To conclude, the results of the analysis established the similarity of ABP 215 and the reference product. Importantly, similarity was demonstrated in all of the functional activities

that address the single mechanism of action that is relevant in all indications binding a neutralization of VEGF.

ABP 215 is highly analytically similar to the reference product, and the results support scientific extrapolation to all proposed indications.

Now, Dr. Markus will continue our presentation.

Applicant Presentation – Richard Markus

DR. MARKUS: Thank you. We have shown the analytical similarity, I will now review the non-clinical development program; I will then review the clinical development program, and also present scientific aspects supporting extrapolation to the additional indications of bevacizumab.

Our non-clinical program included a four-week toxicology study in cynomolgus monkeys. We assessed a 50 mg per kilogram dose administered intravenously twice a week, comparing ABP 215 to U.S. sourced bevacizumab. The 50 mg per kilogram dose was the highest dose evaluated in the

reference product development program for a study of this duration.

The study findings included the expected microscopic finding of physeal dysplasia of the femur, and this was similar in incidence and severity in both groups. There was no unexpected toxicity.

We conducted three additional non-clinical comparative studies; two were human tumor xenograft studies, one using the A431 epidermoid tumor model, and the other using the Colo205 colon cancer model.

Both of these studies were dose response evaluations testing two dose levels of both products, and also included an IgG1 negative control. Both studies showed similar inhibition of tumor growth and tumor vasculature at each dose level for both products.

The third study evaluated vascular permeability in a cell line overexpressing human VEGF using four dose levels and an IgG1 negative control, and this too showed similar activity of the two products. The briefing document included

details on the studies showing the similar pharmacology activity of the two products.

So, we added similar toxicology and similar dose response antitumor effects in the non-clinical models to the evidence of similarity.

We will move on to clinical pharmacology. We conducted the PK Similarity Study in adult male, healthy volunteers, as this is a sensitive population to detect a difference in PK, if a difference exists. Healthy volunteers provided homogeneous population without concomitant medications or disease factors that could decrease the ability to detect a difference if one exists.

The study included a single dose of 3 mg per kilogram administered intravenously, and then 85 days of extensive PK follow-up. Bevacizumab exhibits linear kinetic properties between 1 and 20 mg per kilogram, so any dose in that range would have been appropriate for this study and we selected the relatively low dose of 3 mg per kilogram to minimize the exposure to healthy subjects.

They key endpoints were C-max -- that's the maximum serum concentration, and AUC or the area under the concentration time curve calculated from zero to infinity; and also the AUC calculated to the last observed value.

Consistent with the FDA guidance, the standard bioequivalence margin was used, and this is the 90 percent confidence interval for the ratio of geometric means must fall entirely within the range of 80 percent to 125 percent.

The study was designed with three arms, comparing ABP 215 to bevacizumab sourced from both the U.S. and EU. It was conducted in two sites, one in each region. This three-way comparison provides additional support for the scientific bridge, such that the clinical confirmation study can be conducted as a two-arm comparison, and satisfy both the U.S. and EU agencies.

The primary results are shown here. You can see that ABP 215 has a nearly identical PK clearance as bevacizumab. The figure on the right shows ABP 215 compared to U.S.-sourced bevacizumab

met the prespecified equivalence margin to allow us to conclude PK similarity.

Additionally, the PK similarity to EU sourced bevacizumab, and between the two sources of bevacizumab was demonstrated. All comparisons are within the standard bioequivalence margin of 80 percent to 125 percent. This, along with the analytical comparisons previously discussed, completes the scientific bridge of U.S. and EU sourced bevacizumab.

Finally, the safety assessments showed similar type, frequency, and severity of adverse events. There were no serious adverse events, and no subjects developed anti-drug antibodies.

We have demonstrated pharmacokinetic similarity adding clinical pharmacology to the totality of evidence.

We will now move on to the clinical confirmation of biosimilarity. The purpose of the clinical similarity study is to directly compare the biosimilar with the reference product, evaluating efficacy, safety, and immunogenicity. A

biosimilar study is not intended to reestablish clinical efficacy or safety; instead the goal is to confirm there are no clinically meaningful differences.

In designing the study we considered the different conditions of use of bevacizumab. We looked for a large magnitude of response in order to be able to detect a difference, if the difference exists.

For the primary endpoint we needed a sensitive measure of the product's activity, and we determined that the best study design to assess biosimilarity was to evaluate tumor response in advanced non-small cell lung cancer.

The study was a randomized, double-blind study of ABP 215, compared to bevacizumab when used in combination with carboplatin and paclitaxel in advanced non-squamous, non-small cell lung cancer. The study was a global study, and subjects were to receive 6 cycles of investigational product, that being ABP 215 or bevacizumab, and 4 to 6 cycles of chemotherapy according to local standards of care.

After the sixth dose, represented by the downward arrows, subjects were followed for adverse events for 21 days, and that was the end of the treatment phase. Then, subjects remain on study for observation of survival or progression-free survival events until the end of the study or until they receive any other anti-cancer treatment such as maintenance therapy, again according to local standards of care. If they receive any additional anti-cancer treatment, then that is the end of the study for that subject.

The study ended when the last subject enrolled completed their treatment phase. The primary endpoint evaluated the ratio of the objective response rate for ABP 215 divided by that for bevacizumab.

The secondary endpoints evaluated the difference of the objected response rates, as well as progression-free survival, and duration of response for those subjects who had an objective response. The safety endpoints were adverse events and serious adverse events, overall survival, and

development of anti-drug antibodies.

The primary analysis was based on the objective response rate or ORR, and this can be either a complete response or a partial response. Importantly, the assessment of tumor response was based on CT scans evaluated by an independent central radiology review.

Prior to beginning the study, we had multiple collaborative meetings with the FDA to finalize the study design including the population, endpoint, and the prespecified equivalence margin for the ratio of responses to be 0.67 to 1.5.

Near the time of completing the study, the FDA suggested a revised margin or 0.73 to 1.36 for the ratio of responses. It was too late in the study execution to make any changes, but I will show you the results according to both margins.

It's important to note that the entire confidence interval for the ratio must fall within the equivalence margins, and the prespecified margin generally required the ORR difference to be less than 6 percent.

The study was well-conducted with an expected number of subjects in each group completing all scheduled doses. Considering all subjects were also receiving chemotherapy with carboplatin and paclitaxel.

Here you can see the overall accounting of discontinuations. The primary reason in both arms was due to disease progression. Discontinuations due to adverse events, were as expected and predominantly related to chemotherapy.

The two treatment groups were well-balanced with respect to demographics with the mean age of 61 years, and approximately 40 percent in each group were 65 years or older, and 60 percent in each group were male.

The two treatment group disease characteristics were also comparable, with approximately 92 to 94 percent in each group being stage 4, and 6 to 7 percent in each group entering the study with recurrent disease.

Approximately 12 percent in each group reported weight loss of 5 to 10 percent within the

six months prior to enrolling, 40 percent had an ECOG performance status of zero, and 60 percent had an ECOG performance status of 1.

The primary results are shown here, and they are the results of the independent radiology evaluation of the ITT or intent-to-treat population. There's an objective response in 128 out of 328 subjects in the ABP 215 group, compared to 131 out of 314 in the bevacizumab group. This is a response rate of 39 percent and 41.7 percent with overlapping confidence intervals.

The primary endpoint results in a ratio of 0.93, and a confidence interval for the ratio of 0.8 to 1.09. This is a tight confidence interval, and clearly well within the prespecified equivalence margin and the FDA's revised margin.

In addition to assessing the rate of tumor responses we also evaluated the magnitude of the responses, as shown here in this waterfall plot. Each subject is represented by a vertical line, and the length of the line represents the maximum change in the size of their target lesions. The

shape and dimensions of the two plots are nearly identical, demonstrating a similar reduction in tumor size between the two products.

Secondary endpoints, shown here, include the difference in response rates, and this is again the ITT population with independent radiology evaluation. The result is a difference of 2.9 percent, and a confidence interval of minus 9.26 to 3.45 percent.

Progression-free survival was calculated, though keep in mind the study was not designed to reestablish the overall or long-term progression-free survival, as the study did not include maintenance treatment and if subjects went on to maintenance therapy then that ended the study for the subject.

Thirty-nine point nine and 39.8 percent of the subjects in the respective groups had a PFS event while on study. The resulting Cox proportional hazard ratio is 1.03, and a confidence interval of 0.83 to 1.29.

Finally, we also determined the duration of

response for those subjects who had a tumor response. Thirty-four percent of those in each group who had a response subsequently had disease progression, and hence, had determined a duration for their response. The median time for duration of response was 5.8 months, compared to 5.6 months. So, overall the secondary endpoints also show similar efficacy of the two products.

Here you can see the Kaplan-Meier curve for progression-free survival. The curve represented within the blue shaded box is the controlled treatment period of a study with the 6 cycles of treatment.

After this period, there was censoring for any subject who received additional anti-cancer treatment. The curves are overlapping for the controlled treatment period of the study, and then the curves crisscross afterwards, with the overall hazard ratio being 1.03.

I will now share the safety and immunogenicity results of the study. The adverse events were similar for the two products; this was

terms of type, frequency, and severity.

Moving left to right you see the percentage of the subjects in each group who experienced an adverse event, an AE of grade 3 or greater, a serious adverse event or SAE, a fatal AE, and finally an AE leading to discontinuation of ABP 215 or bevacizumab. In each case the rates are similar between the two groups.

There are known warnings or risks of bevacizumab, and these form the prespecified events of interest. Key events of interest with at least grade 3 in severity are shown here. This includes neutropenia, hypertension, venous and arterial thromboembolic events, gastrointestinal perforation, pulmonary hemorrhage, and infusion reactions.

As typical in a large randomized trial, there are small numerical differences in both directions with no pattern or signal, confirming similar safety between the two groups.

Very few subjects developed anti-drug antibodies in either group. This was expected, as

bevacizumab is not inherently immunogenic.

Four subjects in the ABP 215 group and 7 in the bevacizumab group developed binding anti-drug antibodies after baseline. Three of these subjects in each of the groups had only transient antibodies; that is they had a positive test at some point during the study, but were negative at the end of the study. Finally, no subject in either group developed neutralizing antibodies.

We have now added similar efficacy, safety, and immunogenicity to the totality of evidence in support of licensure of ABP 215 as a biosimilar. The data showed ABP 215 is highly similar to bevacizumab with no clinically meaningful differences.

I would now like to discuss the extrapolation of safety and efficacy of bevacizumab to ABP 215. The basis for the extrapolation involves two main concepts; the first is similarity between products, and we just presented the totality of evidence establishing ABP 215 is highly similar to bevacizumab.

The second concept of extrapolation involves the scientific consideration specific to the conditions of use. The scientific aspects begin with the mechanism of action in each type of cancer being treated. Then also considers potential differences in PK distribution and clearance across the conditions of use.

Finally, clinical considerations such as efficacy, safety, and immunogenicity, if there are differences in the different types of cancers. Thus, biosimilar extrapolation leverages the product knowledge of efficacy and safety of the reference product and applies it to the biosimilar.

The increased expression of VEGF by tumors leading to increased growth of the tumors, associated with increased tumor vasculature, and vascular permeability is common across all proposed indications.

We know the mechanism of action, regardless of tumor type or location is the binding and neutralization of VEGF and we showed a high degree of similarity between the two products. The

mechanism of action of bevacizumab and ABP 215 is binding to VEGF-A and neutralization of downstream signaling for all uses of the products.

We demonstrated highly similar pharmacokinetics in two different populations, specifically, a very sensitive assessment of bioequivalence in healthy volunteers assessing 3 mg per kilogram, and also in the clinical study with repeat doses of 15 mg per kilogram.

The box-and-whisker plot on the right demonstrates the PK trough similarity in the lung cancer study measured at weeks 13 and 19. These two studies showed similar exposures in the 3 mg per kilogram and 15 mg per kilogram doses (all of the clinical doses of 5, 10, and 15 mg per kilogram used in the various indications).

Bevacizumab is administered at the different dose levels and frequency depending on the type of tumor being treated, and this commonly aligns with corresponding chemotherapy. Importantly, the PK properties of bevacizumab do not change when used to treat the different types of tumors at the

different frequencies or doses.

This figure shows the PK characteristics as reported in different pivotal studies for bevacizumab in lung cancer, colorectal cancer, and breast cancer. Specifically, the different study means represented by the circles, and the standard deviations of the volume of distribution, and the clearance rate at steady state are consistent across the different uses.

Finally, the consistent PK properties across indications were concluded from a population PK analysis of bevacizumab including data from 15 studies in the various solid tumor populations. We know the PK characteristics for bevacizumab do not differ if administered at different doses, as used for different types of tumors, and with the pharmacokinetic equivalence shown, we also expect similar characteristics of ABP 215 across the various dosing regimens.

There are known safety observations with bevacizumab, and these are considered anti-VEGF toxicities. In general, we expect these risks

regardless of the specific tumor type or location, and these were evaluated in our lung study where we did have each of these events and they occurred with similar frequency and severity in the two treatment groups.

The safety considerations are generally consistent across uses. Events may take place at different frequencies in the different populations depending on other anti-cancer treatments and tumor location. But, the lung cancer study demonstrated the expected anti-VEGF toxicities to inform the expectation of similar risks for ABP 215 as for bevacizumab in all the indications.

The extrapolation of bevacizumab to ABP 215 is supported given the products are highly similar, the common mechanism of action across types of tumors, consistent PK distribution and clearance, a low risk of immunogenicity in all uses, shared key safety risks, and a lack of additional clinical considerations for efficacy.

In summary, bevacizumab and ABP 215 are expected to have the same risks and benefits in all

uses. Therefore, we are proposing approval in the indications listed here.

I would now like to introduce Dr. Lisa Bollinger, who will provide Amgen's overall conclusion for ABP 215 as a biosimilar.

Applicant Presentation – Lisa Bollinger

DR. BOLLINGER: Hello. My name is Lisa Bollinger, vice president of Amgen's Regulatory Affairs and Safety. I will summarize the data package presented today in the context of the legal and scientific framework required for the approval of a biosimilar.

As presented earlier by Dr. Lim, the statutory definition of a biosimilar consists of two main pillars. First, the biosimilar candidate must demonstrate that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components.

To this end, Amgen has generated a comprehensive analytical similarity data package, and demonstrated that ABP 215 has the same

structure and function as the reference product bevacizumab.

Second, it must be demonstrated that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

The clinical data package presented today has clearly established that ABP 215 has equivalent pharmacokinetics, efficacy, safety, and immunogenicity as the reference product. Thus, it has been demonstrated that the statutory requirements for establishment of biosimilarity have been met.

Once biosimilarity has been established, the PHS Act also allows the biosimilar sponsor to seek licensure for multiple indications. To do so, the claim of biosimilarity should be supported by data from at least one clinical study in an appropriate indication.

This requirement was fulfilled by a robust, double-blind clinical study comparing the efficacy, safety, and immunogenicity of ABP 215 to

bevacizumab in patients with advanced non-squamous, non-small cell lung cancer. This is a sensitive population allowing for the detection of potential differences between these products.

Additionally, the FDA has outlined the concepts to be addressed in the scientific justification for extrapolation. Amgen has addressed all of these required components. Thus, Amgen has fulfilled the legal and scientific requirements to support approval for all indications sought.

Finally, Amgen has a longstanding commitment to the field of oncology, and ABP 215 will allow more patients to benefit from this therapy. Our commitment to patients continues after approval through the life of a product with a strong focus on safety and availability. We intend to utilize the same pharmacovigilance system for our biosimilar products, as for our innovative products, ensuring the safety of our patients.

Amgen also remains committed to the high-quality and reliable product supply that

patients and physicians have come to expect. ABP 215 presents a high-quality biosimilar option for oncology patients. Thank you.

DR. ROTH: Thank you Dr. Bollinger. We'll now proceed with the presentations from the FDA, and we'll begin with Dr. Jee Chung as lead.

FDA Presentation - Jee Chung

DR. CHUNG: Good morning. I am Jee Chung from the Office of Biotechnology Products, and I am the product quality reviewer for ABP 215, the proposed biosimilar product to U.S. licensed Avastin.

After a brief introduction, I will discuss the review of the analytical similarity data. First, I would like to introduce the FDA review team and they are shown on this slide. Today's speakers are highlighted in bold characters and consist of myself for product quality, Dr. Wang for quality statistics, Dr. Casak for clinical, Dr. Yuan for clinical statistics, and Dr. Chow for clinical pharmacology.

The applicant, Amgen, submitted a Biologics

License Application or a BLA under Section 351(k) of the Public Health Service Act for ABP 215, a proposed biosimilar to U.S. licensed Avastin.

The applicant is seeking licensure for metastatic colorectal cancer; non-squamous, non-small cell lung cancer; glioblastoma multiforme; metastatic renal cell carcinoma; and cervical cancer indications approved for U.S. licensed Avastin.

Consistent with the principles outlined in the FDA guidance documents and previously discussed by Dr. Lim, the applicant provided the data, which the FDA reviewed, and determined that ABP 215 and U.S. licensed Avastin are highly similar notwithstanding minor differences in clinically inactive components.

Clinical data obtained in healthy subjects for pharmacokinetics and in patients with non-small cell lung cancer support a demonstration that there are no clinically meaningful differences between ABP 215 and U.S. licensed Avastin. The totality of the data support the applicant's claim that ABP 215

is biosimilar to U.S. licensed Avastin.

Today's presentations will follow the outline as shown on this slide. Now I will present the review of the analytical similarity study the applicant conducted to support a demonstration that ABP 215 is highly similar to U.S. licensed Avastin. Dr. Wang will also present the results from FDA's statistical analysis used to support FDA's conclusions.

U.S. licensed Avastin is the reference product manufactured by Genentech. It is a humanized IgG1 monoclonal antibody expressed in the mammalian cell culture system, and targets vascular endothelial growth factor family member A.

A schematic structure of IgG1 representing ABP 215 is shown in the upper right corner. As shown in the figure, the IgG1 molecule consists of two light and heavy chains linked by disulfide bonds. The FAB region binds to the target antigen, and the Fc region contains the N-linked glycosylation site that plays an important role in antibody stability, half-life, and effector

functions.

We would like to note that although U.S. licensed Avastin and ABP 215 are IgG1 antibodies, because the target is mostly soluble, they do not exhibit effector functions. Therefore, the mechanism of action for U.S. licensed Avastin and ABP 215 is to prevent VEGF-A from binding to VEGF receptors 1 and 2, that are involved in angiogenesis, which is required by many tumors such as colon and lung cancer cells for survival and proliferation.

The applicant's analytical similarity program included a comparison of three products; ABP 215, U.S. licensed Avastin, and EU approved bevacizumab. The analytical similarity program had two goals. First, a comparison of the proposed biosimilar product ABP 215 to U.S. licensed Avastin to support a demonstration that it was highly similar to U.S. licensed Avastin.

Second, parallel comparisons of ABP 215, U.S. licensed Avastin, and EU approved bevacizumab were needed to support the analytical portion of

the scientific bridge between the three products. The scientific bridge is needed to justify the relevance of the data generated using EU approved bevacizumab as the comparator in the non-small cell lung cancer clinical study to support a demonstration of biosimilarity to U.S. licensed Avastin.

This slide shows the product quality attributes assessed by the applicant to support a demonstration that the products are highly similar. The attributes can be grouped into 8 categories and includes structure, both primary and higher order, glycosylation, biological activities looking at both the FAB and Fc portion of the molecule, product-related species, drug product attributes, and stability profile of the products.

For some attributes, the applicant used multiple orthogonal methods, then measured the same critical quality attributes, but from different perspectives and using different methodology.

The applicant used a total of 19 ABP 215 drug product lots to assess the analytical

similarity to U.S. licensed Avastin. The 19 drug product lots were derived from 13 independent drug substance lots, and included lots used in the clinical studies and from the proposed commercial process.

I would like to note that all 19 drug product lots were used only to assess attributes affected by the drug product manufacturing process, for example drug product volume. For all other product quality attributes the statistical analysis focused on independent lots and did not include drug product lots that originated from the same lot of drug substance.

Both drug product strengths, for which the applicant is requesting approval, were represented in the analytical similarity assessment. Not every quality attribute was evaluated using all the lots identified in this table. The number of lots analyzed for each quality attribute was justified by the applicant.

Now, the applicant's approach for data analysis included, first, a risk assessment of each

quality attribute to determine the criticality of the attribute to impact biological activity, pharmacokinetics, pharmacodynamics, and safety including immunogenicity. Based on the risk assessment and other considerations such as method capabilities, each product quality attribute was assigned to 1 of 3 tiers of statistical analysis.

As shown in the table on the right; tier 1 uses equivalence testing, tier 2 uses quality ranges such as mean plus or minus standard deviations to set the acceptance criteria, and tier 3 uses graphical comparisons. FDA's assessment also included independent statistical analysis of the applicant's data.

Now I would like to introduce Dr. Wang, to discuss the results of the equivalence testing.

FDA Presentation - Tianhua Wang

DR. WANG: Good morning. My name is Tianhua Wang, the CMC statistical reviewer. I'm going to present the results of statistical equivalence testing for tier 1 quality attributes.

The assays that assessed as a primary

mechanism of action were tested using equivalence testing. There are two tier 1 quality attributes tested using equivalence testing. The first one is percent of relative potency, as assessed by a proliferation inhibition bioassay. The second one is VEGF-A binding by ELISA.

First, let's talk about the statistical equivalence test. For tier 1 quality attributes, the equivalence test is used to determine whether the mean difference between test and the reference product is within the equivalence margin. Let sigma-R be the standard deviation of reference product, which can be estimated for lots of reference product that the applicant characterized. Then the null hypothesis is that the mean difference is either less than or equal to a negative 1.5 sigma-R, or greater than or equal to a positive 1.5 sigma-R.

And the alternative hypothesis is that the mean difference falls within the range from negative 1.5 sigma-R to positive 1.5 sigma-R. Test of the reference passed the equivalence test if in

equivalence test plot the 90 percent confidence interval for mean difference, showing as blue segment, falls within the equivalence margins marked by two vertical lines.

This plot shows the data set for relevant potency assessed by a proliferation inhibition bioassay. That was used by for the first tier 1 equivalence testing. There were 27 EU approved bevacizumab lots, 13 ABP 215 lots, and 24 U.S. licensed Avastin lots.

Pair-wise comparisons were used for the assessment of relative potency. From the pair-wise comparisons between ABP 215 versus U.S. licensed Avastin, ABP 215 versus EU approved bevacizumab, and EU approved bevacizumab versus U.S. licensed Avastin.

All three comparisons, the 90 percent confidence intervals for mean difference are within the equivalence margins. The relative potency passes the equivalence testing.

This plot shows the data set for VEGF-A binding by ELISA that was evaluated using tier 1

equivalence testing. There were 13 EU approved bevacizumab lots, 13 ABP 215 lots, and 14 U.S. licensed Avastin lots.

Again, pair-wise comparisons were used for the assessment of VEGF-A binding by ELISA. From the pair-wise comparisons between ABP 215 versus U.S. licensed Avastin, ABP 215 versus EU approved bevacizumab, and the EU approved bevacizumab versus U.S. licensed Avastin, all three comparisons, the 90 percent confidence intervals for mean difference are completely within the equivalence margins. The VEGF-A binding by ELISA passes the equivalence testing.

In summary, pair-wise comparisons for both tier 1 quality attributes pass the equivalence testing. This supports a demonstration that ABP 215 is highly similar to U.S. licensed Avastin, and also supports the analytical portion of the scientific bridge to justify the relevance of EU approved bevacizumab data from the comparative clinical study.

This concludes the equivalence testing for

tier 1 quality attributes. I would like Dr. Chung to continue. Thank you.

FDA Presentation - Jee Chung

DR. CHUNG: I will now present additional assessment of the analytical similarity studies conducted for ABP 215. This slide summarizes the overall analytical similarity assessment based on the data provided by the applicant.

To summarize, ABP 215 has the same primary structure as U.S. licensed Avastin. In addition, the higher order structure and biological activity data support the conclusion that the protein folding is similar between the two products, and similar stability profiles were observed in the two products over a variety of temperature storage conditions.

Some slight differences were observed in product-related species such as charge and size variants. Additionally, the glycosylation pattern of ABP 215 was demonstrated to be slightly different as well. These are represented by hashtags in the table on the slide.

In each case the differences were assessed, and where necessary functional assays were used to evaluate the potential clinical impact. The data provided showed that the differences did not impact product performance, and thus, do not preclude a demonstration that ABP 215 is highly similar to U.S. licensed Avastin.

Although the data are now summarized here, the three pair-wise comparisons of quality attributes between ABP 215, U.S. licensed Avastin, and EU approved bevacizumab were also analyzed with these attributes and support the analytical portion of the scientific bridge needed to justify the relevance that the data derived from the EU approved bevacizumab in the comparative clinical study.

In the next few slides, I'll provide examples of the applicant's justification that these differences between products did not influence ABP 215 product performance.

As I showed in the summary table on the previous slide, differences in some quality

attributes were observed between ABP 215 and U.S. licensed Avastin that had the potential to impact the demonstration of highly similar to U.S. licensed Avastin. Specifically, differences were detected in the level of galactosylated and high mannose N-linked glycans binding to Fc gamma IIIa receptor aggregates, fragments, and charge variants.

In all cases, the differences were studied using orthogonal techniques to assess biological activity known to be influenced by such differences. As examples I'll present the case that differences in the glycan map and charge variants resulted in no differences in biological activity between products.

This slide shows a comparison of the glycan maps for three lots each of EU approved bevacizumab shown in blue, ABP 215 in red, and U.S. licensed Avastin in black. The overlays on the right show that each lot has a similar profile with the same glycans present in consistent, but slightly different amounts, as shown on the left.

Graphs on the left depict levels of individual glycans; the red bars reflect the quality range proposed by the applicant. ABP 215 has a slightly higher amount of galactosylated and high mannose N-linked glycans, and falls outside the quality ranges of the U.S. licensed Avastin.

As described in the literature, galactosylation of monoclonal antibodies can affect the in vivo biological activity. Specifically, glycans known to affect clinical performance include galactosylation, in which terminal galactose residues affects binding to complement protein C1q, and influenced complement-dependent cytotoxicity or CDC activity and high-mannose forms can increase monoclonal antibody clearance, and subsequently affect the pharmacokinetic profile of the product.

In addition, high-mannose forms can affect binding to Fc gamma IIIa receptor, and result in enhanced antibody-dependent cellular cytotoxicity or ADCC activity.

As previously mentioned, the mechanism of

action for bevacizumab is not expected to include either ADCC or CDC activities. Nevertheless, as part of the analytical similarity assessment the applicant performed in vitro cell-based ADCC and CDC activity assays, and found that, as expected, all three products did not mediate ADCC or CDC activities.

These results coupled with the results from the PK similarity data, further address the residual uncertainty and showed that the differences observed in galactosylation and high-mannose levels between the three products were unlikely to have clinical impact.

This slide shows a comparison of the charge variants for 3 lots of EU approved bevacizumab, ABP 215, and U.S. licensed Avastin. The chromatographic overlays on the right show that each product has a similar profile with the same peaks present in consistent but slightly different amounts, as shown on the left. ABP 215 has a lower amount of acidic peaks, and consequently higher amount of mean and basic peaks. Levels of these

peaks were shown to fall outside of the U.S. quality ranges.

It is understood from literature that charge variants can result from post-translational modifications of monoclonal antibodies and from the manufacturing process. Examples of charge variants detected as acidic or basic species include product degradants, such as deamidated or oxidized species, sialylated glycan N- and C-terminal variants, such as monoclonal antibodies or C-terminal lysine residue.

In order to determine the impact of the differences, the applicant isolated and characterized fractions containing enhanced levels of acidic and basic peaks from all three products. This characterization showed the same types of product variants were present for all three products, albeit in different amounts. To evaluate differences in basic variants, the applicant analyzed samples with and without carboxypeptidase, an enzyme that cleaves C-terminal lysine residues.

This experiment confirmed the mean

difference in levels of basic variants was due to higher levels of residual C-terminal lysine residue in ABP 215.

Based on literature reports differences in the levels of C-terminal lysine residue of monoclonal antibodies, administered by the intravenous route, are not expected to impact product performance as it is typically removed in vivo shortly after administration.

Characterization of the acidic variants demonstrated that even dramatically enhanced levels had minimal impact on product potency. These results coupled with in vitro potency results in clinical PK data support the conclusion that differences in the amount of charge variants do not have clinical impact.

In conclusion, the totality of the analytical similarity data supports a conclusion that ABP 215 is highly similar to U.S. licensed Avastin, notwithstanding minor differences in clinically inactive components.

Additionally, the pair-wise comparisons of

ABP 215, U.S. licensed Avastin, and EU approved bevacizumab support the analytical portion of the scientific bridge between the three products needed to justify the relevance of the data generated using EU approved bevacizumab in the comparative clinical study.

Now I will invite Dr. Chow, who will discuss the results of the clinical pharmacology studies.

FDA Presentation – Edwin Chow

DR. E. CHOW: Good morning. My name is Edwin Chow, the clinical pharmacology reviewer for this application.

The clinical pharmacology programs aim to support the demonstration of no clinically meaningful differences between ABP 215 and U.S. licensed Avastin by evaluating the single dose pharmacokinetic similarity between ABP 215 and U.S. licensed Avastin, and establishing the PK portion of the scientific bridge between ABP 215, U.S. licensed Avastin, and EU approved bevacizumab.

This slide outlines the clinical study completed by the applicants, and reviewed by the

FDA. As indicated in the red box, the applicants conducted study 216 to evaluate PK similarity between ABP 215, U.S. licensed Avastin, and EU approved bevacizumab.

Study 216 was a randomized, free arm, parallel group study in healthy male subjects following a single 3 mg per kilogram IV dose. The PK similarity results of this study are summarized in the next slide.

The figure on the left depicts the concentration time profile for each product. The X-axis represents the times and day post-dose of the product and the Y-axis is the bevacizumab mean serum concentration in nanograms per mL.

As you can see upon visual inspection, all three concentration time profiles appears to be virtually superimposable. Statistical analysis is shown in the right figure, which depicts the geometric mean ratio for the test versus the reference product and their corresponding 90 percent confidence interval for each pair-wise comparison.

The X-axis is the predefined similarity margin of 0.8 to 1.25, which is represented by the vertical dashed line. The Y-axis represents each pair-wise comparison. The PK endpoints of AUC zero to infinity, AUC zero to last, and C-max are represented by the triangle, circle, and square symbols respectively.

In the first pair-wise comparison for ABP 215 versus U.S. licensed Avastin, highlighted in the blue box, the geometric mean ratio and their corresponding 90 percent confidence intervals for all three PK endpoints of AUC zero to infinity, AUC zero to last, and C-max falls within the predefined similarity margin of 0.8 to 1.25.

Likewise, in pair-wise comparison of ABP 215 versus EU approved bevacizumab the geometric mean ratio and the corresponding 90 percent confidence interval for all three PK endpoints of AUC zero to infinity, AUC zero to last, and C-max fall within the predefined similarity margin of 0.8 to 1.25.

Lastly, in pair-wise comparison of EU approved bevacizumab versus U.S. licensed Avastin,

the geometric mean ratio and their corresponding 90 percent confidence interval for all three PK endpoints of AUC zero to infinity, AUC zero to last, and C-max again fall within the predefined similarity margin of 0.8 to 1.25.

Based on the result from study 216, we conclude that the PK similarity was demonstrated.

In summary, results of study 216 demonstrate PK similarity between ABP 215 and U.S. licensed Avastin. Study 216 also established a PK portion of the scientific bridge between ABP 215, U.S. licensed Avastin, and EU approved bevacizumab, which justified the relevance of the comparative clinical data with EU approved bevacizumab in study 265.

In conclusion, the PK results support a demonstration of no clinically meaningful differences between ABP 215 and U.S. licensed Avastin, and add to the totality of the evidence to support a demonstration of a biosimilarity of ABP 215 and U.S. licensed Avastin.

This concludes the clinical pharmacology

presentation. Dr. Yuan will now present the findings from the comparative study 265.

FDA Presentation – Weishi Yuan

DR. YUAN: Good morning. I am Vivian Yuan. I'm the statistical reviewer for the comparative clinical study in this application. I am here to present the analysis and the results of the comparative clinical study of this BLA.

The goal of the comparative clinical study in the biosimilar exercise is to resolve residual uncertainties and to support a demonstration of no clinically meaningful differences between the proposed biosimilar product and the reference product. The study is not designed to solely demonstrate efficacy of the proposed biosimilar product.

A statistical equivalence test for similarity is used to establish evidence that there are no clinically meaningful differences. The objective of the test is to show the proposed biosimilar is neither superior nor inferior to the reference product by demonstrating that the

difference between the two products lies within prespecified margins. Margins are tools, in such that they rule out what is considered to be clinically meaningful differences between the two products.

Several factors are considered when selecting a similarity margins. These include the reference product effect size estimated from prior studies; constancy -- the assumption that the estimated effect size of the reference product is similar in the current comparative clinical study setting; and other design characteristics such that power, sample size, and the residual uncertainties given what is known about the products.

This is the schema of the study, as Amgen presented. We're referring to the study as study 265 based on an adequately established scientific bridge between the U.S. licensed Avastin, EU approved bevacizumab, and ABP 215.

This study was conducted using EU approved bevacizumab to further assess if there are clinically meaningful differences between ABP 215

and the U.S. licensed Avastin. A total of 642 patients were randomized, with 322 in the ABP 215 arm and 314 in the EU approved bevacizumab arm.

The primary endpoint is the objective response rate ORR, as assessed by central, independent, blinded radiologist based on the recessed version 1.1. ORR as a measurement of the pharmacological action of the biologic has been accepted by the FDA as the primary endpoint for this study. Secondary endpoints included the original response and progression-free survival.

According to the applicant's protocol, the primary objective of the study was to compare the 90 percent confidence interval of the risk ratio of ORR between ABP 215 and EU approved bevacizumab to similarity margins of 0.67 to 1.5. If the confidence interval of the risk ratio of ORR is within these margins, the study results support a demonstration of no clinically meaningful differences between ABP 215 and the reference product. The study was designed with 95 percent power.

FDA's approach to determining the similarity margins differed from the applicant's. FDA issued a letter with recommendations for the similarity margins in December 2014, but as discussed at the meeting held in January 2015, at that time, the study had completed enrollment.

FDA acknowledged that this request of change could not be implemented due to logistics and the timing of the request. FDA stated that the applicant's margins for study 265 would be considered in the context of the totality of the evidence. As shown here, FDA conducted statistical analysis of study 265 using both the applicant's and FDA's margins.

In this slide, I discuss the FDA's margin selection. The first step was to estimate the treatment effect of bevacizumab. A meta-analysis was conducted based on four historical trials that compared bevacizumab plus chemotherapy versus chemotherapy alone.

A total of 1675 patients were included in the meta-analysis, with 810 in the chemotherapy

alone arms and 865 in the bevacizumab plus chemotherapy arms. It was estimated that the ORR for the bevacizumab plus chemotherapy was 37.7 percent. The risk ratio of chemotherapy alone versus bevacizumab plus chemotherapy was 0.53 with 95 percent confidence interval 0.45 to 0.63.

Based on the meta-analysis result and the clinical considerations, the margins 0.73 to 1.36 were selected. In other words, the null hypothesis of the study is that the risk ratio of ORR is either smaller than 0.73 or greater than 1.36. The alternative hypothesis is that the risk ratio of ORR lies between 0.73 to 1.36.

If the result of the study rejects the null hypothesis, the study would be considered to have demonstrated that the experimental product have no clinically meaningful differences compared with U.S. licensed Avastin.

This table presents the primary analysis of the study. There were 128 responders in the ABP 215 arm and 131 in the EU approved bevacizumab arm. Each of the two arms had two complete

responders, and the rest were partial responders. The response rates were 39 percent in the ABP 215 arm, and 41.7 percent in the EU approved bevacizumab arm. The ORR observed in the EU approved bevacizumab arm was comparable to the 37.7 percent generated by historical data.

This is a graphic illustration of the test for similarity using the margins derived by FDA. The observed 90 percent confidence interval of the ORR ratio, which is 0.80 to 1.09, falls within the FDA's selected margins of 0.73 to 1.36, as well as the margins specified by the applicant, which were 0.67 to 1.5.

This result supports a demonstration of no clinically meaningful differences. FDA's analysis on secondary endpoints agrees with the applicant's results.

In summary, objective response rate was accepted by FDA as the primary endpoint because it is sufficiently sensitive to assess for clinically meaningful differences. FDA's similarity margins were selected based on historical data, and the

clinical considerations.

The results of the comparative clinical study showed there are no clinically meaningful differences between ABP 215 and the U.S. licensed Avastin. This concludes my presentation. Next, Dr. Casak will present.

FDA Presentation – Sandra Casak

DR. CASAK: Good morning. My name is Sandra Casak, and I am the reviewer for this application. As you can see in this outline I will briefly touch upon FDA's review of safety; the agency's position on the scientific justification for extrapolation, following the principles summarized by Dr. Lim earlier today; and conclude with a summary of the agency's analysis of similarity.

FDA's analysis of the safety of study 265 concurs with Amgen's analysis. The toxicities observed in study 265 occurred with a similar incidence between arms, and this was similar to the expected incidence of other events describing other studies and the Avastin USPI. There were no new safety signals, and we conclude that there were no

meaningful differences in safety between study arms.

As listed in this slide, Avastin is licensed for the treatment of metastatic colorectal cancer, non-small cell lung cancer, renal cell carcinoma, GBM, cervical and ovarian cancers in different lines of treatments and with different chemotherapeutic partners. Please note that Amgen did not seek licensure for the ovarian cancer indications, and that these indications currently have orphan exclusivity.

As we heard today, the ABP 215 program provided clinical data from the study in patients with non-small cell lung cancer. The agency has determined that it may be appropriate for biosimilar product to be licensed for one or more conditions of use each indications, for which the reference product is licensed based on data from clinical studies performed in another condition of use. This concept is known as extrapolation.

How does extrapolation work? If a biological product meets the statutory requirements

for licensure as a biosimilar product under the PHS Act, the applicant needs to provide sufficient scientific justification of extrapolation, which should address, for example, the following issues; for the tested and extrapolated conditions of use, the mechanism of action if known in each condition of use for which licensure is sought; the PK and biodistribution of the product in different patient populations; the immunogenicity of the product in different patient populations; differences in expected toxicities in each condition of use and patient population; and any other factor that may affect the safety and efficacy of a product in each condition of use and patient population for which licensure is sought.

Amgen has provided justification for the proposed extrapolation of clinical data in study 265 in non-small cell lung cancer to each of the other indications approved for U.S. licensed Avastin, for which Amgen is seeking licensure.

As summarized by the applicant and FDA, there are extensive characterization data

demonstrating that ABP 215 is highly similar to U.S. licensed Avastin. To justify the extrapolation of the data in non-small cell lung cancer to other indications, for which Amgen is seeking licensure, let's go through these points.

I don't have a video, but I would like to emphasize some concepts. The bevacizumab binds VEGF in all indications, which prevents interaction of VEGF with its receptors VEGFR-1 and 2 on the surface of endothelial cells.

Naturalizing the biological activity of VEGF induces regression on the neovascularization of tumors, normalizes remaining tumor vasculature, and it limits the formation of new tumor blood vessels, thereby limiting tumor growth. In each approved indication the mechanism of action of bevacizumab is to inhibit VEGF induced angiogenesis and to restore vascular permeability. Again, this is done because the antibody binds in all indication of VEGF-A.

The applicant submitted an extensive analysis of the role of VEGF and VEGF inhibition in

each one of the indications, for which licensure is sought. FDA agrees that there is no evidence to support claims of a unique mechanism of action in any specific indication.

In addition to the data characterized in the PK profile of bevacizumab we heard in previous presentations, the PK profile of bevacizumab following the IV infusions ranging from 0.1 mg per kilogram to 20 mg per kilogram were evaluated in several dose escalation and dose finding published studies in a variety of solid tumors.

In these studies, as well as in several experimental PK models, the PK properties of bevacizumab appear to be consistent across different indications. There are no interactions observed between bevacizumab and chemotherapy. Most variations in the PK of bevacizumab are related to weight and gender.

Overall, the FDA considers that study 216 adequately demonstrated similarity of PK among ABP 215, U.S. licensed Avastin, and EU approved bevacizumab. Since similar PK was demonstrated

between ABP 215 and U.S. licensed Avastin, a similar PK profile would be expected for ABP 215 in patients across indications being sought for licensure.

The incidence of anti-drug antibodies observed with U.S. licensed Avastin is very low. As described in the Avastin USPI, only 14 of 2,233 evaluated patients or 0.6 percent, tested positive for treatment emergent anti-bevacizumab antibodies, and the clinical meaning of these antibodies is unknown.

The analysis of studies 216 and 265 indicate that immunogenicity was similarly low for ABP 215, which was comparable in the study to EU approved bevacizumab and to historical results with U.S. licensed Avastin. The expected toxicities of bevacizumab are well-characterized and are summarized in the Avastin USPI, as well as multiple meta-analysis of earlier clinical studies in various solid tumors.

While the incidence of specific toxicities may defer a cross indication -- for example fistula

formation is more frequent in patients with cervical cancer, while hemoptysis is more frequent in patients with non-small cell lung cancer -- due to the common mechanism of action, the different toxicities are predictable in each indication for which licensure for ABP 215 is sought.

Data from study 365 demonstrated that the type and incidence of treatment emergent adverse events of special interest were similar for ABP 215 and bevacizumab, and that there were no clinical meaningful differences between arms. No new safety signs were identified that would be indicative of new toxicities for the approved bevacizumab indications.

Finally, classic anti-VEGF-related toxicities, such as hypertension and bleeding, occurred in the ABP 215 clinical studies and were comparable to the rates of anti-VEGF-related toxicities of EU approved bevacizumab. These toxicities clearly demonstrated that ABP 215 binds to VEGF and induces a pharmacodynamic effect.

In summary, we conclude that based on the

totality of the data including analytical and PK similarity, as well as no meaningful differences in anti-tumor activity, safety, and immunogenicity and considering that there were no known differences in the mechanism of action, PK, immunogenicity, and safety across different indications, the FDA believes that the extrapolation of biosimilarity to the indications for which Amgen is seeking licensure is scientifically justified.

To summarize FDA's presentation our review of this application, we conclude that analytically ABP 215 is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. Analytic and PK data support and justify the use of data obtained form study 265 using EU approved bevacizumab.

The PK data support a determination of biosimilarity. Data from the analytical and scientific bridge and anti-tumor activity, safety, PK, and immunogenicity data from study 265 in patients with non-small cell lung cancer demonstrate that there are no clinically meaningful

differences between ABP 215 and U.S. licensed Avastin.

Extrapolation of data supporting approval of all indications, for which the applicant is seeking licensure, is scientifically justified. Again, like U.S. licensed Avastin, ABP 215 binds VEGF in all conditions of use. The totality of the data submitted support a claim that ABP 215 is biosimilar to U.S. licensed Avastin.

These are the issues we would like the committee to discuss today: Discussion point number 1, please discuss whether the evidence supports a demonstration that ABP 215 is highly similar to U.S. licensed Avastin, notwithstanding minor differences in clinically inactive components.

Discussion point 2, please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP 215 and U.S. licensed Avastin in the studied condition of use.

Discussion point number 3, please discuss

whether there is adequate scientific justification to support licensure for all of the proposed indications.

The voting question is, does the totality of the evidence support licensure of ABP 215 as a biosimilar product to U.S. licensed Avastin for each of the indications, for which U.S. licensed Avastin is currently licensed and for which the applicant is seeking licensure as listed in this slide?

This concludes the FDA presentation. Thank you.

Clarifying Questions to Presenters

DR. ROTH: Thank you Dr. Casak. We'll move on now to clarifying questions, both for the agency and for the applicant. If you have a question, comment please just let Jay know here, and we'll try to take these in order.

Maybe I can start off -- and I suppose for Dr. Markus, with reference to 216, remind me, there were some patients who received reference maintenance product after completion of the trial?

DR. MARKUS: In the lung --

DR. ROTH: Yes.

DR. MARKUS: In the lung cancer study, no. If patients received maintenance therapy then they would be censored, that ended the study for that patient.

DR. ROTH: And the implications of that for your secondary endpoints of duration response and progression-free survival, how was that dealt with statistically?

For those patients, and how many were there per arm?

DR. MARKUS: Yes, so for those patients, again, they were censored effectively at the time for which they went on to any other anti-cancer treatment.

DR. ROTH: Okay. Do we know the balance per arm of how many patients there were?

DR. MARKUS: Yes, so maybe Dr. Hanes, want to discuss the number of patients who were censored for maintenance therapy?

DR. HANES: Yes, so approximately 50

subjects, they were censored for continuation of a commercial bevacizumab. Those subjects, they continued outside of the study and were censored.

DR. ROTH: I'm a little slow with statistics, as Dr. Cole knows, so at that point the patients were responding and their response stopped, statistically?

DR. MARKUS: So, Dr. Snappin probably could address if you'd like -- if you're asking about what happened for an analysis --

DR. ROTH: Yes.

DR. MARKUS: -- with the censoring, so discuss the censoring of the patients for the PFS and the duration of the response?

DR. ROTH: Correct. You can define whatever you want; I just wanted to make sure that things are balanced between the two arms in terms of whatever you decide to do with those patients statistically.

DR. SNAPPIN: Steve Snappin from biostatistics. You're correct. At that time, when the patients receive maintenance therapy they would

have been censored from the analysis.

So they're counted in the analysis up until that point, no longer counted from that point forward.

DR. ROTH: Okay. Thank you.

Dr. Nowakowski?

DR. NOWAKOWSKI: Grze Nowakowski. Just a clarifying question, maybe to the applicant and also to FDA; we are referring here to two different Avastins or bevacizumabs, if you would; the EU approved bevacizumab, and U.S. licensed Avastin. It looks like both products were compared in study 216, the PK study, in the clinical study the EU licensed bevacizumab was compared, and presumptively because the study was conducted in Europe, from the PK study from the 216 study it looks like those products are the same.

Are there any known meaningful differences between the U.S. licensed Avastin versus EU approved bevacizumab?

DR. FUCHS: Okay. Chana Fuchs, FDA. So, based on the analytical similarity assessment,

there were no clinically meaningful differences. I think you saw the data, but that's what we found.

DR. LEMERY: Yes, so in order to use the EU product in a comparative clinical study, Amgen had to demonstrate both an analytical bridge and a PK bridge which was three-way, so they demonstrated that in essence EU and U.S. product were similar as well.

DR. ROTH: Okay. Greg? Dr. Armstrong?

DR. ARMSTRONG: Two questions, largely regulatory. The first is; as was pointed out by the FDA, one of the indications, which are the ovarian cancer indications, were not part of your application. I realize they were also the most recent ones, and if that's just by the timing of when you submitted your application, but if you are excluding them, why not?

The second part of that question is to the agency. What if in the future, assuming that we approve this for all the current indications, what if there are future indications for bevacizumab? How is that taken into account? Will that

automatically be approved for the biosimilar or will there have to be a separate evaluation for that?

DR. MARKUS: Maybe I'll take the first question, and Dr. Christl will take the second question there. We're not applying for the other indications that still have regulatory exclusivity, so if it's protected by orphan exclusivity then we respect that exclusivity and won't apply for it until that exclusivity expires, and at that time we'll engage the FDA with appropriate scientific justifications.

DR. CHRISTL: This is Leah Christl from FDA. To add further to that, as was noted, Amgen is not seeking licensure for the protected indications. So, their extrapolation argument, the content of their BLA, does not address those indications. That's not part of the consideration for those protected indications.

As was noted, if Amgen did want to seek licensure for those indications that are currently protected by exclusivity, or if the reference

product did add subsequent indications for which they wanted to seek licensure, they would need to come to the agency with a data package that was appropriate to support licensure and those indications. And we would engage with Amgen at that time as to what that data package needed to look like. But, it is not automatic; they would need to seek licensure and provide an adequate application package.

DR. ARMSTRONG: I had a second question, which was, looking at my math, I think there was just under 400 total patients treated, the normal volunteer patients for the pharmacology studies and the patients in the lung cancer study. And certainly I think with new drugs, that would be a very minimal population for safety issues given.

My question really is for the agency, which is, is that a sufficient number of patients given all of the other data showing equivalence, is that a sufficient number of patients for safety purposes?

DR. KEEGAN: With regards to the safety, I

think -- and again, I think you're applying the standards that we would use for a new drug. So, looking at the totality of the evidence, what we needed was sufficient demonstration that there weren't clinically meaningful differences focusing on the immunogenicity. But, looking at the other data as well, we would not require necessarily the same type of safety database that we would for a new drug. And yes, we concluded that it was sufficient.

DR. ARMSTRONG: Thank you.

DR. ROTH: Dr. Chow?

DR. S. CHOW: Basically, I have one question to the applicant. Basically, I think for the analytical similarity assessment, I was wondering whether the lots used for the analytical assessment were the same lots used for the PK and the clinical studies?

DR. MARKUS: Yes, the lots that were used in both studies, the PK study and the lung study, were included in the analytical assessments.

DR. S. CHOW: Thank you. Another question

is -- actually it's not a question it's just a comment, I just want to let the sponsor know that I think the similarity margin for the different indications may be different.

DR. ROTH: Dr. Karara?

DR. KARARA: Question for the applicant, the sponsor. I'm basically looking for an estimate in the lung patients, for clearance and volume distribution. You had a PK component in study 265. If I need to adjust a dose for a patient in an IV infusion, I need estimates for that.

In that study you had trough samples and you showed similarity, but I'm looking for an estimate of clearance because if I want to do any dose adjustment I need to have those values. Did you estimate with the ABP 215, an estimate for clearance and volume distribution in lung patients?

DR. MARKUS: Dr. Chow?

DR. V. CHOW: Vincent Chow, clinical pharmacology at Amgen. We performed the patient study as a confirmation of the PK similarity, which was demonstrated in our PK study in every 1 tier,

so the trough information in the lung cancer study is to serve as the confirmation in PK similarity in patients.

We also have actually done a search of literature that demonstrates that bevacizumab clearance, and one distribution in general is similar across all the patient indications.

DR. KARARA: Yes, I understand that. But for a particular compound, the ABP 215, you had samples from that study. Did you conduct any population pharmacokinetic analysis? That's what I'm asking -- not just a compare in trough values.

DR. MARKUS: The easy answer there is, no. I think with from all the data we've shown, the clearance of bevacizumab we showed equivalent characteristics as bevacizumab, and hence the clearance rate would be presumed the same.

DR. ROTH: Ms. Chauhan? Forgive me about the pronunciation.

MS. CHAUHAN: Yes you did, thank you. I have a question for the company. If I read it correctly, you used only healthy male volunteers?

Why only male and how do you extrapolated from that to female? And, nowhere in any of it did I see that you looked at race, and could you talk about that?

DR. MARKUS: Sure, so we did not include females or women in the PK study because of the potential risk to reproductive organs of this product, so we didn't want to put them at risk during the PK study in healthy volunteers. But, we did look at the women in the lung cancer study, and Dr. Chow can show you the data there.

DR. V. CHOW: In the lung cancer study, we enrolled about 40 percent of the female patients, in which we subset the data from that study.

In this slide we looked at the female subject trough data, and it was monitored throughout those in [ph] duration. In there, we described data use in box-and-whisker presentation. As shown in here, the ABP 215 and bevacizumab trough concentration held constant and similar across the dosing interval.

MS. CHAUHAN: On the healthy population, I'm

going to challenge you a little bit. You said that you did not use women because of reproductive issues. A highly significant number of us are past reproduction. Why did you not consider that population because we also are very susceptible to the cancers.

DR. MARKUS: Sure. We were not trying to recalculate or establish what the PK characteristics would be. It's a comparative evaluation to bevacizumab, that's the fundamental experiment to be conducted.

Often when you do an innovative product that's absolutely correct, and we have to understand are there gender differences? In this product we know what those are, so we're not trying to reprove those differences.

We were looking for a homogeneous population with as little variability as possible in the base of the subjects, so that if there's a difference it would be attributed to the two drugs being tested. So that's why.

MS. CHAUHAN: And could you address race?

DR. MARKUS: So race -- yes, so the majority, a vast majority, of the population of the lung study was Caucasian. But, it was a global study, and it included North America, Europe, Western Europe, Eastern Europe, et cetera. That is predominantly the population of non-squamous, non-small cell lung cancer. We don't have a by race subset because the overwhelming majority was Caucasian.

MS. CHAUHAN: Can I ask one question to the FDA? In your early slides you said that the decision to choose between the brand drug and the biosimilar would not include input from the prescribing physician? I was interested in that.

DR. KEEGAN: I think you're referring to the discussion regarding interchangeability. That status is not part of this application. So this application would require that the prescriber be contacted before a switch.

DR. LEMERY: So a pharmacist could not switch without the notification of the physician.

DR. KEEGAN: Right.

MS. CHAUHAN: Could or could not?

DR. LEMERY: Could not.

DR. ROTH: Dr. Waldman?

DR. WALDMAN: Small question of curiosity for the agency and the sponsor. How come the margins for the clinical efficacy study were different? How come you guys calculated different margins? Not that it makes a difference because it performed within the more conservative margins, but as I read through this I was just curious how you guys came up with different margins?

DR. MARKUS: Yes, I'll start with the address, and then maybe the agency can comment on their view.

But, we did discuss the protocol clearly well before we started. This has been a collaborative journey for over five years now for this program, and before we started the study there was certainly no disagreement, nor a suggestion of a different margin than what we utilized in our protocol, and I'm not sure what actually provoked an invitation to change that in 2014, but as you

said it really didn't matter; the study results were clearly within both margins.

DR. KEEGAN: So we had an evolution in our thinking about how to address the margin over time. We did accept the margin that was proposed, but over time we assessed which would be the appropriate was to set a meta-analysis and which studies might be included based on the historical data.

We refined our thinking, and at the conclusion of that we asked all of the biosimilar applicants looking at developing biosimilars to U.S. licensed Avastin, and approached them. At the point in time when we approached Amgen, they had essentially concluded enrollment in their study.

DR. ROTH: Dr. Schrag?

DR. SCHRAG: A small clarifying question for the sponsor, which is, the outcome of the lung study depends a great deal on response rate, and response rate is influenced by the chemotherapy backbone. Understanding that the doses planned were identical, can you just briefly summarize the

doses actually received? Because it would be even more reassuring to know that those were balanced across the two arms. If I missed that, and you showed that, I apologize.

DR. MARKUS: No we didn't give that detail yet, so Dr. Hanes?

DR. HANES: So, slide up please. The slide is going to show the exposure summary, and I would like to have the chemotherapy slide up. This is the IP slide, but I would like to have the chemotherapy slide.

This slide shows the exposure summary in the two groups, ABP 215 and bevacizumab, and you can see comparable exposure regarding total number of doses administered in the two groups. The median being 5 in both groups, mean 4.5 and 4.7, and the same for subjects receiving -- I mean for the total number of doses administered. So the exposure was comparable in the two groups.

MS. CHAUHAN: [Inaudible - off mic]. And you had the dose intensity the same?

DR. HANES: Yes.

DR. ROTH: Deb, your microphone, if you could talk into that. Dr. Schiel?

DR. SCHIEL: Yes. I actually didn't hear anything discussed about this in the slides today, but it was in the FDA document, the sequence variant, there was an alanine to serine shift. I was curious if the sponsor could comment on the size of that sequence variant present, and what controls are in place to characterize that?

DR. MARKUS: Sure. Mr. Hotchin?

MR. HOTCHIN: Yes. The sequence variance is something that we've seen through the introduction, and it's a much more sensitive aspect technique that really allow us to delve down into those lower levels. We say that sequence variant at a level below 1 percent as a total of the population of the sequences.

In terms of control, we've looked at different population doubling levels of the cell line to confirm its stable and it is stable. We also looked at different process conditions and how they impact on the sequence behavior and its stable

across different process conditions as well, and the control comes from the fact that this is a stably expressed sequence variant that doesn't change over time or with population doublings.

DR. ROTH: Do you have another question Dr. Schiel?

DR. SCHIEL: I do have one more actually. Yes, one other question I had was about the acidic and basic variants.

There was a lot of discussion about the carboxypeptidase treatment, but I'm wondering if fractions that were the main peak, so basically if lower acidic peak fraction have been tested in some of the bioactivity studies and if there is any correlation to potency or immunogenicity?

DR. MARKUS: Mr. Hotchin?

MR. HOTCHIN: I am not sure if we actually looked at smaller sub-fractions of the acidic peak, but I think across -- we have a lot of confidence in the identity of the different variants because, as well as the fractionation, we had a lot of data from peptide map MS that allowed us to really

identify very specifically what the variants were.

So we're confident there's nothing hiding under the main peak that we haven't talked about today.

DR. ROTH: Dr. Mager?

DR. MAGER: Just a small clarifying point. You had cited a population analysis as justification of similar PK across indications, but I don't think in that study that disease was actually tested as a covariant. Are you familiar with whether or not that was done?

DR. MARKUS: Yes. Dr. Chow could address that. There are two aspects to our conclusions about the stability across indications.

The top data that I had there, I recall, was actually from different pivotal studies and data from the prescribing information that showed the clearance rates on volume distribution, and then Dr. Chow can address the population PK.

DR. V. CHOW: In that study, in our population PK analysis, there's 15 studies included in the data planning and data model building, and

among that there's a number of covariants that have been identified. One thing that they did not identify is disease as a variable, so that concluded disease is not part of the important factors that influence the model behavior.

DR. MAGER: So my question was, was it specifically tested?

DR. V. CHOW: Yes, they have looked into whether disease is a factor to the overall variability of the model.

DR. MAGER: Thank you.

DR. ROTH: Dr. Hendrix?

DR. HENDRIX: Yes, I think this is sort of the other side of Dr. Mager's question. I couldn't find data that was presented with regard to the specific tissue distribution or the cancer distribution -- this relates to the extrapolation question -- because the tissue types are quite different, I don't know enough to know if the tumor types are all that different in each of those tissues.

So the question is given what is known about

the minor analytical differences in the two products, in the reference and the proposed product are there anything about those differences that might influence distribution to the relevant tissues on the list of those that are extrapolated?

DR. MARKUS: Dr. McBride?

DR. MCBRIDE: Helen McBride, biosimilars research at Amgen. It's our understanding that the primary site of action for the inhibition of VEGF signaling is maintained within the vasculature, and so I appreciate your point about there being different tissues and the potential for different distribution if the site of action was actually within the tumors.

But again, that site of action is maintained within the vasculature, and so really the volume distribution and other PK proprieties that are already presented are a very good model for assessing the similarity of ABP 215 and bevacizumab.

DR. ROTH: Are there any other clarifying questions? Go ahead.

DR. COLE: Thank you. I wanted to follow-up actually on Dr. Roth's question. I'm not sure that I understood the answer exactly.

I'm wondering if you have progression-free survival without the censoring at a different line therapy? Because it's a blinded study you would expect that things would be really balanced, and how that is done, and I'm was interested to know if you had an analysis --

DR. MARKUS: Yes, make sure I'm understanding because the patients were censored, not just for the analysis, but if they went on to another cancer treatment or maintenance therapy they actually ended the study, so we don't have following data for those subjects. It's not just that we kept them on study and observations and censored that data.

DR. COLE: Okay. So do you know how many times that happened on each of the two arms?

DR. KEEGAN: I think it would be helpful if you put up your progression-free survival curves that denote the number of patients at risk over

time. I think there's -- I'm hearing a misconception about what got analyzed in the PFS data. I don't think this unusual or atypical for what we would do when we're talking about the censoring.

DR. LEMERY: And I think based on the duration of the study, confirm if I'm wrong, is that a lot of the patients were already censored due to the data cutoff date.

DR. MARKUS: That's correct, thank you for that. And slide up. We can review the progression-free survival analysis. Slide up. It may be faint and hard to see, but the blue shaded region is what we call the controlled period of the time, the six cycles of treatment for which all the patients, until they had actually events or progression, are included. And as Dr. Keegan noted, the number of patients are denoted on the bottom row.

You can see after that period, there is a relatively quick drop off due to censoring for the patients that then either went onto another cancer

treatment, whether it was bevacizumab or something else we don't know, but they went onto another anti-cancer treatment --

DR. KEEGAN: Or progressed.

DR. MARKUS: -- the numbers on the bottom denote the maintained risk population.

DR. KEEGAN: But some of those events were progression?

DR. MARKUS: Correct.

DR. KEEGAN: Right. So I think there's a misconception that patients were being taken off therapy prior to the progression events, and it was not my impression that, that occurred, by and large.

DR. MARKUS: Correct, that's correct.

DR. ROTH: Why I'm raising my hand, I don't know, but -- however, I think the discrepancy is if you go onto maintenance therapy that's presumably for continued response, as opposed to starting some different therapy for presumed progression.

So that's where the disconnect is. If you're going to lump those, then what is the true

duration of response, which is different, if you went on to a different drug for progression versus maintenance therapy for presumed continued response.

DR. MARKUS: If they went onto another agent or regimen because of progression they were captured as progressors.

DR. ROTH: But they're captured the same way that someone who goes on maintenance therapy is for an actual biologic continued response.

DR. MARKUS: No. If they had an event -- a progression event for which they then went onto second line therapy for example, that would have triggered them as progressing and they would have then been captured and calculated within the analysis up until the point where the study ended.

If they were continuing as a responder until the study ended everyone, as Dr. Lemery said, was in essence right censored at the time the study ended.

DR. ROTH: Go ahead.

DR. COLE: Okay. I think this might be like

the third or fourth time it's been asked, but we'd like to know the numbers of patients that were censored because of new therapy, not a progression but new therapy, on each of the two arms.

DR. MARKUS: Okay. Dr. Lim do we have a -- we might not have the exact number then of who went on to which therapy. We know if they progressed, they went on to second line treatment for example, then they counted as progressors.

DR. COLE: So you don't have that information?

DR. MARKUS: Not an exact number.

DR. COLE: Because we don't really care which therapy it was, just how many.

DR. MARKUS: Right.

DR. ROTH: Maybe I'll just ask Ms. Keegan if Dr. Cole and I are way off base in our line of questioning here because --

DR. CASAK: There were 7 patients in the ABP arm that were censored because they selected to go to other treatments, so there were 4 patients in the bevacizumab arm. But of those 7 and 4

patients, some of these patients were also on progressive disease.

DR. KEEGAN: We didn't think that people were basically dropping off of the study after the completion of chemotherapy, I think that's the impression you're getting, and that's not the case. They remained on maintenance therapy and data were collected to contribute to the PFS and the duration of response.

DR. ROTH: Okay, thank you. Dr. Gordon?

DR. GORDON: I think the other question then was the number of patients on maintenance by arm. Was that consistent across the arms or similar across the arms?

DR. MARKUS: So when they -- again the number of patients who, as it was pointed out, discontinued due to these was similar between the arms. But I don't have an exact number of how many went onto maintenance.

DR. ROTH: Dr. Moreira?

DR. MOREIRA: Yes, a question to the sponsor. From your briefing document a number of

the assays were based on what we call an internal evidence standard, ABP 215 reference standard. I was interested in knowing what is the source of that standard?

Also, for instance in some data; like on page 9, figure 2, on the relative binding to VEGF, all the lots are actually less than 100 percent. I was wondering if you can perhaps elaborate on why everything relative to the standard seems to be less than 100 percent.

DR. MARKUS: Sure. Dr. McBride?

DR. MCBRIDE: To answer the first part of your question, the lot that's used as the ABP 215 reference standard was an early lot that's representative of the process used throughout the cycle of development for ABP 215.

That was important to us because the similarity assessment takes place over years, and so we wanted to have a lot that we could use consistently to provide a common standard across assays and across time to compare to.

In terms of -- slide up -- I believe this is

the figure you were referring to, in relative binding to VEGF? All right, so for a lot of these assays you'll see this relative measure that's ABP 215, on that day as a reference standard tested, would come up as 100 percent, and then the other lots would be compared to it.

You can see that the cluster is very tight, whether its bevacizumab being compared or ABP 215 as regards to any particular lot that's a pretty standard range and fairly tight cluster for this type of assay. Really, it's the comparison between, in this case, the mean of the distribution between bevacizumab U.S. and ABP 215 we're concerned with, not any particular value, and those were shown to be equivalent.

DR. ROTH: Any other questions? Go ahead Dr. Lagunes.

DR. LAGUNES: Just a quick question to confirm then it does cross a blood brain barrier particularly for indication for GBM, and there was no differences there?

DR. MARKUS: Dr. McBride?

DR. MCBRIDE: There have been no specific distribution studies conducted by the originator for Avastin, as to whether it can cross the blood brain barrier. But again, our understanding is that the site of action is within the vasculature of those endothelial cells, whether they're the microvascular endothelial cells present in the blood brain barrier, or within the lung, or the colon, or another site of action.

So it's our understanding that the distribution, as we've shown, is similar between ABP 215 and bevacizumab. We can't address that specific distribution.

DR. ROTH: Any other questions?

(No response.)

DR. ROTH: Okay, then let's take a break. I have 10:43. Let's reconvene with the open public hearing at 10:55.

(Whereupon, at 10:43 a.m., a recess was taken.)

Open Public Hearing

DR. ROTH: If you'd take your seats, and

let's resume.

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

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

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

If you choose not to address the issue of

financial relationships at the beginning of your statement it will not preclude you from speaking.

The FDA and this committee plays great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

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

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

MR. PHILLIPS: Good morning. My name is Thair Phillips. I'm the president and CEO of RetireSafe, a nationwide nonprofit advocacy

organization for older Americans. I have nothing to declare. I'm here today representing our 200,000 supporters and activists, many of which are patients receiving there new life-extending and life-enhancing medicines being discussed today.

RetireSafe wants both biosimilars and interchangeable products to be successful. That success in a large part depends on the confidence that doctors, pharmacists, and patients have that these products are safe, effective, and accessible.

In past surveys our people overwhelming confirmed that seniors want clear labeling, distinct names, and effective communication between the pharmacist and the doctor. We will continue to focus on safety, effectiveness, and accessibility.

RetireSafe was also encouraged by the draft guidance dealing with interchangeable products that was recently released. The FDA draft guidance deals directly with how substitution would be regulated at the pharmacy including adherence to the doctor's prescription and adherence to the drug's label.

Many states have laws concerning interchangeable products that outline required communication between the pharmacist and the doctor. What is missing in the recent draft guidance is guidance concerning substitution that occurs outside of the pharmacy.

RetireSafe thinks that the FDA cannot continue to maintain patient safety without extending their final guidance to include not only the pharmacy, but the entire supply line.

Today the FDA monitors closely the manufacturing and shipping of pharmaceuticals. They ensure that no ingredient was substituted, no inferior manufacturing methods were used, and that shipping requirements were adhered to. If a biosimilar was substituted for a reference product during shipping, the FDA would immediately take action.

RetireSafe thinks that a similar type of unauthorized substitution is already taking place when a PBM or insurance company removes a reference product from its formulary. This creates a barrier

to access for the patients, and in many cases forces a substitution. A substitution that would not be tolerate at a pharmacy.

We think that the recent change to the Purple Book concerning substitution reveals the intent of the FDA to limit unauthorized substitution, but it focused on the pharmacy rather than on the entire supply line, and therefore, would not limit this outside the pharmacy-type of unauthorized substitution.

If this practice is allowed to continue, not only will the safety of the patient be threatened, but manufacturers will have no incentive to apply for the interchangeable designation.

We believe that, whether through final guidance or through recommendations to HHS or Congress, the FDA needs to aggressively protect the patient's safety by eliminating this type of unauthorized substitution.

RetireSafe wants the increased access so that biosimilars interchangeables offer. We think that ensuring patient's safety at the beginning

will earn the confidence of the patient, the doctor, and the pharmacist and will allow us to realize there promised savings. Thank you.

DR. ROTH: Thank you. Will speaker number 2 please step up to the podium? State your name and any organization that you're representing.

MR. SPIEGEL: Good morning. My name is Andrew Spiegel. I am representing the Global Colon Cancer Association. I have no true conflicts, but in the interest of full disclosure I will disclose that both Amgen, the sponsor, and Roche and Genentech have provided financial support to my nonprofit organization.

Good morning. As I mentioned my name is Andrew Spiegal, executive director of the Global Colon Cancer Association. Today I am also representing the Alliance for Safe Biologic Medicines, an organization I co-founded about seven years ago, which provides the patient and physician prospective and advocate for patient centered policies on biosimilar policy around the globe.

I've been in the colon cancer community

longer than Avastin's been on the market. I remember when colon cancer patients, 20 years ago, had only once choice and metastatic colon cancer was essentially a death sentence.

Fast-forward 20 years later, we now have more than a dozen approved drugs for colon cancer, and the life expectancy of the metastatic colon cancer patient has tripled.

Biologic drugs have not only helped extend the lives of the metastatic colon cancer, but they have helped more than 800 million people worldwide. Therefore, the patient community has a great interest in seeking more biologic medicines come to market.

We're also excited to see biosimilars entering the U.S. healthcare system, but in order to feel comfortable using biosimilars the patient and physician communities want to know that are as safe and they are as effective as the reference products.

Lack of clinical data and insufficient transparency regarding that data can only serve as

obstacles to patients' and to physicians' confidence, and thus, to widespread biosimilar adoption. We know that because biosimilars, by definition, are not identical to the reference product it's important that the FDA insist upon the high safety standards of safety and efficacy when approving biosimilars.

The committee discussed extrapolation earlier, and I want to spend a minute talking about a concern to the patient community. We feel that at a minimum, approval for each indication should be granted individually rather than in an all or nothing approach.

We are not suggesting that safe extrapolation is not possible, nor are we suggesting that it's not appropriate in this situation; we simply feel that each indication should be approved individually based on solid data.

This panel should have the flexibility and not be forced to approve the drug for all or no indications based on extrapolation. This

constraint is not legally required, nor is it in the patient's best interest.

Again, this is not to suggest that there's a lack of data in this application, but more a comment on the overall process. You, committee members, should have the option of approving based on each indication presented. Once approved, informative and transparent labeling that lets us make informed treatment decisions is critical to building confidence and increasing biosimilar use.

Comprehensive data collection on a biosimilar is also of utmost concern. Strong post-market data surveillance improves care and limits risks to the patients. Real world data helps us better understand these medicines, and promote more efficient, safer, and personalized use.

Clear product identification and naming is also critical to ensure safety and confidence in biosimilar and biologic medicines. We agree with the FDA's approach in promoting distinguishable names for all biologics; including both innovator

and biosimilar drugs.

For patients to realize the benefits of biosimilars we need to be confident that our health and our safety remains the primary concern, and we need to be provided with full and accurate information about each individual medication to make informed choices.

Thank you for the opportunity to provide comments.

DR. ROTH: Thank you. Will speaker number 3 please step up to the podium? State your name and any organization that you might represent.

MS. McCASLIN: Good morning. Distinguished members of the Oncologic Drugs Advisory Committee, Dr. Gotlieb, and other esteemed representatives of the FDA, thank you for the opportunity to comment today.

My name is Tiffany McCaslin. I'm the senior policy analyst at the National Business Group on Health. Our members would like to thank the committee for holding this important meeting on Biologics License Application 761028, for ABP 215.

I have no financial disclosures, but in the interest of full disclosure I will indicate that both the sponsor and Genentech are members of your organization.

The National Business Group on Health represents 413 primarily large employers; including 70 of the Fortune 100 who voluntarily provide group health and other employee benefits to over 55 million American employees, retirees, and their families.

Expenditures for specialty drugs are growing faster than any other component of healthcare spend; well above the rate of over a healthcare inflation and far outpacing that of general inflation, overall growth in the economy, and wages.

Moreover the number of drug approvals, spending, and utilization for specialty medicines are projected to overtake traditional pharmaceuticals over the next several years. These trends add to the growing sense of urgency for large employers who are continuing to strategize on

how best to manage growing pharmacy expenditures, and for employees who are paying more out of pocket for these medications.

The Business Group and our members appreciate the opportunity to state for the public record that we strongly support a regulatory environment that favors the robust uptake of high-quality, safe, and efficacious biosimilars.

Like generic drugs, which reduce U.S. spending by $227 billion in 2015 alone versus the amount that would have been spent had there been no alternatives to brand medications, biosimilars have the potential to increase competition in the market, which will help lower the overall spending for biologic medicines and increase patients' access to biopharmaceutical advances that increase the quality and length of their lives.

Current estimates suggest that consumers could save as much as 250 billion during the first 10 years of biosimilar availability, over what they would spend in absence of competition with brand biologics.

While we appreciate the complexity of competition among large molecules, and that it differs from that of small molecules, we support the notion that, in general, competition fosters innovations that have the potential to redefine markets and benefit patients.

We know that the availability of generic drugs has reduced drug prices and increased patient access to medicines, and we believe that competition in this marketplace may be able to do the same.

Biosimilar competition for market share is expected to lead to lower prices and better patient access to these products, and further as more biosimilars become available we believe that these benefits will only expand.

To this end, we support the direction that FDA has laid out with regard to biosimilar development requiring demonstration that a biosimilar demonstrate biosimilarity to a reference product, and believe that the FDA has put in place the appropriate safeguards to permit data

extrapolation. Thank you for the opportunity to comment.

DR. ROTH: Thank you. Speaker number 4 please step up to the podium. State your name and any organization that you're representing.

DR. CRYER: Good morning. My name is Dr. Dennis Cryer. I'm here today representing the Biologics Prescribers Collaborative. Our members include professional organizations with numerous biologics prescribers.

The BPC is a project of the Alliance for Patient Access, and thus, I am representing their views here as well. I have no financial or other conflicts of interest.

Yesterday you reviewed an innovative breakthrough therapy in oncology. Today you are considering the safe and effective replication of other innovative therapies through the development of biosimilars.

BPC supports policies that promote the fully informed and safe use of biologics; including biosimilars for all patients. The collaborative

encourages the FDA to finalize several biosimilar policies or refine existing final guidances, as well as to thoroughly review biosimilar applications through the AdCom process.

BPC believes that there are four key policy issues that will encourage the development of biosimilar products while protecting patient safety and satisfying the prescriber's need for transparent medical data.

In this session, my comments will address just two of these policy issues. First policy point; biosimilar product labeling, the package insert must contain all necessary data for physicians to make appropriate prescribing decisions for their patients.

The label is a critical tool for physicians to make prescribing decisions, and manage potential adverse events. Thus, it is of utmost importance that any drug label be complete and accurate. The label should include a statement of whether the biosimilar is interchangeable with the reference product and/or other biosimilars on the market.

The label should provide either a summary of the full clinical data submitted and supported by a similar approval or a hyperlink to the FDA's summary basis of approval. Prescribing physicians do want access to this information.

Finally, the label should ensure that all mentions, via the reference biologic or the biosimilar, should include both the proprietary name, if available, and the non- proprietary name.

Second policy point; the FDA should proceed with caution when considering application requests for indication extrapolation. Even though one biologic medicine has been proven effective in multiple disease states, it does not necessarily follow that a biosimilar product will have the same effect or efficacy. As such, BPC urges caution in approving indications for diseases for which no clinical data are produced.

Thank you for the opportunity to share our perspectives on issues critical for both the safe use of biosimilars, as well as other biologics. The BPC looks forward to continuing to work with

the FDA to ensure patient safety and physician confidence as more biosimilars are developed. Thank you.

DR. ROTH: Thank you. Speaker number 5, could you please step up to the podium, state your name and any organization that you represent?

MR. ATOUF: Good morning. My name is Fouad Atouf. I represent the United States Pharmacopeia. I don't have any financial disclosure to make here; however, I will state that both the sponsors of the biosimilar product and the innovator, as well as other companies, support the standard process at USP by providing expertise, but also samples and materials to develop the standards.

On behalf of USP, I would like to thank the agency for the opportunity to comment of the approval application for the proposed biosimilar for Avastin bevacizumab.

USP is an independent scientific nonprofit organization dedicated to protecting and improving public health. We collaborate with the FDA and other stakeholders to develop pubic standards and

related programs to help ensure the quality, safety, and benefit of medicines and foods.

USP supports FDA's effort to broaden access of safe and effective biosimilar product. Biologics medicines, such as Avastin, have transformed quality of life for a patient with chronic conditions and as more biosimilar products come to market, increased competition will provide more treatment options and better patient access for life sustaining medicines.

USP recognizes and applauds FDA's substantial work to advance the successful implementation of the Biologics Price Competition and Innovation Act, BPCI. We support FDA to develop their regulatory pathway while addressing very complicated scientific challenges and implementation challenges as well.

This regulatory pathway, created in collaboration with industry and other stakeholders, provides confidence to healthcare providers, patient caregivers, and the public that approved biosimilar product is a quality medicine that

delivers benefits consistent with the originator product.

USP remains committed to working collaboratively with the agency and other stakeholders to fulfill BPCI's promise, and while USP has a longstanding program in biologic standards development, we're now focusing on a paradigm that would primarily emphasize on the development of standards for raw materials used in biological manufacturing, as well as performance standards to keep pace with the dynamic product developmental landscape.

Performance standards are physical reference standards that support biological analytical testing for quality specification throughout the product life cycle. The standards are used to ensure and demonstrate the amount of effectiveness, as well as process performance throughout the various steps of the process development and manufacturing operations. The standards are broadly applicable to product families or classes opposed to specific drug substance of drug product.

USP is dedicated to working with the FDA and the industry to ensure that performance standards support product quality throughout the biological product life cycle. Thank you very much.

DR. ROTH: Thank you. Speaker number 6, if you'd step up to the podium; introduce yourself and any organization that you might represent.

DR. GEWANTER: Good morning, thank you committee members for the opportunity to speak today. My name is Dr. Harry Gewanter. I'm a pediatric rheumatologist with over 30 years of experience treating children and youth with rheumatic diseases and other chronic illnesses.

I'm the current chairman of the Alliance for Safe Biologic Medicines or ASBM, and they are sponsoring my presence today. ASBM's and organization of patients, physicians, pharmacists, researchers, manufacturers of both innovator and biosimilar products, including Amgen and Genentech, and others dedicate to ensuring patient safety remains the forefront of all biosimilar policy discussion.

Our members include multiple cancer patients advocacy groups, including several representing those with colorectal and kidney cancer; two of the indications for which this proposed biosimilar for bevacizumab is seeking approval.

Biosimilars, as we know, provide opportunities for increased access to more life-altering treatment options at a reduced cost to both the patient and society. We support the FDA's history of intense and appropriate scrutiny of all medications both at time of application, as well as throughout its lifespan. It's the only way to produce the high level of confidence necessary for biosimilars to be fully accepted and utilized by patients and their physicians.

Since repetition and redundancy improves retention, I'm going to be supporting many of the comments that you've already heard this morning. We believe that approval of biosimilars should be decided on a case-by-case basis for each individual indication, rather than supporting a sufficient extrapolation to all indications. This committee,

and all committees, should have the opportunity to decide.

Clear product identification is critical after approval to ensure safety, and add confidence in biologic medicines. We strongly support distinguishable names for all biologics, innovator and biosimilar alike.

We believe the FDA should use its role as the world's leading regulator, to work with the World Health Organization, to advance the WHOBQ's proposal, and establish an international 4-letter suffix system.

The BQ's proposal is critical for global pharmacovigilance, and we hope that the FDA would also encourage other regulatory authorities, for example, Health Canada and Australian TGA, to do the same.

We believe that unique, extensive, transparent, and up-to-date labeling is vital to ensure patient and provider confidence in these products. Our multiple surveys, both in the U.S. and abroad confirm that over 80 percent of

prescribers agree with this position.

Comprehensive data collection on a biosimilar should not end with its approval. Strong post-market surveillance data improves care and limits risks. The FDA's leadership through post-approval pharmacovigilance will improve care, promote more efficient, safer, and personalized use, as well as provide further confidence in these important medications.

Thank you for your diligence on behalf all the American public, and I appreciate the opportunity to provide our perspectives on this important issue. Thank you.

Questions to the Committee and Discussion

DR. ROTH: Thank you. Did speaker 7 show? No. Then the open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

The committee will turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed to the questions, as you've previously seen, if we could put those up. Let me read these again for the record.

Question 1. Please discuss whether the evidence supports a demonstration that ABP 215 is highly similar to U.S. licensed Avastin, notwithstanding minor differences in clinically inactive components.

Question number 2. Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP 215 and U.S. licensed Avastin in the studied condition of use.

Number 3. Please discuss whether there's an adequate scientific justification to support licensure for all the proposed indications, and I think we can discuss these three simultaneously.

So analytically similar, clinically similar, extrapolation to the other approved indications for Avastin. Again, if you'd make known your -- if you want to make a comment to Jay, we'll take these in order. Dr. Hendrix.

DR. HENDRIX: For me the first two are pretty straightforward and well developed within the context of the clinical data that's presented, and I only have a theoretical question about the other. I just don't know if there's enough data to make the judgment.

I asked the question specifically about, and they provided an answer that the question was about compartments related to extrapolation. The video that they showed, which was delightful, showed two different mechanisms -- and I'm just basing this on the cartoon that they showed us, two mechanisms for the neovascularization.

There was neovascularization by extension, for which the plasma compartment is certainly the best model and that would -- except for the blood -- except for the central nervous system tumors that is on the list, that would make sense for all of the tissue types for which they are proposing an indication. But, there were also little islands that were near the tumor, in the movie. If that's important, there is some

requirement for the drug to go as extravascular and have some impact.

Now, I have no idea if the tumor biologists know if that's important or if everything is direct extension, for which case I'm 100 percent satisfied that the plasma models are useful and can be extrapolated into all the other tumor types other than the ones for which there was a convincing clinical study, speaking as a non-oncologist.

It's just a theoretical concern about that, and that's only important in the subset of the very small number of differences in the molecules, which were described as being not -- it's right here, it's clinically inactive.

In terms of impacting the VEGF, and I think the arguments were thoughtful and in my mind conclusive, it was clinically active in terms of if it can get to the point of interacting with the VEGF. But if it can't get to wherever the VEGF is creating new vessels then some of those minor differences could be important.

Does the mannose content, or does the glycan

map differences, or the charge variant differences, can those impact distribution into tissue?

It's a sequence of theoretical questions, and I don't know if anyone else on the panel has sufficient understanding of the biology or the pharmacology of distribution into these local compartments to make some judgment about that.

So it's just -- I'm stating this as a concern of a type, but I just don't have enough information. I don't know the tumor biology because I'm not a tumor biologist.

DR. ROTH: Is your concern about all the other indications, or specifically about glio in terms of --

DR. HENDRIX: Well, I think glio is the standout, and I think the committee member to my left -- when Diane asked the very targeted question -- and I think that's appropriate because there, in particular, some of these thing may be important.

I have no reason to believe any one of these three differences that were clearly listed and

explained away in terms of VEGF interactions, but getting to the compartment is an issue. My biggest concern would probably be glio, but I don't know if it's not relevant in the same way in any of the other tissues.

There isn't the same kind of protected barrier, and yet this large -- this antibody may or may not penetrate as well. I have no idea how much of a difference it could be -- it's somewhere between probably nothing and small. So it's really a question to the rest of the committee if you can allay my theoretical concerns?

DR. ROTH: Dr. Chow?

DR. S. CHOW: At the first beginning, I think the -- a little bit concern regarding the analytical similarity assessment because they are around 50 percent of the critical quality attributes in the category of the product-related substance and impurity, they show some kind of minor differences.

But later on, I see the PK similarity and also the clinical similarity, and I pretty much

cease my concern. But the problem is that I think -- I was wondering whether these minor differences, how these translate to the other indication.

For example, when we're trying -- we identified these minor differences, but I think that we want to extrapolate a list for across the different indication. How the differences may translate to the clinical safety and efficacy regarding the other indications.

DR. ROTH: Dr. Mager?

DR. MAGER: So I'm not a tumor biologist, but I'd like to talk about the extrapolation issue. I asked my clarifying question only as a means of clarifying what was actually presented and what was done, but I've made the argument in the past that even if the pharmacokinetics were different between indications that still would not preclude the conclusion of biosimilarity.

There are biologics for which the pharmacokinetics will be different from one indication to another due to, for example,

expression of the target, there may be differences in expression and turnover, et cetera. However, if the molecule is considered biosimilar, if it's past the analytical piece, it's past the pharmacokinetic comparison, then it too should then be similarly different across indications.

So I think they've shown that molecular similarity there were some residual uncertainties that showed, but I think that was dispelled and when you look at the pharmacokinetics that were comparable and when you look at the safety and immunogenicity. So I think those minor differences ended up not being clinically meaningful.

Once you make the bridge that it is molecularly biosimilar, including PK and the totality of the evidence, then it should have similar interactions at that site.

I think your question is a very good one, and very important. I think it goes actually to the innovator, right? It goes to whether that innovator product is going to be able to get to the site and do all of those things, but I think what's

presented here is, are these two molecules highly similar? And if they are similar, then it will share those same challenges that the reference product will have to phase.

I think once you've shown that molecular similarity and I think once you've shown within one clinical indication very similar safety and efficacy, then it would follow and have the same safety and efficacy in those other indications.

DR. ROTH: Dr. Kozlowski?

DR. KOZLOWSKI: Yes. To follow-up on this comment about minor differences and could they impact other indications, the model, as Dr. Lim talked about, you start out with a foundation of analytical similarity. You may have some differences -- there's a little bit of residual uncertainty, and then you go on to other studies.

I think as you indicated yourself, where you're starting from are these minor differences potentially going to matter? And I think, again, we may not know the exact impact in terms of distribution of everything. But just to think

about this in terms of mass, some of the differences were high-mannose, so going from a little less than 1 percent to 2 percent.

For that to matter across indications, you'd have to postulate that most of one indication is done by 1 or 2 percent of the reference product material.

I think when you put all that together, the fact that we don't have prior knowledge that these attributes matter clinically, that many of the differences we can figure out -- for instance, our C-terminal lysine, which should not matter for these, matter for these products. Some of these differences are such a small mass amount of the product that even if they did matter in some way, it should not matter unless they were the only important part of the product, which really would be extremely unlikely.

I think it's this model of you have a bit of residual uncertainty from these differences. You also put into context that reference products have lot-to-lot variability, as indicated by Dr. Lim

too, that those small differences should matter so much that they would change the impact and indication where the basic biology of blocking VEGF interactions is the same.

DR. ROTH: Dr. Moreira?

DR. MOREIRA: Yes, I was also thinking about this issue of variability, and how much do we know and what is the impact? Certainly the numbers we were given are very good. It's a very good story that has been laid out for us and good rationale.

The question is, how do we know how much can be a problem? We really don't know. And as Dr. Kozlowski was also elaborating on, in that sense, I think that's part of continuing to learn scientifically about these questions.

But to me, what I think makes sense is that I see from the FDA's report or briefing that they have reviewed the information, they have looked at the validation of the manufacturing process, and have found it to meet the requirements from the agency in terms of that process being controlled and validated.

Even if there were lots of product that perhaps could have a different composition of some impurity, this will be taken care of by the validation and by the specifications that are put around in process controls and final product release.

So in that sense, I feel that there is a good way of assuring that within what we know, the product will be biosimilar in my view in terms of its characteristics that we have seen.

DR. ROTH: DR. Waldman?

DR. WALDMAN: Yes, just to add to the discussion, particularly a friendly amendment to Don Mager's comments, I think we heard during the presentation a meta-analysis that separated the effects of the drug from the tumor or compartment from the type of tumor.

So that consistency of clinical efficacy and pharmacokinetics, regardless of what the tumor compartment is, gives some small amount of comfort that the tissue penetration issue is probably not a major component of the activity of the drug since

it doesn't seem to matter where the tumor is, specifically for the innovator drug.

DR. ROTH: Ms. Chauhan?

MS. CHAUHAN: I'm sorry I lost my thought -- I have a question on question 3, can we separate out glioblastoma? Does it have to be all or nothing?

DR. ROTH: Put the agency's perspective out there.

DR. CHRISTL: Right. So the discussion question is framed in a way to allow the committee to opine on extrapolation, and we would expect that the discussion would address the different indications and get your opinion on that.

The voting question is structured as it is because it's the request to the agency for what Amgen is seeking licensure for, and so we're asking the committee to specifically vote on the content of the application, which would include all of the indications. But we wanted to offer an opportunity to the committee to have a discussion, which is why question 3 is written as it is in terms of a

discussion.

MS. CHAUHAN: Okay, thank you. I have two more. Is there discussion or are there plans for post-marketing studies of efficacy and safety?

DR. KOZLOWSKI: When we approve a biosimilar, we approve it because we assume the standards for biosimilarity have been met. However, for all products we want to have pharmacovigilance for all biological products and all products in general.

As you've heard in some of the public comments, the ability to identify and track these products in the marketplace is very important to the agency, and we will want to have surveillance on these products, but not different than any other biological product because any product we want to understand what happens in the marketplace.

MS. CHAUHAN: Okay. My last question is, and I'm going to try to frame this is that I don't move outside of the FDA's purview, but it was brought up by several of the speakers too.

Let's say the biosimilars go to market and

let's say there is a significant price differential, there's a real issue with insurers who will refuse to pay for certain drugs once they know there's a cheaper alternative.

My concern is the safety and efficacy as we go along, how do we account for or do we have concerns about a rush to change that is not based on science but on other issues?

DR. KEEGAN: Our thoughts with approval of the biosimilar is that we have determined that it is safe and effective, that there's no clinically meaningful differences between this and the U.S. licensed Avastin, the reference product. Therefore, we don't see those as risks.

We will continue pharmacovigilance, but the understanding would be with an approval of a biosimilar, you accept that this is safe and effective based on the biosimilarity standard, right, because there's no clinically meaningful differences.

DR. ROTH: Any other comments? Sorry. Dr. Armstrong?

DR. ARMSTRONG: Just because of the issues being raised about the glioblastoma, I guess like the commercial, I'm not a neuro-oncologist but I am in the clinic at the same time as the neuro-oncologist, so you end up soaking up some information.

Any time you're considering these large molecules, that issue of blood brain barrier is always an issue. My neuro-oncology folks tell me that that's unfortunately one of the characteristics of these brain tumors, whether they're metastatic or primaries, that the blood brain barrier is broken down, so you actually do get penetration.

The second is that this agent actually functions a little bit differently for most of the monoclonal antibodies we think about because it doesn't target the tumor cell directly; it basically acts as a sponge for the ligand. The ligand itself is a small molecule, and I'm pretty sure will penetrate into the central nervous system. So by binding it outside of the central

nervous system, you actually have an effect in the CNS.

The third issue that my colleagues tell me is that it may not actually do anything to the tumor. Its effect may be in decreasing edema, which when you have a tumor that occurs in a space where you can't expand without damaging normal tissue, that you get a beneficial effect. You get a clinical benefit by decreasing swelling and edema that's associated with it.

I'm not as concerned about this drug in glioblastoma, as it might be about something where you really require direct tumor binding to get a therapeutic effect. I will say, in spite of the nice cartoon we saw -- and my use of bevacizumab is mostly in ovarian cancer, which we're not considering as a use, but there is actually some data to suggest that there are VEGF receptors on the tumor cells and that you actually have a direct anti-tumor effect that's not dependent on changes, alterations, and vasculature. There may be tumors for which that is important, but we just don't

honestly know.

Even in ovarian cancer where we know that tumor cells do express the VEGF receptor, we don't know what part of the efficacy is due to a direct tumor effect by decreasing the ligand, or a vascular effect by decreasing the ligand.

I think those are things that, in spite of the fact we've been using bevacizumab for FDA approved purposes for over a decade now, we don't actually know much about it, and we aren't going to know anything about the biosimilar as well.

DR. ROTH: Dr. Schrag?

DR. SCHRAG: Sticking with a brain theme here. We saw very compelling data that the toxicity profile is quite similar between the biosimilar and the innovator product, but the one side effect that we don't see, and we can't see because of the design, is a rare but serious one, which is a leukoencephalopathy. It's rare, but it's serious, it's also under detected.

The only reason I mention it is it's seen more in cancers like colorectal cancer where the

bevacizumab can be continued for long, long periods of time and reintroduced because of the natural history of the disease.

I presume that given the analytic similarities, there's no concern, but I think we should acknowledge there's important decisions that need to be considered here. And we have lots and lots of great information, but there's a few bits that we don't have.

I don't know if others who treat other diseases know of other toxicities that are not represented in lung, but leukoencephalopathy is important.

The final issue is does anyone recall what was the objective response rate from the radiologic assessment? Was that blinded as to -

(Affirmative nods.)

DR. SCHRAG: -- it was blinded, okay.

DR. LEMERY: I can --

DR. ROTH: Sorry.

DR. LEMERY: -- sorry, quick point. Yes, it was a blinded review. The study was also blinded,

and they didn't bring up the investigator assessment, but the response rate with the investigators was basically identical.

We acknowledge that RPLS certainly would be a risk. We expect it to be a risk given that it's a risk of Avastin. It wasn't observed in this study, so we expect it to be a low risk similarly to Avastin. We'd expect it to be similar with both products because the mechanism of action is similar -- you have the increase in hypertension for example.

DR. ROTH: Any other comments before we proceed to the vote?

We'll be using an electronic voting system for this meeting. Once we begin the vote the buttons will start flashing, and will continue to flash even after you have entered your vote.

If I could have the question. I'm going to read this into the record. Does the totality of the evidence support licensure of ABP 215 as a biosimilar product to U.S. licensed Avastin for each of the indications for which U.S. licensed

Avastin in currently licensed, and for which the applicant is seeking licensure, as listed below?

Number 1, metastatic colorectal cancer with intravenous 5-fluorouracil based chemotherapy for first or second line treatment;

Number 2, metastatic colorectal cancer with fluoropyrimidine plus irinotecan or fluoropyrimidine, plus oxaliplatin-based chemotherapy for second line treatment in patients who have progressed on a first-line Avastin-containing regimen;

Number 3, non-squamous, non-small cell lung cancer with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease;

Number 4, glioblastoma as a single agent for adult patients with progressive disease following prior therapy;

Number 5, metastatic renal cell carcinoma in combination with interferon alpha; and

Number 6, cervical cancer in combination with paclitaxel and cisplatin or paclitaxel and

topotecan in persistent, recurrent, or metastatic disease.

Once we begin the vote the buttons will start flashing, and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record, and then we'll go around the room and allow people to explain their reasons for their vote. Please go ahead and vote now.

(Pause.)

DR. ROTH: It's on there, but 1 yes, 2 no, 3 is abstain.

(Voting.)

Okay. Votes are in. DFO will record.

DR. FAJICULAY: For the record, the results

are 17 yes, zero no, zero abstained, and zero no voting.

DR. ROTH: Okay. We'll go around the room, and we'll start in this end for voting members only to explain -- well I guess we'll know what their vote was, but explain their vote. Even I can figure that out.

Dr. Moreira?

DR. MOREIRA: Yes, I voted yes. The analytical package I thought was very strong, well laid out, and in my view convincing. The differences that were seen, the minor differences, I think the PK study and the clinical information was to me also persuasive.

As I just mentioned earlier, also the fact that the process is well-controlled and its validated assures me that if there were lots that for some reason there's some unknown impurity or a higher level of an impurity, those lots would be taken care of and not be distributed.

I voted yes overall in the information.

DR. SCHIEL: I also voted yes, as we can

tell. I think the analytical package was definitely very complete. There was a very large number of orthogonal assays looking at the same attributes in a number of different categories.

I did like the fact that there was mention of mass spectrometry data that looked specifically at what the variants were contributing to things like the charge variants. I'd actually like to see more of that data because it is, I think, very important in understanding the true quantities of some of these variants and how they affect the product quality.

But in the end, absolutely those differences were shown with the large number of bioactivity and clinical studies, that it seems they were not clinically meaningful differences, and so I voted yes.

DR. SCHRAG: I'll focus on the clinical data. The analytic package was strong. The perspective clinical trial, although in one indication, was clean, clear, well done, albeit with a short-term endpoint.

I was particularly compelled by the toxicity data, which demonstrated almost near identical toxicity profiles in both arms, which was persuasive that the products behave very similarly.

DR. LAGUNES: I completely agree with everything said. I thought that the totality of evidence was very clear; the molecular similarities were solid; and the efficacy. And actually interestingly more, the side effect profile to me was more powerful to illustrate the similarities.

DR. HENDRIX: I have little to add except it was impressive, the regulatory science that had, to me, a nice balance of precision and flexibility, and the flexibility I think was very important. The sponsor was very responsive to all of that in a way that was very convincing for all the key areas.

To only have a minor theoretical concern over this -- and that will play out, and I think the pharmacovigilance will be important as this goes forward. But I think it was convincing overall in the package.

DR. COLE: Bernard Cole. I also voted yes.

I, as the statistical member -- temporary member, sorry. I used to be a full member but now temporary member of the committee. I'm looking at the clinical data as being useful for ascertaining whether any minor differences at the molecular structural level might translate to clinically meaningful differences. And I would just mention that the statistical analyses that end up getting used are similar.

But, I think interpretation has to be different for biosimilar studies because while you look at confidence intervals that were presented, some of them are a little bit wide. And the equivalence criteria are a little bit wide, but this has to be interpreted in the sense of given the strong alignment at the analytical, functional, structural level of the molecule.

Certainly there's no signal of any clinically meaningful difference, and anything where there were any minor differences that we might see, for example in the lung trial, the overall response rate was a little bit lower with

ABP 215 compared to Avastin, but there was strong alignment and progression-free survival. Where we see those kind of things balancing out, then from a statistical perspective, the totality of the evidence suggests there are no clinically meaningful differences.

MS. CHAUHAN: Cynthia Chauhan, patient representative. I voted yes with some qualification. I remain concerned about the lack of diversity, the lack of representation of non-whites, and in one case the lack of representation of non-whites who are not male.

I really want the FDA to push for these trials to come to us representing the population that's going to be served, and the population of the United States is not white Caucasian. We really need to take that very, very seriously.

MS. PREUSSE: Courtney Preusse, consumer rep. I also voted yes. I found the clinical data compelling. If anything, I would strongly encourage the drug company to expand use for other indications, specifically ovarian and peritoneal

because those are groups that definitely need additional treatment options.

DR. NOWAKOWSKI: Grze Nowakowski, I voted yes. I think the biosimilarity was supported by totality of evidence. Particularly, I was impressed by the analytical part of the analysis.

I think where we had some discussion was extrapolation to other indications; however, considering those minor differences, it would be extremely unlikely that the efficacy would be affected in the other indications. For that reason I voted yes.

DR. ULDRICK: Thomas Uldrick. I voted yes. I think the sponsor and the FDA presented convincing analytical preclinical PK and clinical data demonstrating that ABP is sufficiently similar to Avastin. I also appreciated the sponsor's scientific justification for extrapolation to other indications and believe that the mechanism of action is substantially similar across the tumors for all indications in this application.

DR. ROTH: Bruce Roth. I voted yes as well.

With regard to the extrapolation issue, I understand the concerns, but I think that we extrapolate every day in the clinic. There are things listed in the USP. There are things listed in NCCN criteria that would never have sufficient evidence to get an approval past the agency, and yet there is some evidence of benefit, and that's sufficient for many oncologists who make that leap of faith. I think the magnitude of the extrapolation is no greater here than we experience on a daily basis in the clinic.

DR. RIELY: Greg Riely. I voted yes. I think the data provided and the regulatory framework we have says this compound is biosimilar to the U.S. licensed Avastin, and I'm particularly impressed by the uniformity of the results and the clinical trial.

I think when we do clinical trials, there's all sorts of opportunities for variability, and we didn't see significant variability between the two arms.

DR. WALDMAN: Scott Waldman. I voted yes.

I don't have much to add to everything that's been said. I think the package overall was compelling for biosimilarity, and I actually think the scientific logic and the data supporting extrapolation was very strong in this package.

DR. ARMSTRONG: I'm Deb Armstrong, and I also voted yes. I think the really remarkable data on the actual similarity of the biosimilar was pretty compelling, the clinical data with regard to both efficacy and toxicity.

I think in an ideal world, it would be nice for each of the indications to have a trial like that, but I think that's a hurdle that we shouldn't actually put in the way. And I would agree that we make extrapolations in the clinic all the time, and I think these are all reasonable indications.

DR. KARARA: Adel Karara. I voted yes. The clinical pharmacology study 216 data is very compelling, and I commend the sponsor for really powering the study correctly, even the high variability. It's a high variable drug, 50 percent variability, so they got it right. Very tight

confidence intervals, I'm very impressed with the results.

But this is a healthy volunteer. As I mentioned in my comment, really our lost opportunity was determining the pharmacokinetics in the target population and the lung study. I really would have liked to see population PK because we are approving the drug, but we really don't have an estimate for clearance and volume distribution in those patients. This is a drug given to patients, not to healthy volunteers.

DR. S. CHOW: This is Shein Chow. I also voted yes, although, I have a little bit concern regarding the extrapolation, but I think without any clinical data regulated to the other indication. But I am fully convinced that I think the ABP 215 actually is highly similar to the U.S. licensed product.

DR. MAGER: Don Mager. I voted yes for the reasons that have largely been stated. Analytical data were compelling, residual uncertainties were clearly addressed in the clinical pharmacology

studies, and the justification for extrapolation is scientifically sound.

Adjournment

DR. ROTH: Thank you. We'll now adjourn the morning session of the meeting. Panel members who are not attending the second session please return your name badge to the project specialist outside the meeting room so that they may be recycled. Please also take all personal belongings with you.

For the panel members who are attending the afternoon session, we'll now break for lunch and reconvene in this room at 1:00. Please remember there should be no discussion of the meeting topics during lunch among yourselves or with any member of the audience. Thank you.

(Whereupon, at 11:54 a.m., the morning session was adjourned.)