FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Afternoon Session

Thursday, July 13, 2017

1:01 p.m. to 4:09 p.m.

FDA White Oak Campus

White Oak Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:01 p.m.)

Call to Order

Introduction of Committee

DR. ROTH: Good afternoon. I'd first like to remind everyone to please silence your cell phones, smart phones, and any other devices if you have not already done so. I'd also like to identify the FDA press contact, Angela Stark, who will re-identify in a while.

We'll go around the table -- there are some new members who were not here this morning -- introduce yourselves, and we'll start on this side. Dr. Gordon.

DR. GORDON: Gary Gordon, AbbVie Oncology industry representative.

DR. 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 biopharmaceutical reference materials

and perform analytical chemistry characterization.

DR. SEIDMAN: Andrew Seidman, medical oncologist, 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: Greg Nowakowski, oncologist at Mayo Clinic, Rochester.

DR. ULDRICK: Thomas Uldrick, medical oncologist, CCR NCI.

DR. ROTH: Bruce Roth, medical oncologist Washington University in St. Louis, and chair of the committee.

DR. FAJICULAY: Jay Fajiculay; designated federal officer for this Oncology Drug Advisory Committee, FDA.

DR. RINI: Brian Rini, I'm a GU medical oncologist from the Cleveland Clinic.

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

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

DR. KARARA: Adel Karara, pharmaceutical sciences, University of Maryland Eastern Shore.

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

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

MS. KENNETT: Sarah Kennett, FDA, Office of Biotechnology Products review chief, and product quality team lead for this application.

DR. AMIRI-KORDESTANI: Laleh Amiri, FDA. I'm the clinical team leader for this application.

DR. BEAVER: Julia Beaver, FDA acting director, Division of Oncology Products 1.

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

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

DR. PAZDUR: Richard Pazdur, director, Oncology Center of Excellence.

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. Thank you.

Now, I'll pass it on to Dr. Jay Fajiculay who is acting as our DFO for this afternoon's meeting, to read in 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 discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C., Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves Biologics License Application 761074 for for MYL-1401O, a proposed biosimilar to Genentech Inc.'s Herceptin or trastuzumab, submitted by Mylan GmbH. The proposed indications for this product are:

1) Adjuvant treatment of HER2-overexpressing node-positive or node-negative, ER/PR negative, or with one high-risk feature breast cancer, (a) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; (b) with docetaxel and

carboplatin; or (c) as a single agent following multi-modality anthracycline based therapy;

2) In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer;

3) As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease; and,

4) In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

This is a particular matters meeting, in which specific matters related to Mylan'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, a conflict of interest waiver has been issued in accordance with

18 U.S.C., Section 208 (b)(3) to Dr. Andrew Seidman.

Dr. Seidman's waiver involves his employer's current study involving a potentially competing firm, which is anticipated to be between $850,000 and $900,000 in total funding. The waiver also addresses a consulting agreement with a potentially competing firm, which he receives between $10,001 and $25,000 per year.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are 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 personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to

advice 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 begin the afternoon with some opening remarks from the FDA, and specifically from Dr. Amiri-Kordestani.

Opening Remarks - Laleh Amiri-Kordestani

DR. AMIRI-KORDESTANI: Thank you. Good afternoon chairperson, members of the ODAC, we are here today to discuss an application for MYL-1401O, a proposed biosimilar to U.S. Herceptin.

During FDA's presentation we will use the term Mylan product to describe MYL-1401O and U.S. Herceptin to describe U.S. licensed Herceptin.

This application is being presented at today's advisory committee meeting because this represents the first FDA application for a proposed biosimilar to U.S. Herceptin.

This slide displays the FDA review team. The proposed indications for Mylan product are the same as for U.S. Herceptin. I'm not going to read it, as it was just read for you.

We would like the committee to discuss the following topics today. The first topic is to discuss whether the evidence supports a demonstration that Mylan product is highly similar to U.S. Herceptin, notwithstanding minor differences in clinically inactive components.

The second topic would be to discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between the Mylan product and U.S. Herceptin in the studied condition of use.

The applicant conducted a study to evaluate the PK similarity between their product U.S. and EU Herceptin, and one comparative clinical study to evaluate the efficacy and safety of the Mylan product and EU Herceptin in patients with untreated metastatic HER2-positive breast cancer. Details on the study design, study population, endpoints, and results will be discussed by both the applicant and the FDA.

The third topic for discussion is to discuss whether there is adequate scientific justification

to support licensure for all the proposed indications.

Finally, we would like the committee to vote on the following question. Does the totality of the evidence support licensure of the MYL-1401O as a biosimilar product to U.S. Herceptin for the following indications, for which U.S. Herceptin is licensed and for which Mylan is eligible for licensure, meaning HER2-positive breast cancer in the adjuvant and metastatic settings.

Thank you for your participation today.

DR. ROTH: Thank you. Both the Food and Drug Administration and the public believe in a transparent process for information gathered 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 interest 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 will now proceed with the applicant's presentation, Dr. Annweiler.

Applicant Presentation - Arnd Annweiler

DR. ANNWEILER: Good afternoon, Dr. Roth, members of the advisory committee, FDA. My name is Arnd Annweiler, Mylan R&D. Thirty years ago Dennis Slamon, at the University of California in Los Angeles described HER2-overexpression in a subset of patients with breast cancer. This discovery led to the development and approval of trastuzumab, marking a breakthrough in the treatment of patients with breast cancer.

It is a privilege to be here today, and to present to you the first biosimilar candidate for this lifesaving essential medicine.

MYL-1401O was developed in partnership with Biocon as part of a wider collaboration across a range of biosimilars and insulin analogs.

MYL-1401O is a proposed biosimilar to U.S. licensed Herceptin, and the BLA was first approved in 1998. Trastuzumab is a monoclonal antibody, specific for the HER2 receptor and initiation of treatment is based on the confirmed HER2-positive diagnosis, which tightly links diagnosis and treatment to the mechanism of action.

Central to the mechanism of action is the binding of the antibody to the HER2 receptor. All downstream effects including the inhibition of proliferation and the antibody-dependent tumor cell lysis follow from this specific binding. The mechanism of action is preserved across all approved indications of the reference product, which is important in the concept of extrapolation.

The development of MYL-1401O, followed the

principles and key concepts of the biosimilar development path, and incorporated advice obtained from the FDA throughout development.

Accordingly, a biosimilar must be shown to be highly similar to the reference product with no clinically meaningful differences in terms of safety, purity, and potency. Biosimilarity is then judged on the totality of evidence obtained across all its studies, and in this context the role of the clinically development is confirmatory and not meant to reestablish all indications that have already been tested and approved by the reference product.

Extrapolation to indications is then based on the demonstration of analytical similarity confirmed by clinical testing in a sensitive patient population, and taking into consideration the mechanism of action and other conditions of use. Extrapolation is then based on the expectation that essentially the same molecule will behave and perform in the same way in all indications, for which the reference product was

tested and approved.

Applying this principal to the development of MYL-1401O, followed a step-wise approach and addressed residual uncertainties at each step. At the outset structure and function were compared side-by-side with the reference product using highly sensitive analytical methods, and focusing on aspects of the molecule that are highly relevant to the mechanism of action and clinical performance.

Non-clinical safety was assessed in two cell-based studies and two safety pharmacology studies in cyno monkeys, and as part of the clinical development PK similarity was assessed in two PK studies; including a three-way PK bridging study.

Finally, the HERITAGE study confirmed efficacy, safety, and immunogenicity in HER2-positive patients with metastatic breast cancer, representing a sensitive patient population. The data obtained across all these studies will demonstrate high similarity with no

clinically meaningful differences, and the totality of evidence will support biosimilarity of MYL-1401O to Herceptin.

Based on the totality of evidence we propose MYL-1401O as a biosimilar to trastuzumab Herceptin for the same indications as the reference product, including the treatment of HER2-overexpressing breasts and metastatic gastric cancer.

Our team will now lead you through the development program and the data obtained across our studies. Dr. Vallano will begin with the analytical demonstration of similarity, Dr. Barve will lead you through the confirmatory clinical efficacy and safety program, and we also have the honor to have Dr. Hope Rugo with us; professor of medicine at the University of California in San Francisco, and one of the foremost breast cancer researchers and treating physicians. Dr. Rugo was also our principal investigator in the HERITAGE study, and she will share with you the clinical perspective. We also consulted with Dr. Gradishar and Dr. Henry, and are very happy to have them as

part of our lineup here today.

DR. Vallano, please come to the podium to present on the analytical demonstration of similarity.

Applicant Presentation - Patrick Vallano

DR. VALLANO: Thank you Dr. Annweiler. Good afternoon Chairman Roth, and ladies and gentlemen of the committee.

My name is Pat Vallano. I head Global Biologic Scientific Affairs at Mylan. I've been a Mylan employee now for just under 20 years, most of that as an analytical chemist. It is indeed a privilege to be here before you today to discuss how we demonstrated MYL-1401O to be highly similar to Herceptin.

Trastuzumab is a humanized IgG1 monoclonal antibody. Its characteristic Y-shaped structure is depicted here on the slide. Trastuzumab possesses many molecular characteristics that define it and that are measurable. These include physicochemical, as well as an array of different biologic characteristics. Each of these is

potentially useful when comparing a biosimilar trastuzumab to Herceptin.

At the outset of our analytical similarity program we assessed this constellation of different molecular characteristics from the vantage point of clinical relevance. We assessed each with regard to its potential to impact clinical safety, efficacy, immunogenicity, and PK.

Through this analysis we placed each characteristic into 1 of 4 criticality ranks, as indicated on the slide. We measured and included in our assessment, characteristics across the criticality spectrum, but the ranking was important because it helped inform what the acceptance criteria would be to make the determination of high similarity.

We performed our analytical program in a three-way fashion. The analysis included MYL-1401O, as well as U.S. licensed Herceptin, and also included EU approved Herceptin, which was done in order to bridge to the EU product used in our confirmatory clinical study.

Arguably, the most fundamental aspect of the structure of most any protein is its amino acid sequence. We performed extensive analyses of MYL-1401O and Herceptin using multiple protease enzymes coupled with tandem mass spectrometry, and demonstrated that the amino acid sequence in MYL-1401O was identical to that in Herceptin.

As we know, proteins exhibit multiple levels of structure, in addition to amino acid sequence, proteins assume a characteristic three-dimensional structure that's key for the protein's biologic activity. We evaluated the three-dimensional structures of MYL-1401O and Herceptin using a panel of different analytical methods. One of these was a technique known as differential scanning calorimetry, and in the DSC experiment one heats the protein and detects the temperature at which the protein unfolds.

We demonstrated in our analysis that the unfolding temperatures of MYL-1401O and Herceptin, as indicated by the location of the peak maxima along the horizontal temperature axis, were highly

similar. This constituted a key piece of information that allowed us to conclude that the three-dimensional structures of the products were highly similar.

Aggregates are relevant for protein therapeutics, due to their potential to cause immunogenicity. This slide shows the results of a size exclusion chromatography analysis, whereby the aggregate content in MYL-1401O and Herceptin was assessed.

Just a few points to note on interpretation of the data in this plot. Each individual data point corresponds to a unique lot of either MYL-1401O or Herceptin that was analyzed.

Secondly, there's no numeric significance to the X-axis or the horizontal axis in this plot. The data points were spread along the horizontal axis merely to help visualize the data. You'll also notice two horizontal green lines, these denote upper and lower acceptance limits that were set based upon the mean of the U.S. Herceptin plus or minus three standard deviations.

As you can see, each of the MYL-1401O lots fell within these limits, thereby demonstrating the aggregate content in the products were highly similar.

Glycan variants are another important structural characteristic of an antibody, such as trastuzumab. Again, we employed a number of different analytical methods to characterize glycan variants in the products.

This slide shows the results of a glycan profiling analysis, whereby the glycans were released from the antibody using an enzyme, and subsequently quantified using HPLC. In this particular analysis we demonstrated high similarity for 12 of the 13 species that were quantified.

We did observe a marginal difference in one high-mannose species Man6, indicated here. But, we subsequently demonstrated that this marginal difference observed had no impact on clinical PK.

Coming now to function, we evaluated the binding of MYL-1401O and Herceptin to a panel of different Fc receptors, the most important of which

were the Fc gamma IIIa receptor, which is expressed on the surface of various effector cells that mediate ADCC, as well as the FcRn receptor, which is known to affect clearance of IgG-based antibodies.

With each of these analyses, all of the MYL-1401O lots fell within the limits defined by U.S. Herceptin, thereby demonstrating high similarity of the products with respect to binding to each of these important Fc receptors.

One of the most important components of our analytical similarity program was our panel of clinically relevant functional assays. As Dr. Annweiler mentioned, the central step in trastuzumab's mechanism of action is the binding of the antibody to the HER2 receptor. This binding event gives rise to downstream effects, namely the inhibition of tumor cell proliferation and tumor cell lysis through an ADCC mechanism.

We developed and implemented highly sensitive analytical methods to interrogate each one of these key steps along trastuzumab's

mechanism of action.

This slide shows the result of the HER2 receptor binding analysis that we performed. Given the very high criticality of this particular test, the data was evaluated using statistical equivalence criteria. Briefly, we calculated an equivalence margin based upon a multiplier of 1.5, followed the standard deviation in the reference product. We next calculated 90 percent confidence intervals for the mean difference between the test and the reference products, and in order to conclude equivalence, the confidence intervals had to fall within that prescribed equivalence margin.

As you can see in the upper left portion of the slide, the comparison of MYL-1401O and U.S. Herceptin met the statistical criteria, thus, demonstrating that the HER2 binding of MYL-1401O was equivalent to that of Herceptin.

Similarly in the bottom left portion of the side, the comparison of EU to U.S. Herceptin is shown. Again, those pair-wise comparison met the statistical equivalence criteria.

This slide shows the results of the inhibition of cell proliferation assay. Once again the statistical criteria were met, demonstrating that the inhibition of proliferation of MYL-1401O was equivalent to that of Herceptin.

Then finally the ADCC assay, once again, each comparison met the statistical criteria demonstrating that the ADCC activity in MYL-1401O was equivalent to that in Herceptin.

Collectively, looking across each of these key mechanism of action-based functional assays, we've demonstrated that the biologic activity of MYL-1401O was equivalent to that of Herceptin. A finding that's wholly consistent with a high degree of similarity observed between the products at the physicochemical level.

I would also note that what we've seen and discussed here today constitutes a subset of a much larger body of data. In total we brought to bear over 35 sensitive state of the art analytical methods in our demonstration of similarity between MYL-1401O and Herceptin.

I will now conclude by saying that through an extensive battery of testing, we have established that MYL-1401O and Herceptin are highly similar both with respect to structure and to function. Our non-clinical studies, which I've not discussed, showed no differences in non-clinical toxicity between the products, and thus, provided confirmatory evidence of the high degree of similarity between MYL-1401O and Herceptin.

I'll now turn the podium over to my colleague, Dr. Barve, to discuss the clinical program.

Presentation - Abhijit Barve

DR. BARVE: Thank you, Dr. Vallano. Good afternoon, my name is Abhijit Barve, and I head Global Clinical Research at Mylan.

It is my pleasure to present the PK and clinical program to demonstrate biosimilarity of our product, MYL-1401O.

The PK program included one pivotal study in healthy volunteers, and three supportive studies.

The clinical program included one

confirmatory safety and efficacy study in MBC patients, and supportive study in MBC patients conducted with a slightly different formulation.

This slide provides an overview of the PK assessment done across different studies. The pivotal study, study 1002, was a three-way parallel study in healthy male volunteers. The supportive studies included study 1001, a two-way crossover study in healthy males, and studies 3001 and BM200 where PK was evaluated in MBC patients.

This slide depicts the design of study 1002, three-way PK bridging study in healthy volunteers. Here 132 healthy males received either our product, U.S. Herceptin, or EU Herceptin. An 8 mg per kilogram dose was used, and PK sampling was done over a 10-week period.

This slide shows the time concentration profile for the three products. As you can see here, the profiles are overlapping. The insert here compares our product against U.S. Herceptin, and as you can see, the ratio for both AUC and C-max is close to 1.0 and 90 percent confidence

intervals are within the 80 to 125 percent range. Based on this data, we conclude that our product is bioequivalent to U.S. Herceptin.

We also compared U.S. Herceptin against EU Herceptin. Once again, the ratio for AUC and C-max are close to 1.0, and 90 percent confidence intervals are within the equivalence margin. These data confirm that U.S. Herceptin is bioequivalent to EU Herceptin, thereby establishing a bridge and allowing us to use the EU product in our confirmatory safety and efficacy study.

This slide presents the trough concentration on MBC patients from study 3001. The figure shows concentration prior to dosing in cycles 2, 4, 6, 8, and 9. The ratio of concentration before cycles 2 and 6 are presented in the insert, and are close to 1.0 with 90 percent confidence intervals within the equivalence margin. These data confirm that the exposure is similar in MBC patients.

Here is an overview of the clinical program. Unlike novel molecules, the goal of the confirmatory study within the biosimilar paradigm

is quite different. The goal is to confirm the high similarity shown in analytical development, and to demonstrate that there are no clinically meaningful differences in efficacy and safety.

Our confirmatory efficacy study was conducted in 500 MBC patients, and is referred to as study 3001 or HERITAGE study. Safety and immunogenicity was also evaluated in each of the three supportive studies. In addition, efficacy was also evaluated in study BM200.

Before we get into the design of the study, this slide provides the rationale for the HERITAGE study, and the choice of MBC as the potential patient population and ORR as the primary endpoint. MBC represents a broad and sensitive population. It was the earliest indication approved for Herceptin, and extensive efficacy and safety data is available.

MBC study allowed us to evaluate safety, efficacy, and immunogenicity with taxanes and as monotherapy. It also allowed us to evaluate data beyond 52 weeks of treatment.

With regards to ORR, it is a sensitive endpoint to detect clinically meaningful differences in efficacy. It correlates well with traditional efficacy endpoints like time to progression, progression-free survival in HER2-positive metastatic breast cancer patients.

The choice of ORR and MBC was discussed with both the FDA and EMA, and was appropriate for developing a biosimilar for Herceptin.

This slide provides the design of the HERITAGE study. It was a double-blind study and had two parts. During part one; HER2-positive MBC patients received either our product or Herceptin every 3 weeks for 8 cycles with taxanes.

The sites could choose either weekly paclitaxel or 3 weekly docetaxel for all the patients that were randomized at that site. After 24 weeks patients who had a complete response, partial response, or stable disease continue to receive our product or Herceptin until disease progression. Data until week 48 was included in this application. The study will continue until 36

months from the last patient's first visit, or 240 deaths.

In this study we used a 6 mg per kilogram dose of trastuzumab throughout, except for reloading dose of 8 mg per kilogram. The data for this study was published in JAMA early this year. The selection criteria were standard for a first-line Herceptin study in metastatic breast cancer setting, and included confirmation of HER2 using either FISH or immunochemistry done at a central laboratory.

This slide presents the study endpoints. The primary endpoints for the study was ratio of best ORR by week 24, based on cumulative assessment done by a blinded central oncologist. The equivalence margin to demonstrate similar efficacy between the two products was 0.81 to 1.24, and was based on meta-analysis of multiple studies.

The secondary endpoints included time to progression, progression-free survival, and overall survival at week 48, and comparative safety and immunogenicity with taxanes and as monotherapy.

The disposition and the patient population is presented here. Five-hundred MBC patients were randomized. Of these, 42 patients were randomized under an older version of the protocol that allowed for second-line trastuzumab use. Four-hundred and fifty-eight patients were randomized under first-line protocol, and constitute the ITT1 population. This is the primary population for analysis.

The per-protocol population is a subset of ITT1, while ITT2 includes all the 500 randomized patients. Of the 230 patients randomized in our arm under ITT1, 173 completed part 1 of the study, and 111 completed 48 weeks. In the Herceptin arm, of the 228 patients, 159 completed part 1, and 90 completed 48 weeks.

The key baseline characteristics and disease history are presented here, and are comparable across both arms. Eighty-four percent of the patients received docetaxel, and approximately 8 percent of patient had a history of trastuzumab use in an adjuvant setting.

Coming to the efficacy data, in the ITT1 population the overall response rate at week 24 was 70 percent in our arm, and 64 percent in the Herceptin arm. The ratio of ORR was 1.09 and 90 percent confidence intervals were within the pre-specified equivalence margin of 0.81 to 1.24.

Based on this data, the primary endpoint for the study was achieved and it supports similar efficacy between the two products.

As part of the sensitivity analysis, we also looked at efficacy in the per-protocol population, the ITT2 population, and based on investigator assessment. As can be seen here, for each of these assessments the 90 percent confidence interval was within the equivalence margin. These data further support similar efficacy between the products.

As indicated earlier, all the ORR at week 24 was the primary endpoint. We also analyzed PFS data at week 48. At week 48 there were 102 events in both arms, the P-value of 0.842. The unstratified hazard ratio was 0.97, further supporting similar efficacy.

Based on the 48 week cutoff, the median PFS was estimated to be 11.1 months. The median OS has not been reached.

Moving on to clinical safety. This slide depicts the cumulative adverse events over 48 weeks presented on the left and the new onset adverse events during the monotherapy part on the right. Various perimeters were assessed; like overall adverse events, grade 3 or higher adverse events, and as you can see for each of these perimeters the rates were comparable between the two arms.

This slide lists the serious adverse events occurring in more than 2 percent of the population at week 48. The rates are comparable across both arms; most of these events appear to be related to concomitant taxane use.

The common adverse events occurring in greater than 10 percent of the population through week 48 are presented on this slide. Once again, most of the adverse events are similar across both arms. There are isolated preferred terms that are higher in either group, but the rates are similar

to published literature.

This is a slide comparing safety in part 1 of the study where taxanes were used versus part 2 of the study where monotherapy was given. Clearly, the incidence of adverse events is markedly lower in the monotherapy part. Some isolated preferred terms like arthralgia, nausea, and asthenia that were higher during the first 24 weeks are no longer different in the second part of the study, indicating that these isolated differences are most likely to be due to concomitant taxane use and unlikely to be due to study drug.

Here we are looking at the adverse events of special interest. They include pulmonary, cardiac, and infusion-related events. The overall incidence for each of these categories, in blue, was similar in both arms. Most of these events were mild-to-moderate. There were isolated differences for some of the preferred terms, for which we conducted a detailed assessment. However, it was noted that the differences are due to the granular nature of these preferred terms, and were not

clinically meaningful.

Cardiac toxicity is a known side effect of trastuzumab, and in that context we conducted an objective assessment of left ventricular ejection fraction. LVEF was measured every 12 weeks. The proportion of patients with LVEF less than 50 percent was 4 percent in our arm versus 3.3 percent in the Herceptin arm. When an additional criteria of at least 10 percentage point reduction was added, there were 3.6 percent of patients in our arm versus 2.8 percent in the Herceptin arm. LVEF recovered in the majority of the patients except for 2 patients in the Herceptin arm. Thus, and objective assessment of cardiac toxicity did not detect any clinically meaningful differences.

Moving on to immunogenicity. Although trastuzumab has got a low immunogenic potential, systematic assessment of immunogenicity is an important consideration for a biosimilar. We used state of the art assay and standard three-step approach. This included a screening assay, a

confirmatory assay, and a neutralizing assay for positive samples. ADA assay was a validated bridging immunoassay, while the NAb assay was a cell-based assay.

In healthy volunteer studies there were no treatment emergent positivity that was seen, while in the supported MBC study the positive rate was low and similar in both arms.

In study 3001, the HERITAGE study, immunogenicity was assessed at baseline week 6, 12, 18, 24, 36, and 48 weeks. Thus, we measured immunogenicity at 6 time points post-baseline. Six to nine percent of the patients were positive prior to dosing, possibly due to shared ACD.

Post-baseline, the proportion of ADA-positive patients in our arm was 3.9 percent versus 4.4 percent in the Herceptin arm. The titers were very low. A very small portion of patients were positive for neutralizing antibodies, 0.4 percent in our arm and 1.3 percent in the Herceptin arm.

During the monotherapy phase, the incidence

was also low at 2.1 percent in our arm and 1.5 percent in the Herceptin arm. These data confirm that our product has similar low incidence of immunogenicity as Herceptin both with taxanes and as monotherapy.

In summary, the PK and the clinical program to support biosimilarity has demonstrated that PK is bioequivalent in normal, healthy volunteers, and exposure is similar in MBC patients. The efficacy was similar based on best ORR at week 24, and supported by PFS at week 48. Comparable safety was demonstrated in presence of taxanes and as monotherapy. We have also demonstrated that immunogenicity is low and similar in both arms.

At this point, I would like to invite Dr. Rugo, who will provide a clinical perspective. Thank you.

Presentation - Hope Rugo

DR. RUGO: Thank you. It's a great honor to present on behalf of this first trastuzumab biosimilar to my esteemed colleagues on the ODAC/FDA panel.

My disclosures are here. I received funding through the Regents at the University of California for sponsored and investigator-initiated clinical research studies from Genentech/Roche, and I received travel support from Mylan for this meeting but have not received any other financial compensation.

I focus on breast medical oncology, and as the panel knows, this is the most common cancer diagnosed in women worldwide. In addition, almost a million patients, individuals, worldwide will be diagnosed with gastric cancer.

In the United States over 250,000 women, and a small number of men, are diagnosed with breast cancer each year and 28,000 individuals with gastric cancer. Overexpression of HER2 has been implicated in the pathophysiology of approximately a quarter of breast cancers, and a little under 20 percent of gastric and gastroesophageal tumors.

Worldwide, limited access to treatment is an issue for patients with breast and gastric cancer, particularly for expensive drugs like Herceptin.

In addition, in the United States there is a significant financial impact due to share of cost, an ever-changing issue for our patients for patients with specific types of insurance. Biosimilars for these drugs have the potential to expand patient access and use.

Trastuzumab, in clinical practice, has changed the treatment course of HER2-overexpressing tumors really in a very dramatic way, curing women who otherwise would not be cured of breast cancer, and prolonging survival in metastatic disease.

In 1998, Herceptin was approved for the treatment of metastatic HER2-overexpressing breast cancer, changing the world of treatment for this group of individuals.

In 2006, trastuzumab was approved for adjuvant treatment of HER2-positive breast cancer.

Then in 2010, it was approved for the treatment of metastatic HER2-positive gastric cancer.

In addition, based on randomized trials showing improvement in response rates, trastuzumab

is a standard therapy as part of neoadjuvant treatment for early stage HER2-positive breast cancer.

The data that led to approval has really been quite striking for trastuzumab. In metastatic breast cancer trastuzumab improved response rates, progression-free survival, and overall survival, and in early stage breast cancer at an early time point after initial start of therapy improved disease-free survival and overall survival, and now there has been long-term follow-up showing that these differences are maintained.

As neoadjuvant therapy for breast cancer, as I mentioned, the addition of trastuzumab to standard chemotherapy improved pathologic complete response rates and disease-free survival in limited analyses.

In metastatic gastric cancer the addition of trastuzumab to a subgroup of patients with HER2-overexpressing disease improved response, progression-free survival, and overall survival. Trastuzumab is clearly the gold standard for the

treatment of both early and late stage HER2-positive breast cancer, as well as being well-tolerated with modest and manageable toxicity.

In this slide we put the HERITAGE study data in clinical perspective. It's always helpful for us as clinicians to see how the data from current studies corresponds to our previous gold standard therapy that leads to our treatment practices.

You can see on the left the data from the HERITAGE study that you just saw presented, and on the right the historical data from both the pivotal trials that led to the approval of trastuzumab, as well as data from the control arm of the recently published CLEOPATRA trial that included trastuzumab and a taxane.

As you can see the 24 week overall response rates are similar across all of these trials. The overall response ratio, of course, was calculated for the HERITAGE study based on evaluation of a biosimilar, and you can see that data here with the overall response ratio of 1.0 and the overall response difference of 6 percent.

Time to progression, an important endpoint for us in clinical practice when we look at new drugs, at 48 weeks is almost identical across these trials, which is quite fascinating and suggests that indeed our population represented the HER2-positive population in general.

Overall survival at 48 weeks is also quite comparable, our safety and toxicity is comparable, immunogenicity rates are low. Exposure is, of course, one way that we look at tolerability of drugs and safety, and exposure was comparable in the HERITAGE study to the historical data.

There are a number of reasons to think that MYL-1401O could be used across indications in HER2-positive cancers. We see efficacy with trastuzumab across indications. Breast and gastric cancer require HER2-positive overexpression to qualify for treatment, but we see binding of trastuzumab to HER2 receptors, which is fundamental to activity across all indications. The mechanism is similar with ADCC and inhibition of proliferation; in fact, it's been quite striking to

see how similar the efficacy is of trastuzumab across indications.

We also have seen safety. The same dose of trastuzumab is used across all indications and combinations with different drugs can be used, again, with safety. The current recommended use for trastuzumab and adjuvant therapy is 12 to 18 weeks in combination with chemotherapy, followed by monotherapy for a maximum of 52 weeks.

In metastatic breast cancer we treat for about 24 weeks in combination with chemotherapy, followed by monotherapy as maintenance until progression with a median use of about 12 months. Treatment can continue until or after progression, as is the standard in the United States, for longer than 52 weeks.

In gastric cancer a similar approach is used with 24 weeks of combination therapy, followed by monotherapy until progression. The safety data from the HERITAGE trial with a median use of 12 months is quite important generating additional long-term safety in immunogenicity data.

Approximately 200 patients continued to received MYL-1401O or Herceptin beyond 52 weeks.

The potential use of MYL-1401O in clinical practice is quite significant. Any patient receiving Herceptin, of course, will be a candidate for this agent, and newly diagnosed patients with HER2-positive disease will have the option to start with a lower cost biosimilar.

With that, and again, to thank you for listening to the clinical perspective on this new biosimilar, I'll turn the podium over to Arnd Annweiler.

Presentation - Arnd Annweiler

DR. ANNWEILER: Thank you, Dr. Rugo, for sharing you r clinical perspective on the HERITAGE study and this important treatment option for patients with HER2-positive cancers.

Let me now conclude on the totality of evidence. Beginning with the physicochemical characterization MYL-1401O was shown to be highly similar with the reference product Herceptin across a broad range of analytical studies and attributes

including primary, secondary, and tertiary structure; protein variants; and impurities.

As structure is informing function, we have also shown high similarity across a broad range of functional characteristics including HER2 binding, inhibition of proliferation, ADCC, and Fc binding, which are important determinants of the mechanism of action and clinical performance including efficacy, safety, and immunogenicity.

The non-clinical safety and toxicity profile was comparable and consistent with published information. As one would expect from the high degree of analytical similarity, our clinical program has confirmed PK similarity in healthy volunteers, similar exposure in patients with metastatic breast cancer, comparable safety and immunogenicity across all studies, and equivalent efficacy in patients with HER2-positive metastatic breast cancer in our HERITAGE study as shared by Dr. Barve and Dr. Rugo.

Combined, the data obtained from our non-clinical, analytical, and clinical studies

demonstrate high similarity to the reference product with no clinically meaningful differences in terms of safety, purity, and potency. The totality of evidence therefore supports biosimilarity of MYL-1401O to Herceptin.

In conclusion then, the totality of evidence supports biosimilarity, extrapolation from molecule-to-molecule to all indications in which Herceptin was tested and approved, and once approved MYL-1401O will provide an additional high-quality treatment option for patients with HER2-positive cancers, and is expected to enhance access to this important essential biologic.

This concludes our sponsor presentation, and in the name of our joint Biocon and Mylan team, I would like to thank the committee for your attention.

DR. ROTH: Thank you very much. We'll now proceed with the FDA presentations, and will begin with Dr. Nickens.

FDA Presentation - Kristen Nickens

DR. NICKENS: Good afternoon. My name is

Kristen Nickens, and I will presenting the FDA's analysis and conclusion based on our assessment of the applicant's analytical similarity data to support the Mylan product as a biosimilar to U.S. licensed Herceptin also known as trastuzumab, and for which we will refer to as U.S. Herceptin.

My colleague, Dr. Meiyu Shen, will also present the results of FDA's statistical analysis used to support our conclusions.

I will start by summarizing the structure, cellular target, and recognized mechanisms of action of trastuzumab. Trastuzumab is a humanized IgG1 monoclonal antibody of the kappa-isotype. It contains two identical glycosylated heavy chains and two identical light chains. The target of trastuzumab is the cell surface human epidermal growth factor receptor 2.

HER2 is part of the HER family of transmembrane tyrosine kinases that have been shown to play a role in the regulation of cellular survival, proliferation, adhesion, and differentiation. The mechanisms of action of

trastuzumab are initiated through the binding of the antibody FAB region to the HER2 on the target cell. The binding prevents receptor activation by inhibiting HER2 dimerization; promoting the destruction of the intracellular portion of the receptor; and inhibiting shedding of the extra cellular portion of HER2, which has been associated with a poor patient prognosis.

Subsequently, the binding inhibits HER2-specific signal transduction that leads to cellular survival, proliferation, and differentiation.

Furthermore, the concomitant binding of trastuzumab to HER2 and Fc receptors on certain types of immune cells triggers the release of cytokines, the recruitment of more immune cells, and antibody-dependent cellular cytotoxicity, or to a lesser extent antibody-dependent cellular phagocytosis resulting in cell death.

As previously noted, trastuzumab is glycosylated in its Fc region. This glycosylation plays an important role in these effector

functions, and also PK.

This slide shows the product quality and attributes assessed by the applicant to support analytical similarity. The attributes can be grouped into 7 categories; including primary structure, higher order structure, functionality, product-related species, glycosylation, drug product attributes, and the stability profiles of the products. The applicant used orthogonal methods to assess these attributes.

To assess analytical similarity, the applicant developed a program consisting of analytical comparisons between the Mylan product and U.S. Herceptin to support the demonstration that the products are highly similar, as well as analytical comparisons between the Mylan product, U.S. Herceptin, and EU Herceptin to establish the analytical portion of the scientific bridge to justify the use of clinical and animal data using the EU as a comparator.

The analytical similarity assessment included a total of 16 lots of the Mylan product,

28 lots of U.S. Herceptin, and 38 lots of EU Herceptin. The lots used in clinical studies and the proposed commercial process were included in the analytical similarity assessment, and the drug product presentation for which the applicant is requesting approval was represented. The number of lots analyzed for each attribute were justified by the applicant.

Prior to data analysis, the applicant conducted a risk assessment of each quality attribute to determine the criticality or importance of the various attributes with respect to biological activity, PK, PD, efficacy, and safety including immunogenicity.

For comparative data analysis, the applicant assigned each attribute to 1 of 3 tiers of statistical analysis based on their criticality and other considerations.

As shown in the table on the right, tier 1 analysis used equivalence testing; tier 2 uses quality ranges, such as mean plus or minus 2 or 3 times standard deviations; and tier 3 uses

graphical comparisons. This approach is in agreement with the agency's expectations. FDA's assessment included independent statistical analysis of the applicant's data.

This slide shows the graphical representations of the three quality attributes evaluated using tier 1's statistical analysis by equivalence testing. HER2 binding, inhibition of proliferation, and ADCC activity were assessed using cell-based functional assays.

The data show that the Mylan product lots have overall similar levels of biological activity compared to U.S. Herceptin and EU Herceptin. To further illustrate this, Dr. Shen will present the statistical equivalence analysis of these functional assays.

FDA Presentation – Meiyu Shen

DR. SHEN: Good afternoon. My name is Meiyu Shen, the CMC statistical reviewer from the Office of Biostatistics. I will present the tier 1 statistical occurrence analysis.

In the equivalence test, the null hypothesis

is defined as the mean difference of the quality attribute between the test and comparator is either larger than 1.5 sigma-C or smaller than negative 1.5 sigma-C.

The alternative for hypothesis is that the mean difference with the mean [indiscernible] range from negative 1.5 sigma-C to positive 1.5 sigma-C. We conclude that this quality attribute passes the equivalent test if a 90 percent confidence interval for the mean difference between the test and the comparator falls within the equivalence margin defined by plus or minus 1.5 sigma-C.

Here sigma-C is estimated from the comparative data generated by the applicant. Due to differences in the number of lots between the test and comparator, we adjusted the degrees of freedom used for calculation of 90 percent confidence interval for the mean difference.

For equivalent testing, the review team focused on HER2 binding, inhibition of proliferation, and ADCC activity. These assays acted as the mechanisms of action. HER2 banding

data displayed for three products in the top figure indicates the data spread of the Mylan product is narrower than of U.S. licensed Herceptin and EU approved Herceptin, and the mean of these three products are similar.

The bottom figures show that 90 percent confidence interval for all three pairs are contained within their corresponding equivalence margins, then we concluded that all three pair-wise comparison for HER2 binding plus equivalence testing.

In this slide the inhibition of proliferation data for these three products, showing in the top figure, indicate the mean of the Mylan product is smaller than those of U.S. Herceptin and EU Herceptin. The data spread for these three products are quite similar since the bottom figures show that 90 percent of confidence intervals for all three pairs are contained within the corresponding equivalence margins.

We've concluded that all three pairs with comparison for inhibition for proliferation plus

equivalence testing.

The ADCC activity data, displayed in the top figure, shows that the mean of the Mylan product is slightly higher -- larger than those of the U.S. Herceptin and EU Herceptin, and the data spread of EU Herceptin is wider than those of the other two products, since the bottom figures show that the 90 percent confidence intervals for all three pairs are contained with their corresponding equivalence margins, then we conclude that all three pair-wise comparison for ADCC activity plus equivalence testing.

Based on our independent analysis of the applicant's data, we concluded that all three pair-wise for all three assays passed the equivalence testing. Hence, statistical equivalence testing of the results of HER2 banding, inhibition of proliferation, and the ADCC activity support that the Mylan product is highly similar to U.S. Herceptin, and also support that analytical bridging between all three products.

Dr. Kristen Nickens will continue the CMC

discussion.

DR. NICKENS: Thank you, Dr. Shen. This slide shows the applicant's evaluation of the binding of the Mylan product, U.S. Herceptin, and EU Herceptin to the Fc gamma RIIIa and FcRn receptors.

As previously noted, antibody binding to these Fc receptors contributes to effector functions such as ADCC, as well as the PK of the product respectively.

The graphs on this slide show the surface plasmon resonance-based binding kinetics of the three products with respect to the U.S. Herceptin-based quality range criteria, depicted by the green lines and the EU Herceptin-based quality range criteria, depicted by the dotted blue lines. The analysis shows similar binding kinetics among the three products. Furthermore, because other types of Fc receptors can stimulate effector functions, such as antibody-dependent cellular phagocytosis, the applicant also assessed the binding kinetics of the three products to Fc gamma

RIa, Fc gamma RIIa, Fc gamma RIIb/c, and Fc gamma RIIb receptors. The data analysis showed similar binding kinetics among the Mylan product, U.S. Herceptin, and EU Herceptin.

This is a summary of our analytical similarity assessment based on the data provided by the applicant. The totality of the analytical similarity data supports a conclusion that the Mylan product is highly similar to U.S. Herceptin, notwithstanding minor differences in clinically inactive components and that the analytical comparisons between the Mylan product, U.S. Herceptin, and EU Herceptin support the adequately established the analytical portion of the scientific bridge.

Based on the analytical similarity data and publicly available information, the Mylan product has the same primary structure as U.S. Herceptin. In addition, the higher order structure and functional activity data support that protein folding, biological activity, and the intrinsic properties are similar between the two products.

Similar levels of protein content and most product-related species and similar stability profiles were observed between the two products. Similar product-related species refers to the presence of the same types of and similar amounts of the species of interest. However, minor differences and certain charge variants were detected.

Moreover, while the levels of afucosylation and total galactosylation, as well as the overall glycosylation profile with respect to the presence of the same glycoforms and site occupancy were determined to be similar between the Mylan product and U.S. Herceptin. Minor differences were observed in the levels of some glycosylation species. As I will elaborate in the next slide, these differences in charge and glycosylation do not preclude a conclusion that the two products are highly similar.

To elaborate on the differences in glycosylation, the figure on this slide shows a chromatographic profile of all the glycans and U.S.

Herceptin in green, the Mylan product in red, and EU in blue. The peaks in the chromatogram represent the different glycan species separated by this method. Orthogonal methods were also used to identify and quantitate certain glycan species.

These data show that the Mylan product, U.S. Herceptin, and EU Herceptin have the same glycosylation sites, similar site occupancy, the same glycan species, and similar levels of most glycans.

Importantly, no new glycan species are seen in the Mylan product. There are however, some differences between the profiles of these products due to minor differences in the amounts of some glycan species, as indicated by the yellow asterisk.

Examples of the glycan species that correspond to these differences included high-mannose species and sialic acid-containing species, as shown in the graphs on the left. The content of both of these species can impact the PK of the molecule. For total mannose content, all

lots are within the U.S. Herceptin-based quality criteria, depicted by the red line. However, the Mylan product lots have an overall higher total mannose content compared to most of the U.S. Herceptin lots, as well as most of the EU Herceptin lots.

For total sialic acid content, 31 percent of the Mylan product lots were outside of the U.S.-based quality criteria. However, the overall sialic acid content was very low. The levels were less than 0.12 moles of sialic acid per mole of protein for all three products.

Because a lack of glycosylation in the Fc region of the heavy chain of an antibody is correlated with the loss of effector function, an evaluation of the amount of antibody-lacking glycosylation was conducted by the applicant, as shown in the graph on the right.

The data show that while all lots of the three products were within the U.S. Herceptin-based quality range, the Mylan product lots have lower amounts of non-glycosylated heavy chain compared to

U.S. Herceptin and EU Herceptin.

The overall impact of the differences in glycosylation on functional activity was evaluated by using the cell-based ADCC activity assay that measures the amount of cell death after exposure to the products and through Fc receptor binding kinetics. As previously discussed, the levels of ADCC activity and the binding kinetics were similar among the Mylan product, U.S. Herceptin, and EU Herceptin.

Furthermore, the minor differences shown in sialic acid and high-mannose content were adequately addressed by data showing no impact on PK.

The other minor difference observed was in the amounts of charge species among the three products. The Mylan product lots were within the quality range criteria with the exception of the mean peak content of a single lot of the Mylan product, which was higher than the U.S. Herceptin quality range criteria.

Overall, the Mylan product lots generally

had lower levels of acidic species and higher levels of mean peak compared to U.S. Herceptin and EU Herceptin. These minor differences are shown by the mean percentages of acidic, mean, and basic species presented in the table on the slide. No differences were noted in basic species content among the three products.

The charge variant profile of an antibody can impact biological activity, immunogenicity, and PK. Therefore, to address these differences the applicant conducted characterization studies that revealed a correlation between the differences in charge species with differences in the levels of deamidation at the asparagine 30 residue on the light chain of the antibodies.

Deamidation at the site, which is located in the HER2 binding region of the antibody, was present among all three products but at different levels. The data showed that the levels of deamidation are slightly higher in the U.S. Herceptin and EU Herceptin lots compared to the Mylan product, which may be related to different

ages of the materials evaluated.

Additionally, an evaluation of the ADCC activity of the deamidated charge species was conducted to determine the potential impact of the differences on biological activity, and the data showed minimal impact. Furthermore, the variability in the amounts of these charge species is not expected to have clinical impact because no differences were shown in the biological activity of the Mylan product and U.S. Herceptin. Based on biological activity, immunogenicity, and PK data we do not expect the minor differences in charge species to have clinical impact.

In conclusion, the totality of the analytical similarity data supports a conclusion that the Mylan product is highly similar to U.S. Herceptin, notwithstanding minor differences in clinically inactive components. This concludes the CMC presentation. Our next topic will be clinical pharmacology, presented by Dr. Brian Furmanski.

FDA Presentation - Brian Furmanski

DR. FURMANSKI: Good afternoon. I'm Brian

Furmanski, the senior clinical pharmacology reviewer for this application.

The clinical pharmacology program aims to support a demonstration of no clinically meaningful differences between the Mylan product and U.S. Herceptin by evaluating the single-dose pharmacokinetic similarity between the Mylan product and U.S. Herceptin, and establishing the PK portion of the scientific bridge between the Mylan product, U.S. Herceptin, and EU Herceptin.

This slide outlines the clinical studies completed by the applicant and reviewed by FDA. As indicated in the red box, the applicant conducted study MYL-HER-1002 to evaluate PK similarity between the Mylan product, U.S. Herceptin, and EU Herceptin.

Study 1002 was a randomized, three-arm, parallel group study in healthy male subjects following a single 8 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 time in hours post-dose, and the Y-axis is the trastuzumab mean concentration in microgram per mL. As you can see upon visual inspection, all three concentration time profiles appear to be virtually superimposable.

Statistical analysis is shown in the figure on the right, which depicts the geometric mean ratios for the test, versus reference product and their corresponding 90 percent confidence intervals for each pair-wise comparison. The X-axis is the predefined similarity margin of 80 to 125 percent, which is represented by the vertical dotted lines. The Y-axis represents each pair-wise comparison. The PK endpoints of AUC zero to infinity, AUC zero to T, and C-max are represented by the triangle, circle, and square respectively.

In the first pair-wise comparison, highlighted in the blue box, for the Mylan product versus U.S. Herceptin the geometric mean ratios and the corresponding 90 percent intervals for all three PK endpoints of AUC zero to infinity, AUC

zero to T, and C-max fall within the predefined similarity margin of 80 to 125 percent.

Likewise, in the pair-wise comparison of the Mylan product versus EU Herceptin, the geometric mean ratio and their corresponding 90 percent confidence intervals for all three PK endpoints of AUC zero to infinity, AUC zero to T, and C-max fall with the predefined similarity margin of 80 to 125 percent.

Lastly, in the pair-wise comparison of EU Herceptin versus U.S. Herceptin the geometric mean ratios and their 90 percent corresponding confidence intervals for all three PK endpoints of AUC zero to infinity, AUC zero to T, and C-max again fall within the predefined similarity margin of 80 to 125 percent. Based on the results from 1002, we conclude that PK similarity was demonstrated.

In summary, results from study 1002 demonstrated PK similarity between the Mylan product and U.S. Herceptin. Study 1002 also established the PK portion of the scientific bridge

between the Mylan product, U.S. Herceptin, and EU Herceptin, which justifies the relevance of the comparative clinical data generated using EU Herceptin.

In conclusion, the PK results support a demonstration of no clinically meaningful differences between the Mylan product and U.S. Herceptin, and add to the totality of evidence to support a demonstration of biosimilarity of the Mylan product and U.S. Herceptin.

This concludes the clinical pharmacology presentation. Dr. Gao will now present the findings from the comparative clinical study 3001.

FDA Presentation - Jennifer Gao

DR. GAO: Good afternoon. My name is Jennifer Gao, and I will present the clinical efficacy and safety results.

The applicant conducted one comparative clinical study to evaluate the efficacy and safety of the Mylan product and EU Herceptin in patients with untreated metastatic HER2-positive breast cancer to support a demonstration of no clinically

meaningful differences between the Mylan product and U.S. Herceptin.

This was a multicenter, randomized, double-blinded, parallel group study in two parts. In part 1; patients either received the Mylan product or EU Herceptin with either docetaxel or paclitaxel by physician choice. Patients with at least stable disease after part 1 could continue in part 2 with maintenance monotherapy every 3 weeks until disease progression or death.

The intention to treat population consisted of all patients who were randomized to first-line treatment for metastatic HER2-positive breast cancer. The safety population consisted of all patients who received at least one dose of the Mylan product or EU Herceptin.

In general, per the FDA Guidance for Industry titled Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, an additional comparative clinical study would be needed to resolve any residual uncertainties and further evaluate whether there are clinically

meaningful differences between the two products. Margins are used to assess whether there are clinically meaningful differences.

In addition, the equivalence study needs to be feasible. Note that sample size is not based on establishing efficacy of the proposed biosimilar product.

In this equivalence study the risk ratio of overall response rate or ORR was used to measure treatment effect. For the applicant, equivalence margin per ORR ratio was set as 0.81 to 1.24. The margin was derived based on available data on the reference product from three trials from the literature.

Equivalence would be demonstrated provided that the 90 percent confidence interval of the observed response rate ratio falls in this pre-specified margin interval. The corresponding absolute difference in ORR is negative 13 to 17 percent, assuming the reference product response rate of 69 percent.

Shown in this slide are results for the

primary endpoint of ORR assessed by central review. As you can see here, the 90 percent confidence intervals of the response rate ratio in the intention to treat population is 0.98 to 1.22, which is within the pre-specified equivalence margin of 0.81 to 1.24. The differences of ORR between the two arms are also shown. Overall, the results show that ORR is similar between the two arms.

This is a high level overview of the safety analysis during parts 1 and 2 of the study. There are no meaningful differences in treatment emergent adverse events between the two arms.

Cardiac toxicities, infusion reactions, and pulmonary toxicities occurred in both arms with no meaningful differences and at rates consistent with the prescribing information for the approved drug.

Immunogenicity was reviewed, and found to be similar between the two arms.

Overall, there were no meaningful safety differences between the Mylan product and EU Herceptin, which supports a demonstration of no

clinically meaningful differences between the Mylan product and U.S. Herceptin.

The applicant is seeking indications that are the same as U.S. Herceptin. The clinical studies conducted by the applicant were in patients with metastatic breast cancer, so extrapolation must be used for other indications. Please note Herceptin's indication for treatment in gastric cancer is protected by orphan drug exclusivity expiring October 20, 2017.

In support of extrapolation to other indications, the agency notes that the mechanism of action of trastuzumab is the same across all indications. The applicant has demonstrated a similarity of the product with respect to analytical attributes, pharmacokinetic, immunogenicity, efficacy, and safety. Therefore, the agency considers extrapolation across all indications to be scientifically justified.

FDA Presentation – Jennifer Gao

DR. GAO: I will now review the overall summary of the FDA findings. This provides a

reminder of the description of biosimilarity, which includes 2 components. To be a biosimilar a product must be highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and the product must have no clinically meaningful differences in terms of safety, purity, and potency from the reference product.

The FDA finds that the totality of the analytical data supports a demonstration of the two products as highly similar, notwithstanding minor differences in clinically inactive components.

The clinical data, which includes pharmacokinetics, efficacy, safety, and immunogenicity, supports the finding of no clinically meaningful differences between the two products.

In conclusion, the applicant has established an adequate scientific bridge between EU Herceptin, U.S. Herceptin, and the Mylan product. The totality of the evidence supports biosimilarity of the Mylan product and U.S. Herceptin.

Extrapolation to all indications of use for U.S. Herceptin is supported by the understanding of the mechanism of action across indications and demonstration of biosimilarity.

Please discuss the following, whether evidence supports a demonstration that the Mylan product is highly similar to U.S. Herceptin, notwithstanding minor differences in clinically inactive components; whether the evidence supports a demonstration that there are no clinically meaningful differences between the Mylan product and U.S. Herceptin in the study condition of use; and whether there is adequate scientific justification to support licensure for all of the proposed indications.

We ask the committee to vote on the following question: Does the totality of the evidence support licensure of the Mylan product as a biosimilar product to U.S. Herceptin for the following indications for which U.S. Herceptin is licensed, and for which Mylan is eligible for licensure, namely HER2-positive breast cancer in

the adjuvant and metastatic settings?

Thank you.

Clarifying Questions to Presenters

DR. ROTH: Thank you, Dr. Gao.

We'll move on to clarifying questions, both for the agency and for the applicant. If you have a question or comment, if you could let Jay know, I'll write your name down and we'll try to take those in order.

Maybe I could start things off here for any of my breast cancer colleagues either Dr. Seidman, or Dr. Rugo, or Dr. Gradishar. In terms of the cardiac dysfunction from the reference compound, what we know and can apply to this, is a single peak at the data at 48 weeks sufficient, or do we have to worry about the patients who are getting another year of maintenance therapy? Should we be worried about something that might be looming beyond the 48 week time point?

DR. ANNWEILER: Dr. Rugo, please come to the podium.

DR. RUGO: Hope Rugo, again, from UCSF.

That's a great question, and actually one that we looked at quite a lot in the early development of trastuzumab. Indeed the cardiac toxicity from trastuzumab is an early event almost without exception. We all have a single patient who develops something at 4 months, but after that period of time we really don't see a late cardiac toxicity.

In fact some of the trials that have looked at agents after trastuzumab have been criticized because you already selected out the group of people who don't have cardiac toxicity. It's related to, of course, many different factors, including prior exposure to anthracyclines.

DR. ROTH: Okay. Thank you. Dr. Armstrong?

DR. ARMSTRONG: Hope, why don't you just stay there. I think with regards to the use of this agent, the elephant in the room is pertuzumab. You've requested this for metastatic breast cancer, and when trastuzumab is used in the setting in metastatic breast cancer, at least in the United States, it's almost always used with pertuzumab.

You didn't request the neoadjuvant setting, but our neoadjuvant therapies are usually extrapolated from our adjuvant therapies, and pertuzumab is approved with Herceptin in the neoadjuvant setting. And that's frequently continued, although it's not approved, in those patients after their surgery. With publication of the APHINITY study, I don't know if it's going to be presented for use.

The whole issue becomes the settings in which you're proposing to use this drug as a single agent, a big percentage of those, there are actually going to be use, or people are going to be inclined to use it with pertuzumab.

My question is do you have any studies to look at this in combination with pertuzumab? This now gets pretty technical with regard to binding sites and potentially very minor changes in the structure of this antibody compared to the parent, Herceptin, and the binding and the efficacy in combination with pertuzumab.

DR. RUGO: It is a great question, and I'll

just answer the clinical part of it and then turn it over to my Mylan colleagues, but -- and indeed the elephant in the room because I think the role of pertuzumab, both in the adjuvant setting for lower risk patients and in the metastatic setting in patients who recur on adjuvant trastuzumab or within a year, we don't really understand.

Indeed much of our use of trastuzumab in the metastatic setting is after first-line therapy where we don't use pertuzumab currently. Trastuzumab and pertuzumab given together have shown no interactions, pertuzumab by itself has its own set of toxicities that are maybe enhanced by certain chemotherapeutic agents. But, indeed the combination of those two antibodies had no difference in toxicity, no increase in cardiac toxicity, no increase in things that are generally seen with the addition of trastuzumab like neutropenia just because of longer exposure.

I, myself, as a clinician, have absolutely no concern about the combination of using a biosimilar trastuzumab with pertuzumab. That said,

I think there are many settings where we will be giving trastuzumab by itself. That's after progression where we use it in the United States; usually patients receive it until death, unlike the rest of the world where there's limited access.

In the neoadjuvant setting, we've seen improved PCR rates, but in trials that didn't include anthracyclines. I think we're still really trying to figure out where we need to be using pertuzumab or not in early stage breast cancer. As you know the APHINITY data showed a modest benefit in patients with the highest risk cancers, and essentially no benefit in low risk cancers which allows us, in fact, to give trastuzumab without the worry of pertuzumab.

Then lastly; the very first comment, which was that continuing pertuzumab after the neoadjuvant setting, in fact, I think is not commonly done. I think it's very much dependent of geographic area; for example, in California we never continue pertuzumab. We would not have approval for it based on the FDA indication.

DR. ARMSTRONG: Part of question was actually, not so much about the toxicity because you're right, but the issue about the blocking the binding site.

DR. ANNWEILER: Let me comment on that, I wanted to add on that comment.

In respect to the biosimilar concept, so Herceptin was shown to work in combination with pertuzumab and our data have shown analytical similarity with only really very minor differences and very minor species of the glycol pattern with no differences at all with respect to HER2 binding.

As there's no drug interaction shown for Herceptin, based on the extrapolation concept, we would also not expect any differences as we've also seen in our functional studies.

DR. ARMSTRONG: But you haven't looked at that specifically?

DR. ANNWEILER: No, we have not looked at this specifically.

DR. ROTH: Ms. Preusse?

MS. PREUSSE: Hi. Courtney Preusse, Fred

Hutchinson, consumer rep.

I have a number of questions. I will start with what is, I believe, somewhat a continuation of Dr. Armstrong's question regarding the kinetics of the binding to the HER2 kinase. My understanding of the functional assays, as presented by both the sponsor and the FDA, is that there was really much more of a narrow spread of the potency of this new drug as compared to Herceptin in both the U.S. and the EU. Perhaps I'm not reading this correctly or perhaps it's just a much more limited data set with this new proposed drug, but I'm hoping that you can speak to that and clarify the limited spread.

DR. ANNWEILER: Is your question that the response in the functional test was tight and you don't see much spread?

Well the lots we have sampled from the innovator reference product, it's been about 6 years, whereas our own lots, it's been about 4 years. There could well be a time-related difference where you see some more limited spread across somewhat younger batches from our product

versus the innovator.

Otherwise, they were run mainly side-by-side at the same sensitive assay, so other than that inherent variability that we see as an outcome of products being produced in biological cells, we have no other explanation for that wider variability.

MS. PREUSSE: Sorry, I suppose my question is more for Dr. Rugo, because it -- and more centered around the clinical effects, if any, that you might extrapolate from this data. As Dr. Rugo and the other breast oncologist in the room can speak to much better than me, data has come out to show that early stage HER2-positive breast cancers are recurring much more frequently than non-HER2 expressing. And so, it just gives me a little bit of pause to see that where there's relative potency perhaps there's less of an effect, but maybe I'm reading too much into it.

DR. ANNWEILER: Dr. Rugo, would you like to take the question?

DR. RUGO: Just so I clarify the question;

you're worried about the potency of the drug based on those preclinical or PK assessments, et cetera and potency questions?

MS. PREUSSE: Right.

DR. RUGO: I think that those -- you know it's an interesting thing, as a clinician being part of this development and learning about biosimilars because we really don't think about this when we are using a new drug in the clinic.

Now we have to sort of re-think how we evaluate those agents, but if you show already that in a very sensitive indication that the drug is similar and you understand the variations between different lots, different productions, and different sites of production within the reference compound it makes you realize that those small those small differences that you see on those graphs are meaningless clinically.

Indeed trastuzumab has had a huge impact on outcome for HER2-positive early stage breast cancer changing it from the worst outcome to potentially the best outcome disease that we see in some -- in

many cases, not all.

I don't have any concerns because we've seen the same clinical activity in metastatic disease where in some ways it's a higher bar because it has to keep working.

MS. PREUSSE: Okay.

DR. RUGO: They still have a lot of disease, right, so it has to keep working. We've seen that, in fact, even though trastuzumab lots have changed over time and there's some sort of play in all of those graphs, that trastuzumab remains highly active, so it didn't really concern me as a clinician.

MS. PREUSSE: So there's nothing here to indicate that the higher recurrence in HER2-positive early stage breast cancer has anything to do with the binding mechanisms, especially here with a new drug or with the potency of the drug as it binds to the tyrosine kinase?

DR. RUGO: We didn't see because we studied patients who had chemotherapy naive metastatic breast cancer, so we don't have data suggesting

increased recurrence in HER2-positive early stage breast cancer. I'm not sure where that connection is coming from.

We really looked at patients who had largely -- actually almost identical to the CLEOPATRA population, 90 percent had never seen trastuzumab, they had chemotherapy naive in the metastatic setting metastatic breast cancer, and trastuzumab naïve in 90 percent. So there isn't any data to suggest an early stage differential benefit or any actually because we're not presenting early stage data, but in the metastatic setting the response was maintained after chemotherapy, which is nice people stayed controlled. We have 48 week data, so they were off chemotherapy and that suggests similar potency.

MS. PREUSSE: There was some preliminary data at San Antonio, but I'll sidebar that; we could always talk after.

Lastly, could you speak to whether there were any differences between male and female?

DR. RUGO: The patients enrolled in this

trial were female, and as you know breast cancer in males is extremely uncommon and largely ER-positive, so in fact I don't know that I have treated a man and I treat a lot of breast cancer with HER2-positive breast cancer.

DR. ANNWEILER: Thank you, Dr. Rugo. Maybe to add, our phase 1 three-way PK bridging study was in male volunteers, and we didn't see any difference in PK in exposure.

DR. ROTH: Dr. Uldrick?

DR. ULDRICK: Hi, yes thanks. I was reassured by the results from the routine cardiac monitoring and that it was equal between arms and reversible. One event that did seem to stand out in the Mylan arm was cardiac failure, which was presumably clinical events, 2.4 percent versus 4, in evaluating the safety. I was wondering if the sponsor could provide some additional details around the etiology of the cardiac failure and whether there were risk factors, such as chest wall radiation or prior anthracycline use that potentially contributed to this finding.

DR. ANNWEILER: For this question I would like to invite Dr. Barve to the podium.

DR. BARVE: Abhijit Barve, Mylan clinical -- can we pull the slide on the overall cardiac adverse events please.

Your observation is accurate, while the slide had been pulled up, there were 6 events of cardiac failure. These were investigator assessed events, so there is a granularity that is associated with how the preferred terms are captured and -- yes, slide up please.

What we did was that we actually looked at a modified standardized MedDRA query, so this kind of combines all the terms that could potentially relate to cardiomyopathy or cardiac failure. If you look at it; 6 and 1 for cardiac failure is, is correct, but when you combine that with left ventricular dysfunction or metabolic cardiomyopathy or congestive cardiomyopathy, all of them are known toxicities with trastuzumab, the numbers become 12 in our arm, and 10 in the Herceptin arm, which is 4.9 and 4.1 percent. When you compare that to the

historical data from the CLEOPATRA study, it was 8.3 percent.

You're correct in that 6 of the 12 patients in our arm received anthracyclines versus 6 of the 10 patients in the Herceptin arm received anthracyclines, and one subject each received chest radiation in both arms.

If you go to the next slide, please, we also evaluated it in a much more systematic manner to look at -- because these were investigator assessed events, so we looked at it and said, how does this correlate from a left ventricular ejection fraction measurements, and looked at it from a CTCAE perspective. As you can see here the grade 3, which is left ventricular ejection fraction between 20 and 39 percent and a drop off greater than 20 percent, there are 2 subjects in our arms and 4 in the Herceptin arm and grade 2 it is 13 and 11.

If you look at the data in a very more objective and a systematic manner it looks very similar, as well as when you look at the modifiers. Thank you.

DR. ULDRICK: Thanks, that's very helpful.

DR. ROTH: Dr. Chow.

DR. CHOW: Basically, I have a couple questions. The first question is related to the analytical similarity assessment. Is seems to me, not all of the lots were used for the analytical similarity assessment for the identified CQAs. I was wondering whether the sponsor can talk a little bit about how those lots were selected in order to address the potential selection bias for the analytical similarity assessment.

DR. ANNWEILER: Yes. Dr. Vallano will take this question.

DR. VALLANO: Pat Vallano, Mylan Scientific Affairs. Your question involved the selection of lots for the analytical similarity assessment. Yes, it is true that not all of the lots were included in each of the analytical tests. There were several different factors that drove the conclusion of lots for a particular test.

One was the analytical method itself, the type of method, and whether there were orthogonal

methods available for that particular attribute. Also the analytical method variability drove the lot selection.

Another factor was the availability of unexpired lots at the time that the test method was available, and then primarily for the functional assays the availability of the same reference standard used across analyses. There was no bias selection of lots across the testing regimen.

DR. CHOW: Thank you. The second question is regarding the PK study. Basically, I think, if I understand correctly, pair-wise comparison was conduct in order to establish results of scientific bridging between the EU and U.S. and also the Mylan product.

Then I was wondering, I think that instead of using the pair-wise comparison, because we did not really adjust for the 4-year multiple comparison, that's one thing.

Also the other thing is that for these pair-wise comparisons, actually we have 3 comparisons. Two comparisons; for example the

Mylan product versus the U.S. and the EU versus U.S., those two comparisons were actually used in a U.S. product as a reference, but the other comparison, which is the Mylan product versus the EU that we used a different reference product.

Instead of a pair-wise comparison, I was wondering why not consider the so-called simultaneous confidence interval approach? In other words, you can come with a simultaneous confidence interval approach, which would take all of three product data into consideration and come up with a more reasonable statistical approach in order to establish some kind of bridging among the three products.

DR. ANNWEILER: Dr. Barve, would you take the question, please.

DR. BARVE: I think that's an excellent question, but I think the regulated requirement does in terms of what the regulators look. They typically would like to look at pair-wise comparisons and that is how we did it.

The study was designed to look at multiple

comparisons when we powered the study, and it was powered adequately for doing that comparison.

DR. ROTH: Anybody from the agency want to comment? Because we see this over and over again, we see triple pair-wise comparisons and we're getting used to it. The question is, should we?

DR. SHEN: I think the multiple comparison power, the comparison is okay. We ask for all three pair-wise comparisons have to pass in order to pass the scientific bridging -- two of the comparisons passed the bridging's established, and we asked all. So my understanding is there's no multiple justification.

DR. ROTH: Dr. Karara?

DR. KARARA: Yes, clarifying question for the sponsor. In reading the briefing document on page 76, you did pharmacokinetic analysis on samples from the clinical study, the HERITAGE study, and the statement there you estimated the statement says about drug clearance was not different between the MYL-1401O and Herceptin.

How different or how close were they at the

estimates of the direct clearance in the HERITAGE study?

DR. BARVE: Abhijit Barve, clinical. So we actually -- slide up please, can you get the exposure slide, please? Show the data -- the next slide.

We conducted a plot PK of where a subgroup of patients actually had more extensive sampling, whoever agreed to participate; we had about 46 subjects in our arm and 37 in the Herceptin arm who participated. In addition, we had all the subjects who had PK that was assessed prior to taking their cycles in cycles 2, 4, 6, 8, and 9, which I showed you in my presentation. In addition, there were additional times points that were taken. Slide up please.

This is the data, which is looking at the PK exposure summary estimates based on the Bayesian model at cycle 6. As you can see here the clearance is very similar between both the arms. The dose that was given was also very identical, and we also looked at dose normalized AUC and C-max

as part of that plot PK exercise.

DR. KARARA: Thank you.

DR. ROTH: Dr. Seidman.

DR. SEIDMAN: Thank you. First, I just want to thank both FDA and Mylan presenters for being very, very clear.

My question, without questioning the virtues of extrapolation, has to do with the choice of primary endpoint for response rate at 24 weeks, and the extrapolation of that to the role of this drug in the adjuvant setting, specifically for metastatic breast cancer.

We recognize that patients on this trial received both taxane and trastuzumab for those first 24 weeks, and both the taxane component and the antibody contribute to that response rate at 24 weeks. Some would argue that the taxane is more of the heavyweight if you compare monotherapy activities.

The sponsor, on page 89 of the briefing, showed a very good correlation coefficient between response rate and progression-free survival in

metastatic breast cancer, it was about 0.9.

I was wondering if anyone might be able to comment on that relationship between response rate and outcomes in the adjuvant setting.

DR. ANNWEILER: Dr. Barve, please.

DR. BARVE: Dr. Seidman thank you for the question. What I will show you is the correlation between the ORR and PFS in metastatic breast cancer, and then I will have Dr. Rugo talk about how we can really use that data to take it to that next level.

Can we get a slide on ORR versus PFS? Slide up please.

This is what is available in the literature, as it relates to correlation of the ORR versus PFS from the literature, a P-value of 0.96. This is a paper where it was not HER2-positive metastatic breast cancer, this was a generalized metastatic breast cancer, but if you go to the next slide please. Slide up please.

This is what we did as part of the analysis for our study, where we really looked at 5

different studies. Looked at the time to progression, which is there on the X-axis and on the Y-axis we have got the overall response rate in terms of percentages.

What you can see here is a very strong correlation in terms of the R-squared value. So clearly there is a very good correlation at least in HER2-positive metastatic breast cancer between an ORR and PFS. The applicability in terms of ORR and PFS is relevant, but I'd like Dr. Rugo to talk about how this can apply.

DR. RUGO: HER2-positive disease, I think, is quite unique in this way. I understand your question completely because you're giving the primary endpoint at overall response rate is looking at the combination of a taxane and the trastuzumab biosimilar or Herceptin, but the response rates are very similar, so we'll agree on that.

If you look at that correlation between response and progression-free survival in HER2-positive disease, it's actually tighter than

it is potentially for other subpopulations like ER-positive indolent cancer where we have a harder time with response.

That's actually quite nice. You know the PFS is going to be similar, and we showed the 48 PFS is similar. That involves 24 weeks on antibody therapy alone. That suggests that, first in the adjuvant setting, our approval and the way we give drug is in a very similar way. The chemotherapy is the heavy hitter. We add the trastuzumab to improve response, and that has resulted in improved disease-free survival and overall survival certainly in the adjuvant setting and we've seen that response in the neoadjuvant setting.

And you get the exposure to drug, which we already know is effective from the HERITAGE trial, otherwise people would have relapsed very quickly.

To me that extrapolation seems very comfortable and justified by the data and the inference from all of the studies we've done in HER2-positive disease.

DR. SEIDMAN: This may be for a

statistician, but will reflect my ignorance, but if the correlation coefficient between response rate and PFS in metastatic breast cancer is 0.9, and then if you actually had the data, and no one has shown me the data, of what the correlation between PFS and metastatic breast cancer and relapse-free survival in the adjuvant setting is -- and let's say that were 0.8, would the relationship therefore, between overall response rate in metastatic breast cancer and relapse-free survival in the adjuvant setting be 0.9 times 0.8 or 0.7?

I'm wondering how robust the overall response rate is for that endpoint --

DR. RUGO: You know we can't answer that question --

DR. SEIDMAN: -- and I'm as supportive of extrapolation as anybody in the room.

DR. AMIRI-KORDESTANI: Can I actually add a comment here that basically, we're not extrapolating between the indications in that way because you certainly cannot extrapolate that the ORR in the breast cancer actually relates to

metastatic gastric cancer at all.

Basically, you should look at the totality of the evidence, that the biosimilarity and also the mechanism of action is similar and looks at that evidence to support that extrapolation.

DR. SEIDMAN: I agree, and I understand entirely about extrapolation going beyond breast cancer to other tumor types. We also the difference between the adjuvant setting and the metastatic setting, and the goals are different and the duration on monotherapy with the antibody is different perhaps as well.

I just draw attention to that as a methodological issue.

DR. ROTH: Ms. Chauhan?

MS. CHAUHAN: Thank you. My question is about cardiotoxicity for the sponsor. I noticed that you define it as reduced ejection fraction. In fact, more than 50 percent of the people who have heart failure have preserved ejection fraction. How have you eliminated this group from your consideration for relevant cardiotoxicity?

DR. ANNWEILER: Dr. Barve.

DR. BARVE: We looked at ejection fraction more as an -- I could say that's a slightly different way of looking at it in terms of a diastolic dysfunction, which could happen in a few patients. But, the majority of them, the first thing as it relates to how -- the prescribing information indicates in terms of evaluating left ventricular ejection fraction every 12 weeks, and that's what we did as part of this study. To look at subtle differences, if there is anything really impacting cardiac function, and that's how we approached it.

MS. CHAUHAN: [Inaudible - off mic]. So you just separated it out?

DR. BARVE: Yes. We just looked at it, it terms of left ventricular ejection fraction, as well as the events and we thoroughly evaluated all the events that happened in these patients.

DR. ROTH: Dr. Mager?

DR. MAGER: I just wanted to follow-up quickly on Dr. Karara's question. The slide that

went up that showed the population analysis, it indicated Bayesian parameters. I just wanted to confirm then, this was a stand-alone population analysis and those are post-hoc Bayesian estimates? Or did you have a prior population model and then use a map Bayesian approach to calculate individual parameters?

DR. ANNWEILER: Dr. Barve.

DR. BARVE: The methodology that we used is really to first build a model using the data that is available, and then look at what are the different attributes that could potentially have an impact on these. Then we bootstrapped the model, for goodness of faith, to really come up with the right model, and then evaluated the data based on the available information.

DR. MAGER: So it was a stand-alone model built on the data from that trial then?

DR. BARVE: Yes.

DR. MAGER: Okay. Thank you.

DR. ROTH: Dr. Moreira?

DR. MOREIRA: Thank you. Just a quick

clarification from the sponsor on the two PK studies with the healthy male volunteers, I think I heard that they were with different formulations? I was just trying to find out if that's correct, and then, why so? And if going forward, if you're planning on using different formulations or settle on one or --

DR. ANNWEILER: So the pivotal PK three-way bridging study was performed with a to be commercialized formulation, which differs in two very conservative ways from Herceptin itself, and that was also the formulation that was tested in the metastatic breast cancer study, it was included in the three-way bridging study, and will be the commercial formulation.

The supportive PK study was performed with a former formulation that had the same formulation as Herceptin, but this will not be carried forward in development.

DR. MOREIRA: Okay, thank you.

DR. ROTH: Dr. Gordon.

DR. GORDON: So I'd like to echo the

comments that I think both the sponsor and the FDA have done a nice job with the presentation, but I have a clarifying question around the amount of exposure to both chemotherapy and antibody in the HERITAGE study. I take it, it was roughly the same across both arms?

DR. ANNWEILER: Yes, it was roughly the same.

DR. GORDON: Okay, great.

DR: ROTH: Any other comments or questions? Okay, we're going to take a break. I have that it's 3:00. We'll resume at 3:20 with the OPH. Panel members please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 3:20, thank you.

(Whereupon, at 3:00 p.m., a recess was taken.)

Open Public Hearing

DR. ROTH: Let's go ahead and resume, and we'll proceed with the open public hearing portion of our afternoon.

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

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

Will speaker number 1 please step up to the podium, introduce yourself, state your name and the organization that you're representing?

MS. CRAMER: My name is Angie Cramer. I'm from Johns Hopkins Breast Center. I'm a certified oncology nurse navigator working with breast cancer patients. I do not have any financial interest.

I'm also a seven-year breast cancer survivor, my grandmother and mother both died of

metastatic breast cancer. My sister and aunt are also breast cancer survivors, and between us my sister and I have 5 daughters and 7 granddaughters, so my presence here is not just professional but personal.

My mother had metastatic breast cancer for nine and one-half years. Thankfully, she had adequate healthcare coverage. If she'd had to pay out of pocket for her medications she would not have lived with the disease for 9 and one-half years. In my professional experience, many of my uninsured or underinsured breast cancer patients will choose food on the table over paying for their medication.

As an oncology nurse navigator, I have access to some resources to help these patients, but those agencies have limited funds and often can only help temporarily.

Biosimilars are already available in Europe, what is the point of having products available if patients cannot get access to them here in the United States? We need to get biosimilars on the

market as soon as the brand patent expires.

Having competition will drive medication prices down, brand companies will have to reduce their prices with the introduction of biosimilars. This will enable our patients to have the best of both worlds; brand, drug prices decrease, and the option exists for use of biosimilars by choice.

According to an article by Anders Johnson et al, potentially one-third of all breast cancers are diagnosed among premenopausal women. The Young Survival Coalition reports that more than 250,000 woman living in the United States today were diagnosed with breast cancer under the age of 40.

Breast cancer in younger women is usually more aggressive and can be a life-long condition, which requires close following. Additional diagnostic testing is costly, and the risk for recurrence is higher in younger women.

It's important to have biosimilars on the market as soon as the brand patent expires, so that brand medication costs are driven down, and biosimilars are an option for these women who may

be paying additional testing for much longer than women diagnosed at a later age.

The Young Survival Coalition also reports that African American women under the age of 35 have breast cancer rates 2 times higher than Caucasian women, and die from breast cancer 3 times as often as Caucasian women of the same age. Having biosimilars available to all patients, especially those that have disparities in care, could lessen the gap amongst different socioeconomic groups.

In conclusion, biosimilars provide the same therapeutic value as brand name medications at a much lower cost. Having biosimilar medications available to those patients in the United States will drive the cost of brand drugs down, and thereby reduced financial toxicity for our cancer patients who may have to decide whether to pay their bills or receive life-saving and life-extending therapies. Thank you.

DR. ROTH: Thank you. Speaker number 2, please come to the podium. State your name and the

organization that you represent.

MS. SIMMON: My name is Christine Simmon, and I'm the executive director of the Biosimilars Council. I have no disclosures to make. The Council is the division of the Association for Accessible Medicines; members include those working to develop biosimilars for the U.S. market.

Biologic medicines are often the only lifesaving treatments available to patients, but as we just head first-hand from a nurse on the front lines, the high cost of these medicines can create significant barriers to access. We believe biosimilar competition is critical to ensure in patient access to treatments.

Education is a core component of the council's mission. We strongly believe the success of the biosimilars market will rely on scientifically sound education to build patient and provider confidence in these products.

For that reason, we appreciate the agency's rigorous review of biosimilar applications. We believe the FDA approval of a biosimilar should

function as a clear an unequivocal statement to patients, providers, and payers that, that biosimilar is as safe and efficacious as its reference product.

As such, we strongly encourage the agency to be wary of messaging regarding so-called non-medical switching, which has been used by some to sow doubt within the patient and provider communities.

We are concerned the focus around switching has been deliberately used to create uncertainly. These messages are in direct contradiction with the standards established by statute and enforced by this agency.

Differentiation between biosimilars and their reference products risks undermining the, important and much needed, patient and provider education already being done by FDA. It directly contradicts the medical evidence from Europe and other advanced countries that have much more experience with biosimilars and have seen no measureable clinical differences between those and

their reference products.

We want to thank the agency for the important draft guidance providing helpful clarity for manufacturers seeking an interchangeability designation for biosimilars. We appreciate that the totality of the evidence standard used in previous review was maintained, and we support extrapolation.

While we believe the guidance should go further by allowing biosimilar developers to use foreign-sourced reference product during development, it overall is a positive step forward.

In conclusion, the council commends the FDA on its continued success and implementation of the biosimilars pathway, and we thank you for the opportunity to comment.

DR. ROTH: Thank you. Speaker number 3, if you would approach the podium, state your name and your organization.

MS. GREENBERG: Good afternoon. My name is Sally Greenberg. I am executive director of the National Consumers League. We appreciate the

opportunity to testify today in support of biosimilars.

Since our founding in 1899, the National Consumers League has been concerned ensuring safety, effectiveness, access, and appropriate use of both prescription and over-the-counter drugs and medication adherence is a specialty area of ours.

We have helped to advance our Medication Adherence Program through our Script Your Future Campaign. So in addition to being a champion for safe, effective, and accessible medicines, NCL is committed to ensuring the consumers have the necessary access to quality medicines that are also affordable.

NCL's a strong supporter of biosimilars, and we testified last October here at the FDA in support of the reauthorization of the Biosimilar User Fee Act or BSUFA. We recognize that the entry of biosimilars into the U.S. market presents an opportunity to broaden patient access to lifesaving biologic treatments while bolstering competition, reducing costs, and realizing better health

outcomes.

Biologics are a result of revolutionary advancements in the development of therapies for patients with debilitating and deadly diseases, such as diabetes, multiple sclerosis, rheumatoid arthritis, and various forms of cancer.

Unfortunately, the price for these complex therapies is often prohibitive for the vulnerable patients who need them the most, with some costing upwards of several hundred-thousand dollars a year. Biosimilars provide a less expensive alternative to their reference products, offering the same potency and therapeutic benefits at a fraction of the price.

Similar to the dynamic relationship of generic and brand name drugs, the presence of biosimilars will not only encourage patient choice, but also boost market competition and drive down costs.

The biosimilar being considered here today would be an alternative to the biologic medicine trastuzumab, I'm sure I'm mispronouncing it, which

treats HER2-positive breast cancer and gastric cancer. HER2-positive breast cancer is a particularity aggressive form of breast cancer that affects 1 in 5 women with the disease, and in 2017 alone it's estimated over 300,000 will be diagnosed with breast cancer and over 40,000 women will die as a result of this terrible disease.

Fortunately, biologic therapies have transformed the way in which we treat breast cancer with many patients experiencing decreased odds of recurrence, increased odds of survival, and an improved quality of life.

For all of these reasons the NCL supports the FDA's science-based review of this and other new biosimilar applications, so that patients can have expanded and affordable access to the same and effective biologic medicines they so badly need.

Thank you for the opportunity to testify today.

DR. ROTH: Thank you. Speaker number 4, your name and your organization please.

MR. PHILLIPS: Good afternoon. My name is

Thair Phillips. I'm the president and CEO of RetireSafe, a nationwide non-profit 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 these 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.

Most of you heard my testimony this morning that centered around a process where PBMs and insurance companies would remove a reference biologic from their formulary, thus forcing the

patient to switch to a biosimilar. Many refer to this as non-medical switching. I testified this morning that RetireSafe felt that this was unsafe and should be stopped.

I appreciate the comment this morning by the patient representative on the AdCom panel concerning this type of non-medical switching and the problems it may cause patients. I am concerned with the answer that was given by the FDA.

My take on the answer was that the FDA was not concerned since the biosimilar was deemed similar to the reference product. If this is FDA's approach, then they would not be worried if one of the biosimilars for the reference product, that had already been approved, would be substituted for the reference product at the pharmacy tomorrow.

If this is the case, the whole discussion about interchangeability is moot, since every biosimilar that is approved automatically is deemed interchangeable.

I sincerely hope this is not the case, and would greatly appreciate a clarification on the

answer to the patient representative's question this morning and to this issue in general. Thank you.

DR. ROTH: Thank you. Speaker number 5, your name and organization please.

MS. McCASLIN: Good afternoon. For those who were here this morning I apologize for the redundancy of my comments. But to the distinguished members of the Oncologic Drugs Advisory Committee, Dr. Gotlieb, and other esteemed representatives of the FDA, thank you for the opportunity to comment here today.

My name is Tiffany McCaslin. I'm a 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 761074.

Our organization 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 overall 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 dollars 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 patient's access to biopharmaceutical advances that increase the quality and the 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 differs from that of small molecules, we support the notion that, in general, competition fosters innovation and that those innovations have the potential to redefine markets to benefit patients.

To this end, we support the direction that FDA has laid out with regard to biosimilar development requiring the demonstration that a

biosimilar demonstrate biosimilarity to the reference product, and believe the FDA has put in place the appropriate patient safeguards to permit data extrapolation to inform appropriate biosimilar use.

Again, we thank the committee for holding this important meeting today, as well as all those at FDA, CDER, OND, and other sister agencies. Thank you.

DR. ROTH: Thank you. Speaker number 6.

DR. CRYER: Good afternoon. My name is Dr. Dennis Cryer, and 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 I am thus representing their views here as well. I have no financial or other conflicts of interest.

BPC supports sound policies that promote the fully informed and safe use of biologics, including biosimilars for all patients.

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

In addition to the two biosimilar policy issues I mentioned earlier today, the collaborative encourages the FDA to finalize several biosimilar policies, as well as to thoroughly review biosimilar applications through this AdCom process.

Continuing from my comments this morning, my third policy point would be the FDA should provide clear and concise guidance to industries surrounding interchangeability among biosimilars and their reference products.

To demonstrate interchangeability a robust and risk-based data package is particularly important, as these products may be substituted for the reference product without intervention from the prescribing health provider and this would be paramount for successful acceptance and uptake of biosimilars.

BPC believes that the design and primary endpoints of the clinical switching studies will be critical in determining the safety and efficacy of the medication, as well as the appropriateness of interchangeability.

Fourth policy point -- each biological product needs a distinguishable and memorable non-proprietary name. FDA final guidance states that all biological products will bear a non-proprietary name that is a combination of a core name and a four letter suffix devoid of meaning.

However, as BPC has voiced previously, a memorable suffix could identify the license holding manufacturer and would be easily remembered by those who frequently prescribe biologics. Further, such a suffix would better equip patients, physicians, and pharmacists to accurately recall or ascertain specifics about the biosimilar, which may differ from those of the originator such as approved indications, administration routes, and delivery systems.

Thank you for the opportunity to share our perspectives on issues critical for the safe use of biosimilars, as well as other biologics. An expanded discussion of these four policy issues has been submitted to the docket for these committee meetings today.

BPC looks forward to continuing our work with the FDA to ensure patient safety and physician confidence as more biosimilars are developed. Thank you again.

DR. ROTH: Thank you. Speaker number 7?

MR. McNEELY: Good afternoon. My name is Larry McNeely. I am policy director for the National Collation on Healthcare. We're an alliance of over 80 healthcare stakeholder organizations spanning healthcare provider, payer, consumer, purchaser organizations. Together our members represent, we estimate, close to 150 million Americans.

The National Collation on Healthcare is a strong supporter of a strong biosimilar pathway, and approval of biosimilars. Biosimilars are a

safe and effective way to treat patients, as we've seen in other industrialized nations; Japan, the European Union.

I should also indicate echoing the comments of some of the previous speakers, that drug development is increasingly focused in the biologics base. If we are going to bring the next generation of life-saving, life-extending medicines to actual patients, we're going to need competition to make those medications as affordable as they can be. Biosimilars are critical to that goal.

Frankly, that kind of competition, as folks have eluted to, can bring tens hundreds of billions of savings we believe over the next decades, and it's why we've seen some interested disparagement of the safety of biosimilars.

Because of the high price of brand name biologics, like trastuzumab, the reality is patients are not getting the care that they may need either because of out-of-pocket cost or because of higher premiums rooted in the underlying trend in drug cost. The one thing we know isn't

safe for patients, is for patients to not receive the care that they need.

Again, thank you for the opportunity to testify before this committee today and for your work on this issue.

DR. ROTH: Thank you. Speaker number 8?

MS. MILLER: Good afternoon. My name is Elizabeth Miller, and I'm representing the United States Pharmacopeia today and I have no financial interests to disclose.

On behalf of USP I would like to thank the agency for allocating time for us to comment on the approval application of the proposed biosimilar Herceptin, and to give us the opportunity to articulate USP's support for biosimilars.

USP is an independent, scientific, nonprofit organization dedicating to protecting and improving public health. We collaborate with the FDA and other stakeholders to develop public standards that help ensure the quality, safety, and efficacy and benefit of medicines and foods.

USP shares FDA's goal of advancing and

promoting patient safety across all medicines, and we support efforts to broaden access to safe, effective, biosimilar products. Better access to biosimilar products will facilitate the availability of lifesaving therapies while helping to ensure the cost to patients and the healthcare system remain affordable and sustainable, and upholding the FDA's standard for evidence-based science-based regulation.

The biologic drug, Herceptin, has had an important impact on the treatment of breast cancer since it was first approved in 1998. Biologic medicines, such as Herceptin, have transformed quality of life for patients with chronic conditions. As more biosimilar products gain approval and enter the market, increased competition will provide more treatment options and better patient access to life-sustaining and life-altering medications. The situation is similar in some ways to the advent of generics for small molecule drugs.

USP recognizes and applauds the FDA's

substantial work to advance the successful implementation of the Biologics Price Competition and Innovation Act in efforts to develop the regulatory pathway while simultaneously addressing very complex scientific issues and implementation challenges.

This regulatory pathway provides confidence to healthcare providers, patients, caregivers, and the public that an improved biosimilar is a quality medicine and delivers benefits consistent with the originator product.

USP remains committed to working collaboratively with the agency and other stakeholders to fulfill BPCI's promise. While USP has had a long-standing program in biologic standards development, we are now focusing on a paradigm that will primarily emphasize development of raw material and performance standards.

These standards are used to help ensure and demonstrate method effectiveness and process functioning throughout various steps, investigational work, process development, and

manufacturing operations and are broadly applicable to product families or classes as opposed to specific drug substance or drug products.

USP is dedicated to working with FDA and industry to ensure that performance standards support product quality throughout a biologic's lifecycle.

For many patients access to biosimilars could be the opportunity to delay disease progression or even achieve a cure, and depending on the medical condition and other factors. In order to bring biosimilar medicines to patients who need them, USP is committed to working effectively in collaborator with FDA and other stakeholders.

Thank you for your time today.

DR. ROTH: Thank you. Speaker number 9?

MR. LI: Good afternoon. My name is Edward Li, and I am a professor of pharmacy practice at the University of New England and College of Pharmacy in Portland, Maine.

As a practicing oncology pharmacist and a health outcomes researcher who evaluates practice

trends and the pharmacoeconomics of cancer care. I'm here to advocate for the approval of Mylan's proposed biosimilar to trastuzumab, and provide my perspective on the positive impact that this approval will make for the U.S. healthcare system.

In full disclosure Mylan is reimbursing me for my travel today.

It's a well-established fact that trastuzumab has revolutionized the treatment of patients with HER2-positive breast cancer. It's hard to believe that trastuzumab has been available in the United States for almost 20 years, and we have seen its use evolve from the metastatic setting to early stage disease, all the while gaining experience with how to combine it with other therapies, be a traditional cytotoxic agents or newer biological therapies.

As evidence for the success, spending on trastuzumab in the United States is consistently high. In our 2017 Annual U.S. Prescription Expenditure Report, that we published in the American Journal of Health System Pharmacy, my

colleagues and I report that trastuzumab is the 24th highest expenditure product in the United States with $2.6 billion in spending in 2016; that's up 5.5 percent from 2015.

Specifically in the clinics, trastuzumab is the fifth highest expenditure product with $2.1 billion in 2016 spending -- up 9.1 percent in 2015.

As you can glean from this data, our current healthcare system is paying premium prices for a very effective, but older therapy. That's why I'm here today to advocate for the approval for Mylan's biosimilar trastuzumab.

I've read the publicly available data regarding Mylan's application of the proposed trastuzumab biosimilar, and it's my assessment that their product meets the regulatory standard of being highly similar with no clinically meaningful differences to the reference product.

Approving this product will allow healthcare providers and patients another product option within HER2-positive disease. It will help increase access to medications while reducing

spending on drug therapy.

In closing, I'd like to state that spending on antineoplastics in the U.S. has grown by 56 percent in the past six years, and this is unsustainable. With the addition of new and impending immuno-oncology agents, this is putting great financial pressure on our healthcare system.

We urgently need market competition to reduce overall spending on trastuzumab products, which will help moderate the growth of oncology drug expenditures.

DR. ROTH: Thank you. Speaker number 10?

DR. GEWANTER: Good afternoon. My name is still Harry Gewanter, for those of you were here this morning, and I haven't received any notice that I'm not still the chair for the Alliance for Safe Biologic Medicines since I testified a few hours ago.

They are sponsoring my attendance, and ASBM's an organization of patients, physicians, pharmacists, researchers, manufacturers of both innovator and biosimilar medicines including

Genentech, and others dedicated to ensuring patient safety remains at the forefront of all biosimilar policy discussions.

Our members include a number of patient advocacy groups representing patients with breast and gastric cancers; two of the indications for which trastuzumab is utilized, and one of which is being requested today.

I would like to join with the comments earlier to commend the sponsor on the clarity and extensiveness of their data, and I think that, that shows the potential benefits for biosimilars for everyone in this country.

We support the FDA's extensive intense reviews and analyses of these medications both at the time of application, as well as throughout the medication's lifespan.

To reiterate some of the comments from this morning and from others -- ASBM encourages the FDA to one, continue its thorough evaluations to ensure biosimilarity at both an analytic and clinical level.

Two, approve biosimilar indications individually based on sufficient supporting data and not just provide blanket extrapolations, and provide each of the advisory committees the opportunity to separate out their decisions.

Three, ensure that each and every biologic product, both originator and biosimilar, be uniquely identified with distinguished names. Ideally, ASBM would prefer that the FDA and WHO would use their leadership to agree upon a single international system, such as the WHOBQ proposal. This convergence of naming systems would encourage other regulatory agencies to follow suit, thereby increasing the ability for more robust pharmacovigilance.

Four, institute clear, identifiable, transparent, and up-to-date labeling for all medications so patients, prescribers, and pharmacists will know which products are biosimilars, which indications were studied versus extrapolated, and whether a product is interchangeable, et cetera.

Finally, we strongly, strongly encourage a robust post-market surveillance system designed by real world data in order to further our understanding of these medications, and promote a more efficient, safer, and personalized use, thereby improving patient care and increasing confidence in both originators and biosimilars.

Thank you again for your dedication and essential efforts on behalf of all Americans, and I appreciate the opportunity to provide our perspectives to you on this important issue. Thank you.

DR. ROTH: Thank you. We'll be skipping speaker number 11, so surprise to speaker number 12, if you would like to come to the podium.

MR. VAN DEN HOVEN: Thank you very much. I'm Adrian van den Hoven, director general of Medicines for Europe, which regroups biosimilar medicines and manufacturers in Europe, and I have nothing to declare.

I think the committee for the opportunity to participate in this hearing to present the European

experience with biosimilar medicines, which I hope will contribute to greater public awareness of the huge benefits that these medicines can bring to patient health.

We were fortunate in Europe to have a legal framework for biosimilar medicines since 2004, and we have close to 11 years of practical experience with their use in therapy. I will share three key learnings from that used in Europe. That they are equally safe and effective as the reference product, that they significantly lower treatment costs, that they massively increase patient access to therapies which translates into better health.

The first point, as I mentioned, in Europe we've had biosimilar medicines accessible for over 10 years, and we have a considerable amount of positive data, which confirms that they are safe and effective as the reference product. The data collected from the 700 million patient days of experience has all been confirmatory for biosimilar medicines.

Whether you look at the real world

pharmacovigilance data collected by the European Medicines Agency or at post-marketing clinical studies, these should reassure healthcare practitioners and patients as to the validity of the biosimilar regulatory process and the products that are approved for market.

On this point, I wish to commend the U.S. FDA and the European Medicines Agency for their exemplary scientific cooperation in the field of biosimilar regulatory science.

Second point; biosimilar competition has significantly reduced prices for treatment in numerous therapy areas, which the massive increases in access in this table demonstrate.

While this is the raison d'etre of these medicines, it also shows the huge value for patient health and encouraging this development.

Increased access, and this is my third point, translates into better health. In wealthier populations, like the UK, which I've highlighted on the slideshow, significant changes in treatment protocols -- for example, medically appropriate

earlier use for the prevention of neutropenia in cancer patients or changes to health technology assessment guidelines for autoimmune conditions -- were introduced thanks to biosimilar competition.

In poorer populations like Bulgaria, which is also highlighted on this slide, the poorest state in the European Union, patients have gained access to biological medicines where they otherwise were deprived due to cost. All of this has led to many more patients receiving the treatment their condition requires at the appropriate time in their cycle.

To conclude, Europe's 700 million patient days of experience with biosimilar medicines over the last decade has demonstrated they are safe and effective as the reference product, they lower the cost of treatment significantly, and they massively increase access for patients.

For European patients and healthcare practitioners biosimilar medicines have proven to be tremendous value for health, and I'm convinced that there are similar opportunities for the U.S.

My slideshow is available in the front desk, as well as all of the resources which prove the data points that I've presented. Thank you very much again to the committee.

Questions to the Committee and Discussion

DR. ROTH: Thank you. 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'll now proceed with the questions to the committee and the panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

If we could see the discussion questions -- if we can discuss these at the same time.

Number 1. Please discuss whether the

evidence supports a demonstration that MYL-1401O is highly similar to U.S. Herceptin, notwithstanding minor differences in clinically inactive components.

Number 2. Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between MYL-1401O and U.S. Herceptin in the studied condition of use.

Then thirdly, please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.

Again, just like this morning, a discussion of biosimilarity from an analytic source, biosimilarity from a clinical perspective, and finally whether there's sufficient scientific evidence to extrapolate to all indications.

Again, let Jay know if you'd like to make some comments regarding those. Courtney?

MS. PREUSSE: Courtney Preusse, Fred Hutchinson. Quick question, the proposed indications currently are for breast cancer and metastatic gastric cancer, but the voting question

in parentheses only mentions breast cancer. So I guess I'm confused as to whether or not for discussion point 3 we are discussing that there's adequate scientific justification to support licensure for breast cancer and gastric with this new drug or just breast cancer?

DR. ROTH: Stole my question. Obviously, the gastric issue is not like this morning. It's a looming expiration of an orphan extension, and so, I had the exact same question. Are we voting for a gastric extension, which would then kick in October 20th, or not?

DR. BEAVER: As described in the FDA briefing document for the ODAC, Herceptin's indication for metastatic gastric cancer is protected by orphan drug exclusivity, as you mentioned, expiring on October 20, 2017.

Accordingly, FDA would not be able to license the Mylan product for the proposed indication of gastric cancer until the orphan drug exclusivity expires. But based on the content of the application, which includes a scientific

justification to support licensure for all of the proposed indications for Mylan, including the metastatic gastric cancer indication once the relevant exclusivity expires, FDA has requested that the committee discuss whether the scientific justification is adequate.

DR. ROTH: So we can discuss extrapolation, but we are not voting on the gastric indication.

DR. BEAVER: That's correct.

DR. ROTH: Okay. Thank you. Other comments or questions?

No? Then I suppose we'll proceed to the vote. Let's see the voting question please.

Oh, sure. Sorry.

DR. HENDRIX: They've requested us to discuss. Do you want to say something briefly about the particular issue since it's clearly not going to vote on it?

DR. ROTH: In my own mind this met the criteria for a highly similar, both in terms of analytics and in terms of clinical outcomes, for the trial that was described. My personal bias is

to go ahead and extrapolate to another indication, specifically in the gastric cancer population. That's my personal bias, but I'm open to comments from other panel members. Dr. Nowakowski.

DR. NOWAKOWSKI: Greg Nowakowski, I agree with those comments. I think the provided evidence of clinical activity is very solid, the analytical data was very solid as well, and I think, based on those and the totality of evidence, I think extrapolation to other situations including gastric cancer would be appropriate.

DR. ROTH: Other comments? Now I'm afraid to close the discussion. Okay, let's put the voting question up.

Does the totality of the evidence support the licensure of MYL-1401O as a biosimilar product to U.S. Herceptin for the following indications for which U.S. Herceptin is licensed and for which the applicant is eligible for licensure; HER2 positive breast cancer in both the metastatic and adjuvant settings?

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've entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen, and the DFO will read the vote from the screen into the record and then we'll go around the room and give people opportunities to explain their votes.

(Voting.)

DR. FAJICULAY: For the record, the results are 16 yes, zero no, zero abstained, and zero no-vote.

DR. ROTH: Let's go around the table, and start on this side. Dr. Moreira.

DR. MOREIRA: All right, I guess I get to go

first. Well based on the totality of evidence, I voted yes.

I think the sponsor's and the FDA presentations were very clear and the analytical similarity, to me, was well-justified.

Again, the minor variations that we discussed, given then the information of PK and clinical studies, were to me compelling to vote yes.

DR. SCHIEL: I would echo that thought. I thought the presentation of numerous orthogonal assays was very nice. The use of tier 1 and tier 2 statistical presentations was also very clear. So the analytical similarity was well-demonstrated and the use of numerous bioactivity studies related to the mechanism of action cleared up any residual uncertainty, so I also voted yes.

DR. SEIDMAN: I --

DR. ROTH: State your name before you --

DR. SEIDMAN: -- Andrew Seidman, Memorial Sloan Kettering. I also voted yes, and was happy that those who could be more critical about the

preclinical analytics were happy with that.

The clinical data were very compelling in the setting in which it was studied. I just will reiterate my comment that I think in the extrapolation, not necessarily across diseases but form the metastatic to the adjuvant setting, that careful attention needs to be paid to the trial design, the endpoint selection, and the correlation coefficient between that and outcomes in the early stage setting.

DR. HENDRIX: Craig Hendrix, John Hopkins. I voted yes. I thought there was very strong evidence that they were highly similar and there was no clinically meaningful differences, and it was reasonable for the proposed indications for extrapolation.

DR. COLE: Bernard Cole. I voted yes as well, largely for the same reasons that had already been mentioned. Just simply to add that the clinical studies showed no signal at all of any clinically important differences.

MS. CHAUHAN: Cynthia Chauhan. I voted yes,

also for the reasons already stated.

MS. PREUSSE: Courtney Preusse. I also voted yes, and just wanted to add that despite my earlier questions and perhaps skepticism, I would like to strongly applaud the sponsor for equivalence results that were very solid and for what appears to be the first proposal of a biosimilar for a drug that's been on the market for almost three decades.

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes, based on the totality of evidence as already discussed by others. In addition, I think our current understanding of the mechanism of action support extrapolation of the results to adjuvant setting.

DR. ULDRICK: Thomas Uldrick, CCR. I also appreciated the totality of evidence presented very clearly, and the thoughtfulness of the responses to clarifying questions.

This agent appears highly similar, and I think the scientific justification for extrapolation to HER2-positive gastric cancer is

also reasonable.

DR. ROTH: Bruce Roth, St. Louis. I voted yes, and for a change I have nothing to add.

DR. RINI: Brian Rini, Cleveland Clinic. I voted yes for all the same reasons. I thought it clearly met the regulatory standard, and I agree with the comments on extrapolation.

DR. WALDMAN: Scott Waldman. I voted yes, I have nothing to add to the other comments. I will agree with the extrapolation, and I also agree to extrapolation to gastric cancer.

DR. ARMSTRONG: Deb Armstrong, Johns Hopkins. I also voted yes, and I would agree with the extrapolation to gastric cancer as well.

I will say, just to reiterate what I discussed before, which is that if this is approved and is used in the metastatic setting it will almost immediately be used with pertuzumab, and I would really -- it would be very nice for us to have some data on the use of the biosimilar with pertuzumab. But we're really asked to say, do we really think its bioequivalent or do we not? I do

think its bioequivalent, and therefore I approved it.

DR. KARARA: Adel Karara. I voted yes. The data from the clinical pharmacology package was compelling, and I commend the sponsor for conducting the population pharmacokinetic analysis in the HERITAGE study and generating clearance and [indiscernible] comparative data in metastatic breast cancer patients.

DR. CHOW: Shein Chow. I also voted yes. Actually, I have nothing to add, but I think the package presented by the sponsor is very solid.

DR. MAGER: Don Mager. I voted yes, largely for the reasons that are stated, and I agree with the extrapolation as being scientifically sound.

Adjournment

DR. ROTH: My thanks to the committee. We'll now adjourn the meeting. Panel members please leave your name badge here on the tables so that they may be recycled. Please also take all your personal belongings with you, as the room is cleaned at the end of the meeting day. Meeting

materials left on the table will be disposed of. Thank you again.

(Whereupon, at 4:09 p.m., the afternoon session was adjourned.)