FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Thursday, June 9, 2016

8:30 a.m. to 2:30 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh, PharmD, BCPS

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE

MEMBERS (Voting)

Ellen Andrews, PhD

(Consumer Representative)

Executive Director

CT Health Policy Project

New Haven, Connecticut

Lindsey R. Baden, MD

(Chairperson)

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

Associate Professor, Harvard Medical School

Boston, Massachusetts

Amanda H. Corbett, PharmD, BCPS, FCCP

Clinical Associate Professor

University of North Carolina

Eshelman School of Pharmacy and School of Medicine

Global Pharmacology Coordinator

Institute for Global Health and Infectious Diseases

University of North Carolina

Chapel Hill, North Carolina

Demetre C. Daskalakis, MD, MPH
Assistant Commissioner
Bureau of HIV Prevention and Control
New York Department of Health and Mental Hygiene
Queens, New York

Dean A. Follmann, PhD
Assistant Director of Biostatistics
National Institute of Allergy and Infectious Diseases
National Institutes of Health (NIH)
Bethesda, Maryland

Michael Green, MD, MPH
Professor of Pediatrics and Surgery
Pediatrics and Surgery Division of Infectious Diseases
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Barbara M. Gripshover, MD
Associate Professor of Medicine
University Hospitals Case Medical Center
Case Western Reserve University
Division of Infectious Diseases and HIV Medicine
Cleveland, Ohio

Jonathan Honegger, MD
Assistant Professor of Pediatrics
The Ohio State University College of Medicine
Division of Infectious Diseases and Center for Vaccines and Immunity
Nationwide Children's Hospital
Columbus, Ohio

Joanna Schaenman, MD, PhD
Assistant Professor of Medicine
Division of Infectious Diseases
UCLA David Geffen School of Medicine
Los Angeles, California

Peter Weina, MD, PhD, FACP, FIDSA

Colonel, Medical Corps, USA

Chief, Department of Research Programs

Walter Reed National Military Medical Center

Bethesda, Maryland

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Barry M. Bernstein, MD

(Industry Representative)

Vice President

Infectious Disease Development

AbbVie

North Chicago, Illinois

TEMPORARY MEMBERS (Voting)

Juan C. Gea-Banacloche, MD

Chief, Infectious Diseases Section

Experimental Transplantation and Immunology Branch

National Cancer Institute, NIH

Bethesda, Maryland

Matthew B. Goetz, MD

Chief, Infectious Diseases

Department of Medicine

Veteran Affairs Greater Los Angeles

Professor of Clinical Medicine

UCLA David Geffen School of Medicine

Los Angeles, California

Joan Hilton, ScD, MPH

Professor in Residence, Epidemiology and

Biostatistics

University of California

San Francisco School of Medicine

San Francisco, California

Thomas A. Moore, MD, FACP, FIDSA

Clinical Professor of Medicine

University of Kansas School of Medicine-Wichita

Campus

ID Consultants of Kansas

Wichita, Kansas

Christina Surawicz, MD

Professor of Medicine

Division of Gastroenterology

Associate Dean for Faculty Development

University of Washington School of Medicine

Seattle, Washington

Jeanine Thomas

(Patient Representative)

Founder and President

MRSA Survivors Network

Joliet, Illinois

FDA PARTICIPANTS (Non-Voting)

Edward M. Cox, MD, MPH

Director

Office of Antimicrobial Products (OAP)

Office of New Drugs (OND), CDER, FDA

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products (DAIP)
OAP, OND, CDER, FDA

Dmitri Iarikov, MD, PhD
Medical Team Leader
DAIP, OAP, OND, CDER, FDA

Hiwot Hiruy, MD, PhD
Medical Officer
DAIP, OAP, OND, CDER, FDA

Shrimant Mishra, MD, MPH
Medical Officer
DAIP, OAP, OND, CDER, FDA

Cheryl Dixon, PhD
Statistical Reviewer
Division of Biometrics IV (DB IV)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: Good morning. It is now 8:30. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices, if you have not done so already. I would also like to identify the FDA press contact, Theresa Eisenman. If you are present, please stand in the back.

My name is Lindsey Baden. I'm the chairperson of the Antimicrobial Drug Advisory Committee. I will now call this meeting of the Antimicrobial Drug Advisory Committee to order. We'll start by going around the table and introducing ourselves. Let's start on the right.

DR. BERNSTEIN: Barry Bernstein, vice president, infectious disease development, AbbVie, retired, the industry representative.

DR. SURAWICZ: Chris Surawicz, University of Washington. I'm a gastroenterologist.

DR. GOETZ: Matthew Goetz, infectious diseases at the VA Greater Los Angeles and UCLA.

DR. HILTON: Joan Hilton, professor of biostatistics, UCSF.

DR. MOORE: Tom Moore, infectious disease in Wichita, Kansas at the University of Kansas.

DR. GEA-BANACLOCHE: Juan Gea-Banacloche, infectious diseases, NCI.

MS. THOMAS: Jeanine Thomas, Founder, President, MRSA Survivors Network.

DR. HONEGGER: Jonathan Honegger, pediatric infectious disease, Ohio State University.

DR. SCHAENMAN: And I'm Joanna Schaenman, infectious diseases, David Geffen School of Medicine at UCLA.

DR. WEINA: Pete Weina. I'm infectious disease and director of research programs at Walter Reed National Military Medical Center.

DR. GRIPSHOVER: Hi. I'm Barbara Gripshover from University Hospitals of Cleveland, Case Western Reserve, infectious disease.

DR. BADEN: Lindsey Baden, infectious

diseases, Brigham and Women's, Dana-Farber, and Harvard Medical School.

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

DR. GREEN: Michael Green, pediatric infectious diseases, Children's Hospital Pittsburgh and the University of Pittsburgh.

DR. DASKALAKIS: Demetre Daskalakis, adult infectious diseases. I work for New York State Department of Health and Mental Hygiene.

DR. ANDREWS: Ellen Andrews from the Connecticut Health Policy Project, and I'm the consumer representative.

DR. CORBETT: Amanda Corbett. I'm a clinical associate professor at the University of North Carolina, Eshelman School of Pharmacy.

DR. FOLLMANN: I'm Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. DIXON: Cheryl Dixon, statistics reviewer, FDA.

DR. HIRUY: Hiwot Hiruy, clinical safety

reviewer.

DR. MISHRA: Shrimant Mishra, clinical efficacy reviewer.

DR. IARIKOV: Dmitri Iarikov, clinical team leader.

DR. NAMBIAR: Good morning. Sumathi Nambiar, director, Division of Anti-Infective Products, CDER, FDA.

DR. COX: Ed Cox, director of the Office of Antimicrobial Products, CDER, FDA. Good morning.

DR. BADEN: 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, a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine

Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you very much.

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

Conflict of Interest Statement

DR. TESH: Good morning. The Food and Drug Administration is convening today's meeting of the Antimicrobial 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 the 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 the committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services,

which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of the 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, 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 a discussion of biologics license application 761046, bezlotoxumab injection, submitted by Merck Sharpe & Dohme Corp., for the proposed indication of prevention of Clostridium difficile infection recurrence. This is a particular matters meeting during which specific matters related to Merck Sharpe & Dohme's bezlotoxumab will be discussed.

Based on the agenda for today's meeting, and all financial interests reported by the committee

members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or financial imputed interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for

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

DR. BADEN: We will now proceed with Dr. Nambiar's introductory remarks.

FDA Introductory Remarks – Sumathi Nambiar

DR. NAMBIAR: Thank you, Dr. Baden. Good morning, everybody. Welcome to today's meeting of the Antimicrobial Drugs Advisory Committee to discuss the biologics license application 761046 bezlotoxumab injection.

The applicant, as you've heard, is Merck Sharpe and Dohme Corp. The proposed indication is prevention of Clostridium difficile infection recurrence in patients 18 years of age and older. The proposed dose is a single dose of 10 milligram per kilogram administered intravenously over 60 minutes. The application was granted priority review. There are no approved therapies for prevention of C. diff infection recurrence.

Bezlotoxumab is a fully human monoclonal

IgG1 kappa antibody that binds to the C. difficile toxin B. The development program was initially focused on the combination of an antitoxin A antibody, actoxumab, and antitoxin B antibody, bezlotoxumab.

The applicant has conducted two phase 2 trials, Study P017, P018, and two Phase III trials, Studies P001 and P002. In these studies, bezlotoxumab was administered in combination to the standard of care therapy. The duration of standard of care therapy prior to receipt the bezlotoxumab infusion varied.

The first phase 2 trial compared antitoxin A antibody to placebo. This trial was terminated early as emerging nonclinical data suggested that the combination of antibodies was more effective.

The second phase 2 trial compared antitoxin A, actoxumab, plus bezlotoxumab, antitoxin B, to placebo. Of the 200 patients, 101 were randomized to the antibody arm and 99 to the placebo arm.

The initial cure rates in the antibody arm was 79 percent compared to 76 percent in the

placebo arm, and recurrent rates in the antibody arm was 7 percent compared to 25 percent in the placebo arm. There was no phase 2 trial that evaluated bezlotoxumab alone.

The first phase 3 trial, trial P001, was a 4-arm factorial trial design with 1 to 1 to 1 to 1 randomization antitoxin A, antitoxin B, the combination, and placebo. The placebo was normal saline. And this design was used to assess the contribution of the individual components consistent with 21 C.F.R. 300.50.

In December 2010, a special protocol agreement was reached on the design and endpoints for this trial. The primary endpoint for this trail was recurrence of C. diff infection, and this trial was conducted from 2011 to December 2014.

This trial included an interim analysis that allowed for halting enrollment in one or both of the individual antibody arms if there was sufficient evidence of superiority of the combination over the individual antibody arms.

After 235 patients received anti A,

enrollment in this arm was stopped due to safety concerns relative to placebo and low efficacy compared to the combination arm.

The second phase 3 trial, P002, was a 3-arm trial, bezlotoxumab, actoxumab plus bezlotoxumab, and placebo. This protocol was not submitted for a special protocol assessment. Upon review of this protocol, we recommended that the primary endpoint be changed to global cure, and this was to be defined as a patient being cured and having no recurrence.

The two main concerns we had with the proposed recurrence endpoint were that when one calculates CDI recurrence, subjects who failed initial treatment would be counted as not having a recurrence. And secondly, if there was any imbalance between the treatment arms for the clinical cure rate of the initial episode, the assessment of recurrence rate could be confounded.

The applicant preferred to retain CDI recurrence as the primary endpoint and global cure as a key secondary endpoint in both trials. At

that time, we noted that if the monoclonal antibody arm had a lower initial cure rate than the placebo arm, interpretation of the recurrence endpoint would be difficult.

We also did not agree with the proposal to evaluate global cure by analyzing pooled data from the two phase 3 trials and noted that assessment of the global cure endpoint would be based on the analysis from each individual trial. This trial was conducted from February 2012 to May 2015.

So for today's discussion, the key topic areas from an efficacy standpoint are as follows. There are differences in the assessment of the primary endpoint between the applicant and the agency. There are differences in the clinical outcomes between the two phase 3 trials. And there are also differences in the approach to analyses conducted between the applicant and the FDA.

From a safety standpoint, there are no major differences in the assessment between the applicant and the FDA. There'll be some discussion about a higher frequency of adverse reactions seen in

patients with baseline congestive heart failure and who were treated with bezlotoxumab.

So we'll hear presentations by the applicant. This will be followed by presentations from the FDA. We have two presentations. Dr. Cheryl Dixon will present data on the efficacy assessment. And Dr. Hiwot Hiruy will discuss the safety assessment. After break, we have time for open public hearing, followed by questions for the committee.

We have one voting question for the committee, which is, has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of C. difficile infection recurrence in patients aged 18 years and older? Vote yes or no.

If yes, please discuss your rationale and provide any recommendations concerning labeling. If no, please discuss your rationale and what additional studies or analyses are needed. Thank you.

DR. BADEN: Thank you, Dr. Nambiar. Both

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

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We shall now proceed with the sponsor's presentations. And I think Dr. Staas will be the

first presenter.

Sponsor Presentation - Donnette Staas

DR. STAAS: Thank you Dr. Nambiar, and members of the committee, and the FDA. Good morning. I'm Dr. Donnette Staas, and I'm in the Regulatory Affairs group at Merck. It is our pleasure today to bring you the data on bezlotoxumab for the prevention of C. difficile infection recurrence.

After this brief introduction, Dr. Dalya Guris will present the clinical efficacy data for bezlotoxumab, and then Dr. Yoshihiko Murata will present the clinical safety data. Professor Mark Wilcox will conclude the presentation with a summary of the benefit-risk profile.

Clostridium difficile is a spore-forming, rod-shaped anaerobe bacterium that is easily spread and difficult to eradicate. The bacterium is ubiquitous in the hospital environment, and C. difficile infection, or CDI, has become the leading cause of nosocomial infection. The incidence of community-acquired CDI is also on the rise. There

are an estimated 453,000 incident Clostridium difficile infections in the United States in 2011 and an additional 83,000 first recurrences of CDI.

The associated mortality is high, with an estimated 29,000 CDI-associated deaths that year. In fact, the deaths associated with CDI exceeded those associated with MRSA and multi-drug resistant Gram-negative infections combined.

As a result, C. difficile has been declared one of only three urgent antibiotic-resistant threats by the Centers for Disease Control and Prevention, and the disease has aptly earned the pseudonym of deadly diarrhea.

As the graph on this slide illustrates, approximately 20 to 35 percent of patients with a primary episode of CDI will go on to have a recurrent episode. The risk of recurrence increases with each subsequent episode, with a recurrence rate of approximately 60 percent after two or more recurrences. CDI recurrence is associated with increased disease severity and higher mortality.

Treatment options for both primary and recurrent CDI include oral metronidazole, which is typically limited to mild cases of CDI, intravenous metronidazole, oral vancomycin, and oral fidaxomicin. These treatment options will be referred to as standard of care therapies throughout today's presentation.

Antibiotic treatment of CDI does not prevent recurrent disease. Indeed, treatment with vancomycin or metronidazole leads to disruption of the normal gut microbiota, which in turn facilitates CDI recurrence.

CDI also recurs at a substantial rate following treatment with fidaxomicin, particularly in those patients infected with ribotype 027. The ribotype 027 strain is one of a group of C. difficile strains that have been associated with poor clinical outcomes. There are no approved therapies for the prevention of CDI recurrence, thus prevention of CDI recurrence represents an unmet medical need.

I will now present an overview of the

pathogenesis of the infection. The primary risk factors for developing CDI are, one, the disruption of the normal gut microbiota, which occurs secondary to antibiotic treatment or other factors such as receipt of chemotherapy, and, two, the acquisition of toxigenic C. difficile.

C. difficile expresses two functionally and structurally homologous toxins, toxin A and toxin B. While their relative contribution to disease pathogenesis is an area of ongoing research, the toxins cause the symptoms of CDI by targeting the epithelial cells of the gut, causing damage and inducing inflammation within the intestinal wall.

Some patients become asymptomatic carriers and may active as reservoirs for spread of C. difficile. Others go on to develop C. difficile infection with a spectrum of illness ranging from mild diarrhea to extensive diarrhea with abdominal pain, with potential complications including toxic megacolon and colonic perforation, sepsis, and death.

Those who develop C. difficile infection are

treated with standard of care antibiotics. Following treatment, although some patients will be cured with no further complications, approximately 20 to 35 percent of patients will go on to experience a recurrent episode. Of note, circulating antitoxin antibodies are protective against primary and recurrent CDI.

Monoclonal antibodies directed against the toxins of C. difficile represent a novel, non-antibiotic approach to the prevention of CDI recurrence. The premise of this approach is that, as noted on the previous slide, immune responses against toxins A and B are associated with reduced recurrence of CDI.

Bezlotoxumab, which will also be referred to as BEZLO throughout this presentation, is a fully human, monoclonal antibody of the IgG1 class. BEZLO binds with high affinity to C. difficile toxin B and neutralizes its activity by preventing the binding of toxin to host cells. In clinical trials, BEZLO has been evaluated both alone and in combination with actoxumab, or ACTO, which is the

fully human monoclonal antibody targeting toxin A.

The phase 3 clinical development program, which is the focus of this morning's presentation, is summarized briefly on this slide. MODIFY I and MODIFY II are the two pivotal phase 3 trials that demonstrated the safety and efficacy of bezlotoxumab for the prevention of CDI recurrence in patients receiving standard of care antibiotic therapy for CDI.

The trials were conducted concurrently at over 300 sites across 30 countries in 6 continents. The global phase 3 program is the largest clinical development program conducted to date in assessing outcomes for CDI, randomizing a total of 2,655 patients with a primary or recurrent CDI. Both clinical trials are complete.

The results of the pivotal phase 3 trials demonstrate that a single dose of bezlotoxumab is highly efficacious in preventing CDI recurrence, significantly decreasing the proportion of subjects with CDI recurrence by 10 percentage points compared to placebo, which translates to a 40

percent reduction in relative risk for CDI recurrence.

As you can see in this table, the results were consistent across the two trials with a 10.1 percentage point absolute difference in CDI recurrence rate between the BEZLO and placebo arms in MODIFY I, and a 9.9 percentage point difference in MODIFY II. Bezlotoxumab is well tolerated with a safety profile similar to placebo. Bezlotoxumab has been shown to have a positive benefit-risk profile.

The proposed indication for bezlotoxumab is for the prevention of Clostridium difficile infection recurrence in patients 18 years or older receiving antibiotic therapy for CDI.

The recommended dose of bezlotoxumab is 10 milligrams per kilogram of patient body weight administered as an intravenous infusion over 60 minutes as a single dose. BEZLO may be given at any time during the course of antibiotic therapy for CDI.

Regulatory agency guidance was obtained

throughout the BEZLO clinical development program. In October 2009, an end-of-phase 2 meeting was held with FDA, during which agreement was reached on the definition and time point for assessment of the primary efficacy endpoint of CDI recurrence for the phase 3 trials.

Fast track designation was granted for ACTO plus BEZLO in May 2010 in recognition of the potential of the drug to treat a serious or life-threatening disease or condition and to address an unmet medical need for such a condition.

The MODIFY I trial was a subject of a special protocol assessment in 2010 in which agreement was reached on the implementation of a 4-arm factorial design to evaluate whether the combination of ACTO plus BEZLO provided additional benefit over the individual monoclonal antibodies in accordance with the combination drug product rule.

In August 2012, the FDA recommended that Merck change the primary efficacy endpoint in MODIFY II from CDI recurrence to global cure.

Merck considered the CDI recurrence endpoint to be a more appropriate measure to assess efficacy of a therapy that does not treat the incident CDI episode but only prevents CDI recurrence, which is consistent with the mechanism of action of bezlotoxumab.

Thus, Merck retained CDI recurrence as the primary endpoint in MODIFY II. Sensitivity analyses were added to assess the impact of clinical cure on CDI recurrence.

Following completion of the pivotal phase 3 trials, the biologics licensing application was submitted for review in November 2015 with priority review designation granted for the application in January 2016.

Merck has several consultants in attendance today and I'd like to acknowledge them. We have Dr. Karen Kelly, professor of medicine at Beth Israel Deaconess Medical Center and Harvard Medical School; Dr. Gary Koch, professor of biostatistics at the University of North Carolina, Chapel Hill; Professor Mark Wilcox, consultant, and head of

microbiology and professor of medical microbiology at Leeds Teaching Hospitals and University of Leeds in the United Kingdom and lead on Clostridium difficile at Public Health England; and Dr. Janet Wittes, founder and president of Statistics Collaborative Incorporated.

I will now invite Dr. Dalya Guris, who has led the bezlotoxumab clinical development program, to present a detailed discussion of the efficacy data that support the use of BEZLO for the prevention of CDI recurrence. Dalya?

Sponsor Presentation – Dalya Guris

DR. GURIS: Thank you, Donnette. Good morning. My name is Dalya Guris. I'm with Merck Infectious Disease Clinical Research. I will present an overview of bezlotoxumab mechanism of action, bezlotoxumab properties, phase 3 program, and the efficacy results.

First, I will begin by illustrating BEZLO's mechanism of action. During the initial episode of CDI, the patient is treated with standard of care antibiotics and also receives a single IV infusion

of BEZLO while on antibiotic treatment. The CDI resolves due to antibiotic treatment.

However, after initial episode is cured there is a period when the gut microbiota has not yet recovered. And with the outgrowth or newly-acquired C. difficile spores, the patient is at risk for recurrence.

The magnified portion of this slide illustrates what occurs at the cellular and molecular level in the gut. The cells in the center represent epithelium of the gut wall.

Pre-clinical data have shown that BEZLO enters the gut lumen via paracellular transport, which is facilitated by toxins disruptions of the epithelium. BEZLO binds to toxin B, in turn blocks the binding of toxin to the mucosal cells, and prevents damage and inflammation of the gut wall.

BEZLO has a long half-life in circulation, with measurable systemic concentrations throughout the window during which the patient remains at risk for recurrence. During this period, gut microbiota recovers and CDI recurrence is prevented.

Bezlotoxumab is a fully human monoclonal antibody specific for an exogenous toxin, toxin B. It is administered as a single dose of 10 milligram per kilogram actual body weight IV infusion over one hour. This dose was selected based on efficacious exposures of ACTO and BEZLO in preclinical studies and was confirmed as efficacious in preventing CDI in phase 2.

As it is specific to an exogenous toxin, no off-target activity, including an immune mediator response, is expected. And because it is fully human, potential for immunogenicity is low.

Bezlotoxumab is eliminated by protein catabolism with a half-life of 19 days, and it has low drug-drug interaction potential. Bezlotoxumab is not renally or hepatically eliminated, or affected by hepatic drug metabolizing enzymes or transporter proteins.

There are no clinically meaningful PK differences between subpopulations such as elderly, patients with hepatic or renal impairment, or by patient weight, and therefore it can be given to a

diverse patient population without dose adjustment.

The phase 3 program included 2 large, double-blind, randomized clinical trials, which were identical in design except the number of treatment arms included. MODIFY I included 4 treatment arms where the patients were randomized to receive either a single infusion of ACTO, BEZLO, ACTO plus BEZLO, or placebo. MODIFY II included 3 treatment arms, BEZLO, ACTO plus BEZLO, and placebo.

Stratification was identical in MODIFY I and II. Patients were stratified by oral standard of care antibiotics that they were receiving, and their hospitalization status at the time of randomization.

Stratification strata for standard of care antibodies were metronidazole, vancomycin, and fidaxomicin, and strata for hospitalization status were inpatient versus outpatient. Hospitalized patients as well as patients from long-term care facilities were included in the inpatient stratum.

Four hundred patients per treatment arm was

planned in each trial, targeting a total of 1,600 patients in MODIFY I and 1200 in MODIFY II. MODIFY I had an adaptive design with an interim analysis. MODIFY I included an interim analysis because, in a small phase 2 study, ACTO alone was found not efficacious in preventing CDI recurrence.

ACTO arm was included in the phase 3 program to fulfill FDA's combination product rule, but it was included in only one study and with an interim analysis to allow discontinuation of individual monoclonal antibodies if they were inferior to the combined product.

At the interim analysis, ACTO arm was discontinued following the recommendation of the external data monitoring committee based on both efficacy not being achieved and safety findings.

MODIFY II had a traditional design without an interim analysis. Adult patients with confirmed CDI were eligible for enrollment. Confirmation was based on both clinical and microbiological criteria, and patients had to be receiving standard of care antibiotic for CDI.

The trials had limited exclusion criteria, which allowed a diverse group of CDI patients with multiple underlying comorbidities. Risk factors for CDI recurrence were predefined and patients at risk for CDI recurrence were included. These were elderly patients with multiple previous episodes of CDI, severe CDI, immunocompromised, or infected with hyper-virulent strains associated with poor outcomes.

In this slide, you see an outline of the phase 3 trial design. Patients with confirmed CDI were enrolled. To be confirmed, patients had to have diarrhea, which was defined as having 3 or more loose stools in 24 hours, and a positive stool test for toxigenic C. difficile. Bristol Stool Chart was used as a method to standardize presence of loose stools using types 5 to 7.

Also, patients had to be receiving 10 to 14 days of standard of care antibiotic treatment for CDI. Options and dosage for antibiotics were prespecified in the protocols, and choice of antibiotic was left to the treating physician.

Standard of care antibiotics were oral metronidazole and oral vancomycin or fidaxomicin with or without IV metronidazole.

The antibiotic therapy had to be initiated no later than the day of the infusion. On day 1 of the infusion, patients were randomized equally to one of the treatment arms. Patients could receive study infusion at any time during standard of care antibiotic therapy. Study infusion was given through in-line filter, which is commonly available.

During the 85-day follow-up period, patients kept diary to record daily loose stool counts. In the first 2 weeks, patients were contacted every day for loose stool counts and compliance with standard of care medications. Thereafter, patients were contacted twice weekly.

If diarrhea returned, stools samples were collected and tested at both local and central laboratory for toxigenic C. difficile. Recurrence of diarrhea was assessed throughout the 85-day follow-up period. Primary efficacy endpoint was

CDI recurrence after clinical cure of the baseline episode.

The primary efficacy endpoint was CDI recurrence. CDI recurrence was defined as a new episode of diarrhea associated with a positive local or central laboratory stool test for toxigenic C. difficile, following per protocol definition of clinical cure of the baseline CDI episode.

Clinical cure definition included two requirements. The first requirement was to receive a regimen of 14 or fewer days of standard of care antibiotics. The second requirement was the resolution of diarrhea for 2 consecutive days immediately after completion of standard of care antibiotics. Clinical cure was programmatically derived by the sponsor.

Efficacy was assessed through 12 weeks and it was assessed in the full analysis set FAS population. Twelve weeks is substantially a longer follow-up period than what has been studied with other therapeutics of CDI.

All randomized patients were in the FAS population except those who did not receive an infusion, did not have a positive local stool test for toxigenic C. difficile at study entry, or did not initiate protocol defined standard of care therapy before or on the day of infusion. FAS was the main efficacy population in secondary and exploratory analyses as well.

This diagram describes how CDI recurrence rate was calculated. First, in each treatment group, the full analysis set population shown at the top was programmatically assessed by the sponsor for clinical cure of their present CDI episode.

Among those who achieved clinical cure, shown in green, patients were evaluated for CDI recurrence, shown in orange. CDI recurrence rate is the proportion of patients with CDI recurrence among the full analysis set population.

Patients who did not have clinical cure, shown in black, according the sponsor's programmatic assessment, were not considered to

have CDI recurrence given the failure to achieve cure of the baseline episode. They were included in the denominator of the CDI recurrence rate. Later in this presentation, I will show you some alternative definitions that are supportive of the primary endpoint results.

Global cure, also known as sustained clinical response, was a secondary endpoint and was defined as having clinical cure of the initial CDI episode and no recurrence in the 12-week follow-up period. As shown in blue in this diagram, global cure rate is the proportion of patients who achieved clinical cure and did not develop CDI recurrence.

MODIFY I and II are two independent superiority trials. Each had 95 percent or higher power to detect a clinically relevant absolute difference of 8 percentage points in the rate of CDI recurrence, assuming an underlying placebo rate as low as 16 percent. This would correspond to about a 50 percent reduction in the relative risk of CDI recurrence.

Multiplicity strategy controlled the study-wise type 1 error at 0.025, one-sided, for the primary endpoint of CDI recurrence. The prespecified integrated analyses of MODIFY I plus II increased precision to estimate treatment effect of BEZLO on CDI recurrence within important subgroups and on global cure.

This slide shows the number of patients randomized and were eligible for safety and efficacy analyses in each treatment group in MODIFY I. A total of 1,452 patients were randomized in MODIFY I.

Approximately 400 patients were in each treatment arm, with the exception of the ACTO arm shown in the column far right. Because enrollment in this arm was discontinued at interim analysis, the number of patients randomized was lower.

All patients who received a study infusion were evaluated for safety. This population is called all patients as treated, APaT. Few patients were excluded from the efficacy analysis due to not receiving standard of care antibiotic, or not

having a confirmed CDI, or being enrolled in a single site from which data could not be verified.

Across treatment groups, 95 to 98 percent of all randomized patients were included in the full analysis set population for efficacy analyses. A large proportion of patients completed the 12-week follow-up period across all treatment groups. Main reason for discontinuation was death, as expected from this elderly population with CDI and underlying comorbidities.

A total of 1203 patients were enrolled in MODIFY II. Similar to MODIFY I, a high proportion of patients were qualified for safety and efficacy evaluation and completed 12-week follow-up period across all treatment groups.

This table shows baseline characteristics of patients by treatment group in MODIFY I and MODIFY II separately. The median age and the proportion of patients by gender, region, hospitalization status and standard of care antibiotics received were comparable between treatment groups in each trial. Median age ranged

between 63 and 70 years, and a slightly higher proportion of women were enrolled into the study than men.

Nearly half of the patients were from North America in MODIFY I, and in MODIFY II a larger proportion of patients were enrolled from Europe and Asia-Pacific.

Proportion of patients from the United States ranged between 44 and 52 percent in the treatment groups in MODIFY I and 34 to 35 percent in MODIFY II. Overall, two-thirds of the patients were inpatients at the time of randomization, and distribution was comparable across the treatment groups.

The proportion of patients who received metronidazole or vancomycin as standard of care antibiotic for CDI treatment was similar to each other and across the treatment groups. In each treatment group, approximately 3 to 4 percent of the patients received fidaxomicin, which reflects standard of care for CDI at the time of trials.

As I mentioned, there are certain risk

factors that are associated with high rates of CDI recurrence. These factors were prespecified in the trials, and patients with these risk factors were included. Overall, the proportion of patients 65 years of age or older were comparable between the treatment groups.

Nearly one-third of the patients had at least one previous episode of CDI in the past 6 months before enrolling in the trials, and the proportion of such patients was comparable across the treatment groups.

In addition, 11 to 18 percent of subjects across treatment groups had experienced at least 2 episodes of CDI before enrollment.

Severity of CDI was assessed at the time of randomization and was defined as having a Zar score of 2 or more. The Zar scale is a method that has been used in clinical studies to assess CDI severity. It takes into account age, body temperature, albumin level, peripheral white blood cell count, presence of endoscopic evidence of pseudomembranous colitis, and treatment in

intensive care unit.

At the time of randomization, 14 to 21 percent of patients had severe CDI across treatment groups. Similarly, a substantial proportion of patients enrolled were immunocompromised, and distribution was comparable across treatment groups.

More than 130 distinct C. difficile types were identified at baseline. Among the patients with C. difficile organism isolated, a large proportion of patients were infected with a hyper virulent strain, including 027 strain. Overall, 76 percent of patients had at least one risk factor for CDI recurrence.

Now, the efficacy results -- this slide presents the primary efficacy endpoint of CDI recurrence from left to right in MODIFY I, MODIFY II, and the integrated analysis of MODFIY I plus II.

Bezlotoxumab was superior to placebo in MODIFY I and MODIFY II and the integrated dataset and significantly reduced CDI recurrence rates

compared to placebo, resulting in a relative reduction of CDI recurrence rate by approximately 40 percent.

Both the CDI recurrence rates and reductions in CDI recurrence were consistent across the two trials. In each of the trials, as well as the integrated data, ACTO plus BEZLO also reduced CDI recurrence rates, but the addition of ACTO did not have an efficacy benefit over administration of BEZLO alone.

As indicated before, in MODIFY I, ACTO alone was discontinued at the interim analysis for both efficacy and safety findings. Given the primary efficacy findings, BEZLO was selected as the product for licensure. From this point on, I will present efficacy data related to BEZLO and placebo only.

This graph presents cumulative rate of CDI recurrence by weeks post-infusion. Gray line shows the cumulative incidence of CDI recurrence in the placebo arm, and the blue line shows the incidence in the BEZLO arm.

As seen here, impact of BEZLO on reducing CDI recurrence rate became apparent soon after infusion. The difference between the recurrence rates in placebo and BEZLO increased by week 4, and remained consistent through week 12, resulting in highly significant efficacy in reducing CDI recurrence in the BEZLO group.

This is a forest plot where the differences between CDI recurrence rates and BEZLO and placebo recipients in the integrated dataset are shown for the two stratification factors in the trials.

The horizontal lines show the 95 percent confidence interval for the absolute difference in recurrence rates, with the point estimate of the difference as the diamond shape in the center of the horizontal line. The vertical line intersects zero on the X axis, indicating where the point estimate would lie if there was not difference between the CDI rates between BEZLO and placebo arms.

The horizontal lines that fall to the left of the vertical line demonstrate a difference

favoring BEZLO, meaning that the CDI rate is lower in the BEZLO arm compared to placebo.

As data show, the differences in CDI recurrence rates were in favor of BEZLO in all strata. BEZLO arm had lower recurrence rate compared to the placebo arm, irrespective of hospitalization status and standard of care antibiotics received. Reduction in CDI recurrence rates in each stratum was consistent with the 10 percentage point absolute reduction seen in the overall population.

In the fidaxomicin stratum, given the small sample size, 95 percent confidence interval is wide crossing over zero, but the point estimate indicates a difference favoring BEZLO consistent with other strata.

This graph shows CDI recurrence rates among placebo recipients in the integrated MODIFY I plus II dataset among the important subgroups at high risk for CDI recurrence.

As gray bars indicate, CDI recurrence rates were high in the high-risk groups, reaching 28

percent in immunocompromised patients, 31 percent among those 65 years of age and older, 34 percent among those infected with 027 strain, 41 percent among those who had at least one previous CDI episode over the past 6 months, and 42 percent among those who had at least 2 episodes in the past.

As presented in the blue bars, BEZLO resulted in a substantial reduction in CDI recurrence rates compared to placebo in all the subgroups, including those risk groups with higher recurrence rates.

The forest plot on this slide is another demonstration of the data that I just presented. It shows the differences in CDI recurrence rates between BEZLO and placebo arms in the subgroups at higher risk for a CDI recurrence. Seventy-six percent of the patients had at least one risk factor.

As seen here, in all the subgroups, efficacy data favored BEZLO, meaning BEZLO resulted in a robust reduction of CDI recurrence rate compared to

placebo. The difference in CDI recurrence rates was at or above the 10 percentage point absolute difference seen in the overall population.

In summary, each of the phase 3 trials demonstrated that BEZLO is superior to placebo in preventing CDI recurrence, and the treatment effect is remarkably consistent between the trials. In addition, BEZLO consistently reduces CDI recurrence rates compared to placebo across important subgroups at high risk for recurrence.

Now, I would like to revisit the endpoint definitions and discuss additional analyses conducted to assess the robustness of the primary efficacy results.

In order to have CDI recurrence, a patient must first achieve clinical cure of the baseline episode. Rather than randomizing patients in the study who had already achieved clinical cure of the baseline CDI episode, we randomized and treated patients during standard of care therapy of the baseline episode.

This is because, for prevention of CDI

recurrence it was important for the monoclonal antibody to be present before at-risk period for recurrence begs, which is immediately after standard of care therapy ends.

Due to this design feature, subjects who did not achieve clinical cure, as defined in the protocol, shown in black circle, could not be counted as recurrence. This is approximately 20 percent of the population.

In the presence of standard of care antibiotic, which is very effective in treatment CDI, BEZLO was not expected to impact the clinical cure rate, and indeed it did not as we'll see in a moment.

Nevertheless, to assess the impact of the post-randomization event of clinical cure on the primary efficacy results, we conducted sensitivity analyses. Global cure, as mentioned before, is the secondary endpoint of the study, defined as achieving clinical cure and having no subsequent recurrences.

It is a supportive measure of the treatment

effect of BEZLO. It also supports the robustness of the primary analysis because unlike the primary analysis, which counts subjects who did not achieve clinical cure as treatment successes, the global cure analysis takes the opposite approach and counts such subjects as treatment failures.

Before we look at the results of global cure, we need to understand the results of clinical cure, so let's look at the clinical cure data.

As seen here, efficacy of the standard of care antibiotic was not impacted by administration of BEZLO. Consistent with the idea that this endpoint is not expected to be impacted by BEZLO, in one trial, MODIFY I, the clinical cure rate was slightly higher in placebo versus BEZLO arm, whereas in the other, MODIFY II, the clinical cure rate was higher in the BEZLO arm versus placebo.

The differences between the arms in each trial were small, similar in magnitude, and opposite direction. The differences were not statistically significant or clinically meaningful.

In the integrated dataset, MODIFY I plus II,

the rates were nearly identical, 80 percent clinical cure rates in the BEZLO and placebo arms. In the presence of standard of care antibiotics for CDI, BEZLO does not improve or diminish clinical cure rates.

Here are the data for global cure. Analysis of the integrated dataset was prespecified to provide increased precision for estimating treatment effect for this endpoint. However, this endpoint is a composite endpoint, which includes both clinical cure, which BEZLO has no effect on, and CDI recurrence.

As mentioned before, patients without clinical cure are considered a failure for global cure, which makes this a less specific endpoint for the intended indication, but allows us to assess robustness of the primary endpoint.

BEZLO resulted in higher global cure rates compared to placebo. The difference in global cure rates favoring BEZLO reach statistical significance in MODIFY II and the integrated dataset from both trials.

CDI recurrence and global cure endpoints have advantages and disadvantages in assessing treatment effect on prevention of CDI recurrence. CDI recurrence endpoint is a more appropriate measure to assess efficacy of therapy that does not treat the incident CDI, but only prevents CDI recurrence, whereas global cure is a more appropriate measure to assess efficacy of therapy that does not only prevent CDI recurrence, but also treats the incident CDI episode.

These two endpoints lie on the two extremes of measuring treatment effect because CDI recurrence counts patients who do not achieve clinical cure as not having CDI recurrence, and global cure counts such patients as having CDI recurrence. The way clinical cure failures are counted in either endpoint is not completely representative of the true rate of CDI recurrence.

Since BEZLO dosing was not mandated to occur at the point of clinical cure of the incident CDI episode, both the CDI recurrence and global cure endpoints are impacted by the definition of

clinical cure.

We have conducted sensitivity analyses to explore the robustness of CDI recurrence endpoint. Sensitivity analyses focused on the impact of clinical cure or the impact of incomplete data on CDI recurrence.

The first set includes assessment of CDI recurrence in the subset of patients who achieved clinical cure, an assessment of CDI recurrence in the full analysis set using an expanded definition of clinical cure.

We also assessed global cure using the expanded clinical cure definition. In a moment, I will present the sensitivity analyses conducted to evaluate impact of incomplete data on primary efficacy.

First, let's look at the results from the CDI recurrence analysis in the subset of patients who achieved clinical cure. Perhaps the most natural endpoint, given the impact of clinical cure on CDI recurrence, is to look at CDI recurrence in the subset of patients who achieved clinical cure

rather than the full analysis set.

In other words, the denominator for this assessment of recurrence is the subset of clinical cure, not all subjects in the full analysis set. This endpoint was a prespecified secondary analysis in both trials. This analysis provides critical supportive information in interpreting primary efficacy.

The graph here shows that, among those who achieved clinical cure, BEZLO significantly reduced the proportion of subjects with CDI recurrence as compared to placebo. The absolute differences between treatment arms are consistent with the primary analysis.

Recall the protocol definition of clinical cure. Subjects had to receive 14 or fewer days of standard of care therapy and have no diarrhea for the 2 consecutive days immediately after completion of standard of care therapy.

The reason for using this definition of clinical cure was to standardize standard of care duration and the follow-up period for recurrence

across patients. This definition resulted in a larger than expected proportion of subjects failing to achieve clinical cure. with The incidence of clinical cure was approximately 80 percent in MODIFY I plus II, versus approximately 90 percent in the fidaxomicin phase 3 studies, which used investigator assessment for clinical cure.

As a result, approximately 20 percent of patients in the MODIFY program FAS population were imputed as success for CDI recurrence and failure for global cure. These were the 20 percent of patients represented by the black circle in our previously shown diagram.

It should be noted, however, that even though 20 percent of subjects did not achieve clinical cure by the protocol definition, the vast majority of those patients did eventually achieve clinical cure on study.

In fact, by expanding the clinical cure definition, 95 percent of subjects achieved clinical cure, and we were able to assess CDI recurrence for all those patients. That is what

our second sensitivity analysis does.

This sensitivity analysis used an expanded definition of clinical cure, in which patients with no diarrhea on two consecutive days after completion of any duration of standard of care therapy were considered to have clinical cure.

This definition is more clinically relevant for patients and prescribers, as it does not exclude patients who receive standard of care for longer durations or resolved diarrhea at a later time point.

This sensitivity analysis with an expanded definition of clinical cure minimizes the number of patients for whom CDI recurrence is imputed as success or failure and also uses all observed data on the presence or absence of CDI recurrence in the two trials.

This graph shows time to clinical cure using the expanded definition. The blue line shows BEZLO group and the dotted gray line shows placebo group in MODIFY I. The majority of patients achieved clinical cure by the third week after infusion,

which corresponds to the time frame in which their standard of care therapy is ending, just a few days beyond the window allowed by the protocol definition of clinical cure.

As seen here, time to clinical cure rate is nearly identical between BEZLO and placebo. There are days when the proportion of patients achieving clinical cure is slightly higher in the BEZLO group, and other days when it is slightly higher in the placebo group.

By week 3, proportion of patients who achieved clinical cure exceeds 90 percent in both treatment groups and reaches a plateau. This allows nearly all patients to be assessed for CDI recurrence for at least 9 weeks, which is ample time for CDI recurrences to be observed.

As seen here, BEZLO does not impact a patient's likelihood to achieve clinical cure or on the timing to develop clinical cure. Data from MODIFY II on this slide indicate that time to clinical cure using the expanded definition is nearly superimposable to what was seen in MODIFY I,

demonstrating that BEZLO does not impact clinical cure.

Here, clinical cure rates using the original definition and expanded definition by week post-infusion are shown for MODIFY I and II. In both trials, great majority of the patients achieved clinical cure in both trials by week 3, reaching 93 to 95 percent by week 6. Clinical cure rates were similar in the treatment arms at various time points.

We applied this expanded definition of clinical cure to the assessment of primary endpoint, CDI recurrence, in the full analysis set. Despite an increase in CDI recurrence rates across all subgroups, all groups, the absolute difference between the treatment groups was maintained with highly significant p-values.

On this slide, you see global cure rates calculated using the expanded definition of clinical cure. The proportion of patients achieving global cure increased and a substantial difference between the treatment groups is

observed. By week 3, at which time over 90 percent of patients had achieved clinical cure, the difference between treatment groups was highly significant in both trials.

Using the more clinically meaningful expanded definition of clinical cure, global cure rates are not influenced by the small differences seen in clinical cure rates as an artifact of the strict definition of clinical cure used originally.

On this forest plot, you see for MODIFY I and II separately a summary of the primary endpoint and the sensitivity analyses conducted. In all sensitivity analyses, BEZLO resulted in reduction in CDI recurrence rates consistent with the overall primary efficacy analyses, indicating robustness of the primary endpoint.

The robustness of primary endpoint was also assessed by evaluating the impact of incomplete data on primary efficacy. Incomplete data included patients who had incomplete follow-up or diarrhea following clinical cure that was not tested for toxigenic C. difficile.

As I previously showed, the majority, 85 percent of patients, completed the full 12-weeks follow-up period. In fact, 92 percent of patients had at least 4 weeks of follow up. Incomplete follow-up was mainly due to deaths, withdrawal of consent, or loss to follow-up.

Eighty-six percent of all of diarrhea recurrences were tested for toxigenic C. difficile. Of those not tested, the majority, 78 percent, had only 1 or 2 days of diarrhea. We also assessed patients who did not have CDI recurrence but received a CDI active therapy during follow up.

In order to evaluate impact of incomplete data, we prespecified an exploratory endpoint that is diarrhea recurrence. In this endpoint, all recurrences of diarrhea were included, irrespective of whether the test for toxigenic C. difficile was negative or not performed.

In addition to diarrhea recurrence endpoint, three different sensitivity analyses were conducted. And these patients with possible incomplete data were imputed as failure for CDI

recurrence and were added to the primary endpoint cases.

These analyses imputed the following patients as having CDI recurrence; those who discontinued from study, those who discontinued from study and/or had diarrhea with no toxigenic C. difficile test in the follow-up period, and those who discontinued from study and/or had diarrhea with no toxigenic C. difficile test and/or received any dose of a potential CDI active therapy in the follow-up period.

Here are the efficacy data for recurrence of diarrhea irrespective of etiology. As expected, the rates of diarrhea recurrence were higher than the rates for CDI recurrence, but the treatment differences observed for CDI recurrence in the primary analyses are supported by these data. BEZLO resulted in significantly lower diarrhea recurrence rates compared to placebo.

Here are the results from the primary efficacy endpoint and diarrhea recurrence endpoints, shown on the forest plot. The

consistency of efficacy in diarrhea recurrence with the primary endpoint demonstrates robustness of the primary efficacy.

Now let's add the results from the sensitivity analyses that evaluated impact of incomplete data. Consistent with previous findings, these analyses also indicate reduction in CDI recurrence in favor of BEZLO.

In summary, multiple prespecified endpoints and sensitivity analyses assessing impact of clinical cure on CDI recurrence, and impact of incomplete data consistently demonstrate robustness of the primary endpoint of CDI recurrence and efficacy of BEZLO in reducing CDI recurrence.

Similar to the data from individual trials, the integrated dataset also demonstrate consistency of efficacy findings from sensitivity analyses with the primary efficacy results and indicate that the primary efficacy of BEZLO is robust.

In conclusion, a single dose of 10-milligram-per-kilogram BEZLO is superior to placebo in preventing CDI recurrence through

12-weeks follow-up period in patients receiving standard of care antibiotics for CDI. Bezlotoxumab reduced CDI recurrence rate by approximately 40 percent relative to placebo. And efficacy is consistent across MODIFY I and MODIFY II.

Furthermore, across important subpopulations, BEZLO consistently reduces CDI recurrence rate compared to placebo.

Multiple prespecified and post hoc sensitivity analyses consistently demonstrate that assessment of the primary endpoint of CDI recurrence and efficacy of BEZLO in reducing CDI recurrence are robust. And finally, efficacy of the standard of care antibiotic in achieving clinical cure is not diminished by BEZLO.

Now I will hand it over to my colleague, Dr. Yoshi Murata who will present the safety data. Yoshi?

Sponsor Presentation - Yoshi Murata

DR. MURATA: Thank you, Dalya. I'm Yoshi Murata, clinical director in infectious diseases at Merck. I will now present the safety overview of

bezlotoxumab.

The safety assessments performed by the site investigators during the MODIFY I and II trials are shown on this slide. During the protocol-specified monitoring period after the study drug infusion, the following adverse events were recorded: infusion specific adverse events reported on the day or day after infusion; non-serious adverse events reported during the first 4 weeks following infusion; and serious adverse events and deaths reported during the 12 weeks after infusion.

The safety monitoring also included protocol-specified vital sign measurements, electrocardiograms pre- and post-infusion, physical examinations, and monitoring of clinical laboratory parameters. Laboratory results determined by the study investigator to be clinically relevant were recorded as adverse events.

To assess the immunogenicity potential for BEZLO, anti-drug antibody levels were measured at baseline at prespecified time points during the trial. The safety assessment data were then used

to characterize the safety profile of BEZLO.

In the next several slides, I will summarize the results of the safety monitoring during the MODIFY I and II trials.

The immunogenicity risk of BEZLO was expected to be low because BEZLO is a fully human monoclonal antibody. After administration of BEZLO alone or in combination with ACTO, no anti-BEZLO toxin of antibodies, either binding or neutralizing, were detected in any of the 96 healthy subjects in phase 1 trials, including 29 subjects who received 2 doses given 3 months apart or in subjects with Clostridium difficile infection in phase 2 and phase 3 trials. The administration of BEZLO is not associated with a generation of binding or neutralizing anti-drug antibodies.

On this slide, a summary of the most common infusion specific adverse events that were reported on the day or day after infusion is shown. This and other analyses to be shown in successive slides was based on the all-patients-as-treated population of the MODIFY I and II integrated dataset.

The safety profiles of subjects treated with BEZLO are compared to those who received placebo. As supporting safety data, the safety profile of subjects treated with BEZLO with actoxumab are also presented. It should be noted that subjects enrolled in MODIFY I and II trials were treated with standard of care antibiotics for their CDI at time of enrollment and infusion of placebo, BEZLO, or ACTO plus BEZLO.

The adverse events reported during the phase 3 trials are expected to include those commonly seen in CDI subjects following treatment with standard of care antibiotics.

Specific adverse events to be monitored during and shortly after the study drug infusion were prespecified in the MODIFY I and II protocols to ascertain if hypersensitivity reactions may be associated with such infusions.

As shown on this slide, the incidence of infusion-specific adverse events was similar across treatment groups. Also, there were no clinically relevant trends in changes in ECG parameters of

vital signs between pre- to post-infusion measurements. The majority of the infusion-specific AEs were mild to moderate in intensity. No anaphylactic, anaphylactoid, or hypersensitivity reactions are observed.

The summary of adverse events during the first 4 weeks following infusion is shown on this slide. Approximately 60 percent of subjects experienced 1 or more adverse events during the 3 treatment groups during the first 4 weeks following infusion. Approximately 4 percent of subjects in each treatment group died during the first 4 weeks following infusion.

The proportion of subjects who experienced drug-related adverse events and those with serious drug-related adverse events were relatively low and were comparable across treatment groups. There were no association detected between BEZLO administration and changes in clinical laboratory parameters.

The most common adverse events reported during the first 4 weeks following infusion are

shown on this slide. For this and other slides to follow, the adverse events are listed by specific incidence cutoff values, as shown on the bottom of each slide and then shown in order of decreasing incidence rate in the placebo group.

The most common adverse event was Clostridium difficile infection, which was to be reported as an adverse event only if it was serious. CDI was noted in a higher proportion of subjects in the placebo group than in the BEZLO or ACTO plus BEZLO groups.

Given the previously discussed efficacy results for BEZLO, to reduce the CDI recurrence rates in the MODIFY I and II trials, this observation is not unexpected. The incidence of adverse events other than CDI was similar across treatment groups during the first 4 weeks following infusion.

I will now discuss the serious adverse events, including deaths that were reported during the 12 weeks following infusion, a summary of which is shown on this slide. Across the three treatment

groups, approximately 30 percent of subjects experienced serious adverse events. Approximately 7 to 8 percent of subjects across treatment groups died during the 12 weeks.

There were 3 subjects who had drug-related serious adverse events assessed by the investigator to be related to study medication and who died during the 12 weeks following infusion. Of these 3 subjects, 1 received BEZLO and experienced cerebral hemorrhage with fatal outcome. The other 2 subjects received ACTO plus BEZLO and the adverse events of fatal outcome were sepsis, hypoglycemia and respiratory arrest for 1 subject, and small bowel obstruction for the other subject. All 3 subjects had been hospitalized for serious medical conditions at the time of diagnosis and study entry.

The serious adverse events reported during the 12 weeks following infusion are summarized on this slide. The most common serious adverse event was Clostridium difficile infection followed by sepsis, both of which were noted in a higher

proportion of subjects in the placebo group than in the BEZLO or ACTO plus BEZLO groups. The incidence of other frequently reported serious adverse events was generally similar across groups.

For additional analyses of the serious adverse event profile of bezlotoxumab subjects experiencing one or more of the following cardiac failure adverse event terms, the preferred terms. Cardiac failure, cardiac failure acute, cardiac failure chronic, and cardiac failure congestive were counted once and categorized as experiencing cardiac failure.

A total of 41 subjects experienced a serious adverse event of cardiac failure, of which 7 were in the placebo group versus l7 in each of the active treatment groups. To further characterize this observed numerical imbalance of subjects experiencing cardiac failure, a series of analyses were performed.

The baseline characteristics of subjects who experienced a serious adverse event of cardiac failure are shown on this slide. As compared to

the overall all patients as treated population, such subjects were older and almost all were inpatients at the time of enrollment, with a higher incidence of comorbid conditions and a higher rate of severe CDI.

Across the treatment groups, nearly 90 percent had a medical history of any cardiac system organ class condition, and approximately 70 percent had a history of cardiac failure and/or cardiomyopathy. Overall, this was an extremely ill patient population with advanced age.

The safety profile of the 41 subjects with cardiac failure was analyzed with respect to timing to cardiac failure event. In the placebo group, 5 of 7 subjects experienced a cardiac failure event before week 4, while in the BEZLO and ACTO plus BEZLO groups the majority of such events occurred after week 4. None of the cardiac failure events was deemed drug related by the investigator.

A higher proportion of subjects in the placebo group than in the BEZLO or ACTO plus BEZLO group died before week 4. Their events were often

associated with concurrent conditions, such as infection and a worsening CDI that are known to exacerbate congestive heart failure, further supporting the assessments that these events were not drug related.

This slide places the cardiac safety data shown on the previous two slides in the context of available preclinical data for BEZLO. BEZLO targets a non-endogenous bacterial toxin. BEZLO is distinct from monoclonal antibodies with known cardiac signal and which functionally interact with endogenous target molecules.

There was no tissue cross-reactivity of BEZLO in mouse and human tissues tested in vitro. In repeat dose toxicity studies of BEZLO in mice, there were no histological findings in cardiac tissue or changes in hemodynamic parameters. Taken together, there is no evidence of preclinical cardiac safety findings with bezlotoxumab.

To further evaluate the cardiac safety profile of bezlotoxumab, 325 subjects with congestive heart failure at baseline as indicated

on the Charlson Comorbidity Index were identified. This group of subjects will be called the CHF subset, and a summary of the baseline factors is shown on this slide.

The baseline factors are not entirely balanced across treatment groups. More subjects in the BEZLO group had higher Charlson Comorbidity Index scores at or above 5 and were receiving diuretic therapy. Not unexpectedly, the CHF subset was an elderly population with a higher proportion of inpatients and with more comorbid conditions than the overall population.

The safety of the CHF subset to week 4 and week 12 post-infusion is summarized on this slide. At week 4, there were more adverse events observed in the BEZLO group than in placebo or ACTO plus BEZLO groups. However, the incidence of cardiac adverse events was comparable with 10 to 11 percent among the 3 groups. There were more deaths observed in the BEZLO containing groups than in the placebo group.

This imbalance correlates with a difference

in the numbers of deaths across the non-cardiac categories, including neoplasm, renal and urinary disorders, and respiratory disorders. There was no appreciable difference in the number of cardiac deaths across all treatment groups in the CHF subset. At week 12, the overall trend of serious adverse events and deaths seen across treatment groups was similar to those at week 4 and with increasing numbers. Again, most of the deaths were due to non-cardiac causes and consistent with pre-existing comorbidities.

In the CHF subset, all cardiac serious adverse events through week 12 were reviewed and deemed consistent with poor underlying cardiac health, often with precipitating events such as infection or anemia, leading to worsening cardiac status. None of the cardiac serious adverse events was drug related.

The conclusions from the safety analysis of bezlotoxumab are as follows. A single infusion of bezlotoxumab therapy in patients 18 years or older and receiving antibiotic therapy for CDI is

generally well tolerated.

Bezlotoxumab has a safety profile that is similar to that for placebo. The overall incidence of adverse events in the bezlotoxumab treatment group was comparable to the placebo group. In summary, BEZLO has a favorable safety and tolerability profile.

I will now invite Professor Mark Wilcox to present the benefit-risk profile for bezlotoxumab.

Mark?

Sponsor Presentation - Mark Wilcox

DR. WILCOX: Hello. Good morning. Thank you for the opportunity to speak today. I'm not going to read through my roles that have been already talked about and are up on the slide here. But what I would like to emphasize is that I've spent a considerable proportion, indeed the majority of the last decade of my professional career, dealing with C. difficile at a local, regional, and national level, as those roles show there.

I'm also involved internationally in C. diff

infection. I'm the only non-North American author on the 2010 IDSA SHEA guidelines. And similarly, I'm the only non-North American author on the currently revised version of the same guidelines.

The reason I particularly wanted to be here today is that I passionately believe that patients should have better treatment options than are currently available for CDI, and I'd like to explain why I think that's the case. So I'm going to talk about patient perspective, medical perspective and societal perspectives in terms of unmet needs, so I'm going to start, quite rightly, with the patient perspective of unmet need.

So patients with CDI suffer from a debilitating, life-changing, painful diarrhea that can lead to other complications as well. And the key point from a patient perspective is that there are no optimal treatment options for recurrent CDI. That's where the need is from a clinical perspective.

Out of every 10 patients with CDI -- and I've colored the patients here green and red

appropriately -- approximately 4 have an unsatisfactory outcome. The minority of those 4 is a failure to achieve a clinical cure.

The majority of those 4 with unsatisfactory outcome is because of recurrent CDI. Even worse, by day 30, between 1 in 6 and 1 in 16 patients are dead after the diagnosis of CDI. Those data come from large and indeed national datasets.

Despite this unacceptable situation from a patient perspective, there are 2 plus 1, the plus 1 being metronidazole, which is not formally FDA approved, therapeutic options for CDI, which is unsatisfactory.

Indeed, as has already been pointed out, there are no approved therapies for the prevention of CDI recurrence. And ironically, antibiotic treatment for CDI doesn't prevent recurrence, and indeed it may exacerbate the risk because of the damage to the gut microbiota.

Bezlotoxumab offers here something different from a patient perspective, a novel approach not based on antimicrobial therapy per se, to blocking

the untoward events following of toxin production.

From a medical perspective, CDI is clearly a global health problem and indeed it's increasing in incidence in the U.S., in Canada and in multiple European countries, Spain, Germany, Eastern European countries for example, CDI incidence increasing. In the U.S., you've already seen some of these data earlier, almost half a billion CDI cases in 2011, nearly 30,000 associated deaths, over 80,000 first recurrences, and over 50,000 follow-on additional recurrences. This is an unacceptable medical burden of CDI.

If we now turn to the unmet medical needs in respect of recurrent CDI, those episodes are associated with a third increase in mortality, a 2 and a half fold increase in hospital readmission rates, and a 4-fold increase in hospital readmission days.

Together, that represents not only a very significant medical patient burden, but a significant cost burden. I haven't shown costs, specific costs here. As you would expect, with a

condition like this, it's difficult to get an accurate cost, but the range of costs associated with CDI, indeed recurrent CDI, ranges from $10,000 to tens of thousands of dollars per case.

What about the unmet societal need of CDI? Well, not only the patient has to cope with the illness, but the families have to cope with the illness in terms of the debility, isolation and loss.

What do I mean by debility? I'll give you two prime examples. Patients with CDI are often frightened to leave the house. That's because they're frightened to be too far away from the toilet. It's as basic as that. It's a very unpleasant condition. They're worried about recurrent symptoms.

It's known from work particularly carried out by Kevin Garey's group in Houston, that anxiety is a particularly prominent symptom, anxiety because of the complications of CDI and anxiety because of the current episode of CDI. This is a debilitating condition. And indeed, few infectious

diseases arouse quite as much concern, and that reflects, in my opinion, the protracted nature of recurrent CDI. That's where the prime unmet need is.

I'm going to show evidence to support the next bullet points that families and patients often use words like battle and war. Yes, they're emotive terms, but they're emotive for good reason. And indeed, it's notable the number of different patient support groups that exist. I've only listed some, not all, only some of the U.S.-based patient support groups. And if we just ask ourselves the simple question, why are there so many patient support groups? There are many in Europe, in the U.K. as well. I'll come back to that point.

Here's an example of probably the most well-known patient support group, U.S. support group, namely the C Diff Foundation. This is their home page detailing information about Twitter activity. You can see that in the middle of the slide. Also you note from this slide that the

C Diff Foundation is extremely active. It organizes an annual meeting, which is well attended.

I spoke at the last meeting in Boston. I'm due to speak in the meeting advertised here in Atlanta in the fall of 2016. An extremely passionate group of individuals, why do they exist? Because of the unmet needs relating to CDI. And I put it to you that that's mainly because of recurrent CDI, which blights people's lives.

The second example from those 3 support groups that I listed two slides ago is this one, to prove that the words battle and war are real words used by real patients. The names of the patients have been obscured, as I'm sure you realize why, on this slide.

This is a screenshot of this case history page from this support group taken last week. So you can see the words on the right-hand side, battle with the beast, where am I with this battle. These are, again I put it to you, extremely emotive terms, and I feel passionately for these patients

who have to put up with this disease.

Lastly on this slide, if you look at the far right-hand side, look at the numbers of hits that these sites and these case histories are generating. Why? Because of the unmet need.

So I'd like to talk about the benefit-risk assessment. We've heard that this is a single IV dose of bezlotoxumab 10 milligrams per kilogram given to patients aged at least 18 years of age, whilst, at any point, which I think is a clinically useful attribute, at any point during the standard of care therapy for CDI.

On the right-hand side, I believe that the data supports the fact that bezlotoxumab is generally well tolerated with a similar profile to that of placebo. On the left-hand side, from a clinical perspective, the efficacy provided by bezlotoxumab is the prevention of CDI recurrence throughout the 3-month, 12-week at-risk period. And I think you've been shown, I believe you've been shown, clinically meaningful sensitivity analyses that back up and confirm the consistency

of that reduction in CDI recurrence risk.

I think also importantly, the efficacy has been demonstrated across predefined, multiple, clinically relevant, clinically important subgroups at high risk for recurrence. And on that last point, that links to my first point on this slide.

You see the number needed to treat in those at risk patients is 6. It's a very low NNT. But contrast that with the NNT for the overall study population of 1 in 10, which I still think, believe, is a low NNT for the entire population comprising those predefined as being at risk, but also those not predefined as being at increased risk.

We've heard that bezlotoxumab reduces CDI recurrence by approximately 40 percent. If you translate that into real-life potential, then the number of potentially prevented CDI episodes, recurrences, is 50,000 in the U.S., per annum, recurrent.

Add to that the reduced CDI-related readmissions and all-cause cumulative hospital

days, these data have been obtained by a post hoc analysis of the phase 3 database that's being talked about today. They're important clearly from a medical perspective.

Add to that the fewer CDI cases that are preventing recurrence that would therefore need antibiotic treatment. And that then potentially reduces the chance of antibiotic resistance, not particularly in C. diff, but actually in other organisms in the gut that are exposed to these antibiotics. And we know that CDI treatments, vancomycin and metronidazole for example, are both associated with increased risk of VRE, last but not least the potential benefits to other patients by preventing recurrences and therefore the spread of strains that can be harmful and indeed that includes epidemic strains as well.

This is a reasonably busy slide on purpose. It can get a lot worse than this, but I'm not going to -- this is the simplified version, you'll be relieved to know. On the left-hand side, you'll see the complication of surgical aspects, and that

hasn't been talked about today. It's not really relevant today to talk about that.

What I wanted to summarize briefly are the other 3 major categories of outcomes shown on this slide due to CDI. Recurrent CDI has rightly been the theme of today's presentation and my risk/benefit analysis.

I point out that between half and three-quarters of first recurrences lead to new readmissions, enormous patient, medical and societal impact. The length of hospital stay data is shown on the right-hand side of the slide, with between 5 and 15 days increased length of stay due to CDI. The mortality is shown at the bottom of the slide. I'm not going to repeat that there.

But the common theme between the top, the right-hand side, and the bottom of this slide is recurrence. That drives to a greater or lesser extent elements of each of those three major outcome categories.

I'd like to summarize -- this is my final slide -- by congratulating the CDC. I couldn't put

it better myself. I don't think anybody could. This is the 2013 CDC document that has rightly received so much airtime.

The quote from CDC is that, "C. diff is an immediate public health threat that requires urgent and aggressive action." I point out that this document was published in 2013. Since it was published, zero additional treatment options for CDI have become available, approved options.

I'd like to summarize by saying that I believe that bezlotoxumab helps to address unmet patients' medical and societal needs due to CDI, all three of which are clearly important and, lastly, that bezlotoxumab has a positive benefit-risk profile for the prevention of CDI recurrence. That concludes this presentation. Thank you for listening.

DR. KARTSONIS: Good morning. My name is Nick Kartsonis. I am an infectious disease clinician, and I serve as the section head for antibiotics and CMV at Merck. And I'm going to help with the redirection and the answering of the

questions during the clarification section. So we turn it back to the committee.

Clarifying Questions to the Presenters

DR. BADEN: Thank you all for a wonderful set of presentations covering a lot of data encompassed by those studies.

At this time, I'll open the floor to the members of the committee for clarifying questions for the sponsor. Remember to state your name for the record before you speak and, if possible, direct to a presenter. Dr. Kartsonis will facilitate the answering of questions. To members of the committee, please look to Lauren to make sure we acknowledge you and then can sequence the questions properly. So Dr. Corbett?

DR. CORBETT: Thank you. This is just a clarification on the efficacy discussion with Dr. Guris, I believe it was, her slide 47 perhaps. I just want to kind of hear again the discussion about -- I wrote down 95 percent achieved clinical cure during the study period and I want to make sure that was what I heard.

DR. KARTSONIS: In the expanded clinical cure definition, when we look at it, we do indeed see an increase in the number of patients who achieved clinical cure. In fact, if we can go to the time of clinical cure slide, there you go, slide 49, if you could, put the slide up for me, please.

As you can see on this slide, which is from the presentation, slide 49, indeed, by approximately day 21, we are approaching 90, 95 percent of the patients. If you could look at the numbers down below, 94 percent of the patients in the 2 groups have achieved clinical cure with this expanded definition.

DR. CORBETT: Thank you.

DR. BADEN: Building on that clarifying question at this point, the basis for the initial definition of clinical cure being 14 days, what was the basis for that definition, and what is the basis for this revised definition?

DR. KARTSONIS: Thank you for that question. The original definition, as we noted, was based on

the receipt of -- and you can put the slide up. Slide 47, we mentioned this.

The receipt of less than 14 days of standard of care regimen, as well as no diarrhea for the immediate 2 days following the completion of standard of care therapy, that definition was defined with an effort to standardize the amount of follow-up period that the patients had actually received.

As you can see there in the original study, by doing that we indeed ensured that we would have approximately 10 weeks of follow-up period for all the patients in the study.

But clearly, what we found when we looked at the data as to why patients had failed from the clinical cure standpoint, there were really 2 main reasons. One was that patients had received more than 14 days of the regimen -- and I'll get back to that in just a second -- and secondly was that the patients had persistent diarrhea in the 2-day period following the completion of that regimen.

What's interesting is that when you look at

the patients who got more than 14 days, there was a common theme. In fact, we looked at all of those patients who had more than 14 days of therapy, and it turned out that, in 90 percent of them, you could explain it based on four reasons.

The patients were either immunocompromised. They were patients who had had prior episodes of CDI. They were patients who were receiving a concomitant antibiotic for another condition, or they had an initial non-response to their regimen very early in the first 3 days and required a change in their regimen, which was allowed in the study. We did allow for switches. It was not common. It was only seen in about 6 percent.

So 90 percent of the patients in all the treatment groups were for those particular reasons.

It wasn't because the patients had still diarrhea. In fact, in 80 percent of those patients who had received more than 14 days, they had already resolved their diarrhea by the time they had completed the standard of care regimen.

Furthermore, most of them had resolved it by

day 10 of the study. So the important point is that the physicians felt it was important for them to continue the regimen because they had other factors that were driving the underlying condition.

The second reason that people failed was because of the fact that they had persistent diarrhea for the first two days following the completion of standard of care. Well, it's not uncommon in C. diff for patients to have trickling of diarrhea for the first few days following the completion of standard of care.

It's interesting that when we actually looked at the data for those people, most of them subsequently resolved their diarrhea by day 3, day 4, and in fact 75 percent of those people who still had diarrhea in those first 2 days had resolved it by 7 days following the completion of standard of care.

So when you go back to that expanded clinical cure definition, you really are encompassing how, in our opinion, the patient is feeling. And we think it's more clinically

relevant because it's taking into consideration the fact that the investigator felt that the patient needed that therapy, and they continued the patients accordingly. And so that's why we've presented that data today.

Again, as Dr. Guris nicely mentioned in her presentation, this is based on all observed data. Clinical cure was never evaluated by the investigator. It was all programmatically assessed by the company.

Since we have all the data, all the loose stool data for 85 days of therapy, we can look at the observed data as opposed to imputing patients as potential failures for a CDI recurrence definition or for the global cure definition. This is, in our opinion, the purest way to look at clinical cure, and in fact the best way to look at the endpoints of both recurrence as well as local cure.

DR. BADEN: Thank you. Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis from New York Department of Health, New York City Department

of Health. Just a question. The idea of readmissions was mentioned. Have you looked at readmissions among your hospitalized patients?

DR. KARTSONIS: Yes, we did. We actually have a post hoc analysis that did that. I can actually call Dr. Guris to the stand to present that data. We did collect it systematically in our studies. It wasn't a primary or secondary endpoint of the study, but we did systematically collect it and we can look at that data.

DR. GURIS: Slide up, please. So in this analysis, we looked at patients who were inpatients coming into the study. They were discharged from hospital and then they were readmitted. And you see overall the reduction, approximately 60 percent between bezlotoxumab and placebo, 9.6 percent of the placebo patients were actually readmitted for CDI-associated reasons within the 30 days.

In BEZLO, it was 4 percent. We see 60 percent reduction, relative reduction in BEZLO group compared to placebo. And we see consistent results across different groups, including elderly,

those with one or more previous CDI episodes, and severe CDI.

DR. BADEN: Dr. Goetz?

DR. GOETZ: I have a couple. This is Matthew Goetz, VA and David Geffen School of Medicine. I have two questions here. I'd like to turn to -- let me get to my note here -- I guess it's the impact of BEZLO on high-risk versus low-risk populations, which was discussed, I think, in slides 39 and 87.

What I'm interested in is sort of the converse, the benefit of BEZLO in low-risk populations rather than high-risk populations. So I don't know if you -- one way of looking at that would be populations that have had zero prior episodes as were the benefit is there.

Then you have a series of -- you have a slide that shows a series of parameters that define high-risk populations and I'm interested in looking at the inverse of that.

DR. KARTSONIS: Thank you. And here's just a reminder to the committee of the high-risk

groups. As you can see, BEZLO did reduce it across all of the high-risk groups. We did also look at the converse and we have that data as well from the groups.

Why don't we show that, please? Yes. Slide up please.

Here's the full set of data for each of the risk factors. You see both the high-risk and the low-risk groups all shown on the same slide. And indeed you can see in this forest plot, again just to remind you how the forest plot's laid out, if it's favoring bezlotoxumab it's on the left-hand side for recurrence with the actual point estimate shown as the diamond, and the 95 percent confidence interval shown as the lines around that.

As you can see, in both high-risk as well as in low-risk patients, we do see a consistent effect. And in fact, in many of these, as you can see, it excludes zero and it still remains significant in both high risk and low risk. So we actually think it's appropriate that bezlotoxumab is made available to all patients, including low

risk as well as high risk. And in fact, as Dr. Wilcox mentioned, a number needed to treat to prevent one recurrence amongst all the patients was as low as 10.

DR. GOETZ: To follow up on that a little bit.

DR. KARTSONIS: Sure.

DR. GOETZ: If you look at people who have none of the high-risk factors, you've looked at each of the individual high-risk factors, but still, people could have had one factor and not the other. I don't know whether you looked at the data in that fashion.

DR. KARTSONIS: Sure. Dr. Guris had mentioned in her presentation that 74 percent of the patients had one of the risk factors. And in fact, if we look at the patients who had one or more of the risk factors, there is a significant reduction in the patients. In fact, it's a difference between 30 percent having a high factor of recurrence versus 17 percent. So the difference is 13 percent absolute difference.

In the low-risk group, as you might expect, the differences are smaller. It's about 3 percent. And the confidence intervals do not exclude zero. So we do see still an effect, but it's not as pronounced as it is. The recurrence rates in the BEZLO group in that situation are low, but it's generally the same.

DR. GOETZ: Then I had one other question about -- you've touched on it obliquely, but the exposure of patient populations to antibiotics not active against C. diff, as to whether that had any impact on the efficacy of BEZLO.

DR. KARTSONIS: If I could ask a clarifying question, do you mean sort of concomitant antibiotic use?

DR. GOETZ: Concomitant antibiotic.

DR. KARTSONIS: Are you interested in the data in recurrence or are you interested in clinical cure, just curious there?

DR. GOETZ: Obviously globally, I'm interested in both.

DR. KARTSONIS: Okay. So can we start with

the clinical cure data first and then we'll move into the recurrence data, if that's okay. So, indeed, if you could, put the slide up, please.

Approximately 40 percent -- this is actually a high number -- 40 percent of the patients were receiving concomitant antibiotics for another bacterial condition while they had their C. diff episode. As you can see, about 41 percent on placebo, 37 percent, as you might expect, patients who were receiving concomitant antibiotics did worse from a clinical cure standpoint.

Now again, as I mentioned earlier, a lot of these patients were patients who required more than 14 days of additional therapy and were thus being counted, per the per protocol clinical cure definition, as a failure. However, as you can see, there's really no differences between the two treatment groups, BEZLO versus placebo. And as expected, the patients who weren't receiving concomitant antibiotics had a higher response rate as opposed to those who did receive concomitant antibiotics.

We also do have the recurrence data. So now, when we did this analysis, we actually looked at concomitant antibiotics use after the patient got clinical cure and during the follow-up period, because that's the best way to then look to see if the patients had that influence on their ability to develop recurrence.

If we could put the slide up, please, you can see there's about a third of the patients who had concomitant antibiotic use after SoC. And in that particular setting, you see that, irrespective of whether or not they received concomitant antibiotics or not, we still see a notable effect for bezlotoxumab in both settings.

Let me orient you to the slide a second. The concomitant antibiotic use is shown on the left-hand side, about 35 or 36 percent. The people who were receiving antibiotics following standard of care, the placebo was 26 percent versus 16 percent on BEZLO, or 17 percent on BEZLO, and those without was 27 versus 17 percent, so consistent effects for bezlotoxumab both whether or not

patients had to go on and receive concomitant antibiotic therapy or did not.

DR. BADEN: Building on that slide, the antibiotics were anti-anaerobic all in the assessment of the qualitative impact of the choice of antibiotic?

DR. KARTSONIS: Sure. We haven't gone down to the level of looking at the specific antibiotics. We've really focused mainly on all antibiotic therapy. This would be all concomitant antibiotic use, but we didn't break it down if it was for Gram-positives versus Gram-negatives versus anaerobic.

But I can tell you from reviewing the data and our team reviewing it, people received these antibiotics for a lot of different conditions, including both Gram-positive, Gram-negative, and anaerobic conditions, and that's an important thing to keep in mind because a lot of these people had to then be re-exposed to metronidazole in the follow-up period.

DR. BADEN: Dr. Moore?

DR. MOORE: Hi. So it wasn't specifically stated, but I assume it was -- it seemed to be implied. None of these patients received fecal transplants during or after the study period?

DR. KARTSONIS: Sure. We did allow -- if patients had had a prior episode and had received a fecal transplant, they were still potentially eligible if they now came in with another CDI episode to receive bezlotoxumab and be enrolled in the study. That happened in only one case.

But we did allow, once a patient had developed recurrence, that in that setting they could then go on and receive an FMT. FMT was not allowed while the efficacy was under evaluation, but if the physician determined that the patient developed CDI recurrent and wanted to then allow that in the follow-up period, they could indeed do so.

We examined that data. It's actually very fascinating data. What we found was that the use of FMT in the follow-up period was significantly higher in the people receiving placebo as opposed

to the people receiving either BEZLO or ACTO plus BEZLO.

In fact, there were 23 patients in the placebo group who went on to get FMT because of their recurrence as opposed to only 4 in both of the BEZLO as well as the ACTO plus BEZLO group.

Let me put that in a different way, that if you compare it relative to all of the recurrences that occurred in each of the groups, that would have been 11 percent of the patients in the placebo group who recurred went on to get FMT as opposed to 3 percent of the patients in the active groups. That's an 80 percent reduction in the use of FMT by giving bezlotoxumab.

DR. MOORE: Okay, that's a real game-changer, and I think that has significant implications. Do you have those data available for evaluation?

DR. KARTSONIS: We actually recently did these analyses. I don't have it available as a slide for you, but we could prepare one for you and share it after the lunch time meeting if you'd

prefer.

DR. MOORE: Thank you very much.

DR. KARTSONIS: You bet.

DR. MOORE: That would be great.

DR. BADEN: Dr. Weina?

DR. WEINA: Pete Weina from Walter Reed. I noticed that the proposed dosing is for 60 minutes. Was that chosen because it's longer than 30 and less than 90? Or was there a specific reason and if there was an evaluation as to any kind of adverse events associated with less-than-60-minute infusion rates?

DR. KARTSONIS: Sure. Thank you for that. We've actually evaluated -- bezlotoxumab has only been administered to patients in a range between 60 minutes and 120 minutes, so we don't have any data with regard to its use over 30 minutes. Now, keep in mind it is a large dose. It's given in a 200-mL infusion. It does take some time to actually deliver the drug. So we recommend and would be recommending that we give it as we studied it, which was over a 60-minute period.

I can tell you, when you compare 120 versus 60, there's no difference. We've looked at that in a specific phase 1 study and didn't see any impact with regard to either pharmacokinetics or even the safety, but I don't have any data to provide you with regard to less than 60 minute infusion.

DR. BADEN: Comments to the committee. If any of you have a question that immediately builds on the prior question, please raise your hand so that we can follow any line of thinking before we move on to multiple additional topics. Dr. Hilton?

DR. HILTON: I'm building on an earlier question about the enhanced definition. And I wonder if at baseline you know the history of standard of care use in the previous two weeks, for example.

DR. KARTSONIS: In terms of the actual way the study was administered, we allowed for the monoclonal therapy to be given at any time while the patients were on standard of care, standard of care therapy. I can tell you that the mean day of administration of the study infusion and the median

day was day 3. So patients had already been on standard of care on average about 72 hours prior to receiving the standard infusion.

It did range over the course of the entire period. In fact, 70 percent of the patients received the standard of care within the first 4 days of the study. We did allow for it to be at any time, but I think that also speaks to how people want to use these agents.

Keep in mind a lot of these patients are in the hospital setting and, while a patient is getting better and as they're responding, they're probably considering the patient to be discharged home. It's an option for the patients to then get their bezlotoxumab to be given as an administration of therapy and then they can go home and administer it accordingly.

We did not see any differences in terms of clinical cure or recurrence based on the timing of the study infusion relative to when the standard of care antibiotic was administered.

DR. HILTON: I have a couple of other

questions.

DR. KARTSONIS: Sure.

DR. HILTON: In MODIFY I the global cure rate difference was 5 percent, and in MODIFY II it's 15 percent. And I'm trying to understand why the difference was so much larger in MODIFY II.

Looking at the baseline characteristics, one thing that comes to mind is region, country. And I wonder if you have a forest plot to show us differences in results of the two trials by region of the world.

DR. KARTSONIS: Okay. Let me just take a moment and talk about the global cure as we're pulling up the data with regard to the data by region. So it is true that, in MODIFY I, the global cure difference was 5 percentage point and in MODIFY II it was 15 percentage point. And a lot of that, again, relates back to what the differences were in clinical cure.

If you recall, there was a 4 to 5 percentage-point difference in MODIFY I in favor of placebo, which then brings down the global cure

rate difference in MODIFY I. And then in MODIFY II, there was a 5 percentage point advantage for bezlotoxumab versus placebo. So if you add that to the then 10 percentage-point difference for recurrence, you get the 15 percentage-point benefit that you're seeing in global cure.

Now again, when you look at the integrated data, the differences in terms of clinical cure were the same. And not surprisingly, the global cure results when you look at the integrated data are essentially the difference in recurrence, which we feel also speaks to the value of -- that the effect of bezlotoxumab is really on preventing recurrence, not necessarily on impacting on their initial episode.

But going on to your question, if you could put the slide up, please, we did look at the global cure by different regions, including the U.S. versus ex-US. And you can see, there is an advantage whether it's in the U.S. or ex-U.S., so the difference isn't region. You can see the difference was over 8.5 percentage points in the

U.S. and in the ex-U.S. was about 10 percentage points.

So region didn't make a difference. And this is again because there really was no difference in terms of clinical cure when you look at the totality of the data across the two studies, which speaks to the fact that there were recurrence differences if you look at a regional level of U.S. versus ex-U.S.

DR. HILTON: My last question, thank you. Just thinking in terms of -- we talk about precision medicine nowadays and who should get a specific treatment. And you talked about toxin type A and B and that one of the treatments you studied is targeted to A and the other is targeted to B. Is there an assay for toxin type, and do you know toxin types of the patients who were in the studies?

DR. KARTSONIS: Sure. So there is -- I mean, there are commercial assays that look at toxin types, but it's not a readily-assessed test in the clinical setting, and I turn to the

clinicians in the room to also speak to this issue.

People are not necessarily looking at their C. diff at the level of is it producing toxin A versus toxin B and how much of it is it producing? And similarly they're not necessarily having ribotype data that might be indicative of how much toxin A or B that they have. So for example, if they had 027 they might have potentially higher levels of toxin A or toxin B.

So to answer your question, there really isn't a tool that you can use from a toxin test standpoint to look at this issue.

DR. BADEN: Dr. Follmann, you had a follow-up question?

DR. FOLLMANN: I had a question that sort of relates to what was talked about earlier at the very start.

DR. BADEN: Did you have a follow-up question, Dr. Moore, for this topic?

DR. MOORE: I do. Just a follow-up question to Dr. Hilton's enquiry about toxin testing. Would you be able to -- sorry. It's been recently

established that use of PCR for diagnosing patients who have C. diff is a bit too sensitive and there's discussion about scaling that back. In the U.K. they're doing toxin testing, going back to the toxin screening, sorry, the ELISA. Do you have any data with regard to enrolling your patients as to who was diagnosed by PCR?

DR. KARTSONIS: Let me explain to what we allowed from a diagnostic standpoint so folks can understand it. We allowed a number of different tests that patients could be diagnosed based on C. diff. I mean, we allowed -- obviously someone if they had C. diff culture that was also in the setting of toxin growth following the culture, we allowed cell cytotoxicity assays. As you know, both of these are sort of the gold standard, but are very laborious to do.

So it's not surprising that the vast majority of the patients in the study who got enrolled actually got enrolled either to measure toxin directly via an EIA test or to measure the presence of the toxin gene with regard to PCR. In

fact, it was about 48 percent EIA, 48 percent PCR, and the remainder were cell cytotoxicity assay- and culture-based regimens.

We did look at the efficacy of bezlotoxumab relative to what their entry criteria, and we still see efficacy. We see efficacy I should say with regard to bezlotoxumab, irrespective of whether or not the test that they got enrolled on was an EIA, which is probably a little bit more toxin specific, as opposed to PCR, which as you mentioned has been more called into question because you're necessarily picking up -- you're only measuring the potential of the presence of the toxin gene. That said, the differences were significant irrespective of whether or not it was EIA versus PCR.

DR. MOORE: Do you have data to show that?

DR. KARTSONIS: Sure, absolutely, if you wouldn't mind putting the slide up for me, please. This is the data with regard to EIA versus PCR. Slide up, please. Thank you very much. You can see there that we saw a greater effect with EIA versus PCR. The difference, as you can see, was on

the order of about 45 percent relative risk reduction with EIA versus about 28 percent if you looked at PCR.

However, if you do a statistical test around this, they're both significant and the confidence intervals exclude zero. So it didn't matter necessarily with regard to EIA versus PCR. We did see efficacy in both of them.

DR. BADEN: Dr. Andrews?

DR. ANDREWS: I can see why -- I'm not a clinician, totally not a clinician -- you're spending a lot of time talking on the recurrence, and did it recur, and whether the infection came back, and it looks like it depends on how you look. But for patients, they're very concerned about symptoms, so I appreciate your description of how many times are you having diarrhea. That's a really important improvement in somebody's life.

A really bad outcome in somebody's life is a death. And I know this was in the safety data, but it occurred to me that you spend a lot of time saying -- I don't see anything that just talks

about deaths. I see deaths among people with adverse events or with heart failure, but I didn't see any data, and maybe you have that, but these are people with a lot of problems, so I get that. But shouldn't there be a difference? Shouldn't you see a lower number?

DR. KARTSONIS: We'd love all our therapies obviously to not only have a clinical benefit but also to produce a mortality benefit in our setting, and, actually, if I could have slide 655, please. This is the time to death, so you can see over the course of the study the differences. If you could put the slide up, please.

We did look at the time to death in the study. And as you can see, about half the deaths occur within the first 4 weeks. And about the other half deaths occur between weeks 4 and weeks 12. There is no difference between the treatment groups with regard to overall death. But I think it's important to keep in mind the patient population that we're treating here. We're treating very sick elderly patients where their

mean age is over the age of 65.

We're following them for a relatively -- which for some of these patients who are 80 years plus, 3 months is a notable amount of time of follow-up, and we did not see a difference with regard to overall mortality. But you can see here that there was no negative effect of giving bezlotoxumab based on mortality.

DR. BADEN: C. diff-associated death, C. diff-associated colectomy, any differences?

DR. KARTSONIS: Yes, we did look at -- we did not do an analysis of death due to C. diff because there really were no differences. But we didn't predefine an attributable mortality definition, so to speak, so it's hard for us to tell you that.

However, what we did do, as you saw on the safety side, is we allowed for the physicians to report those C. diff infections that they considered were serious.

Remember, serious could mean they could lead to hospitalization, they were considered life

threatening, and there were differences, 48 versus 23 patients in the safety side of patients who had serious CDI infections, even if there was no difference from deaths.

As Dr. Guris mentioned just earlier, we also saw a reduction in 30-day readmissions as well following that. So from the hardest event points, which is obviously mortality, there is no difference, and I think it's a very fair comment that you're raising there.

But when you look at the totality of the data, we do believe not only are we impacting on CDI recurrence, but we're also impacting on significant CDI recurrence that would matter to the patient in how they feel, function, and survive.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you. Mike Green, Pittsburgh. Both my questions, or several questions really, I think now follow on to the committee's. The first is really an extrapolation and an ongoing exploration of the last topic. So I think it's clear that sometimes biologics may not

prevent but may modify, and I want to just explore this a little bit more.

So Dr. Baden was asking about differences in death associated with recurrence, and you also shared with us rehospitalizations. But some patients with C. difficile stay in the hospital despite that they were there for a different reason, they stay for other reasons.

So just exploring further amongst patients who have a recurrence in the treated versus placebo group, if you saw a difference in progression to ICU, progression to colectomy associated with the recurrence, I think you just answered the question with death, and then I think you said separately the question of rehospitalization and those who get cured and go home. So it's really sort of looking at those different issues.

DR. KARTSONIS: Sure. So we did carefully look at all the C. diff recurrences to see were there any differences, particularly among the patients who got C. diff in terms of the severity of the disease.

I mentioned earlier the FMT differences that were noted. We also looked at the maximum number of loose stools. We looked at time to resolution of their C. diff infection. In fact, we did see a numerically higher percentage of patients resolve their C. diff infection if they had developed in the setting of bezlotoxumab as opposed to developed a placebo.

If you could put the slide up, please. So this is a slide that shows the data from the 335 patients in the placebo and bezlotoxumab group who had recurrent CDI episodes. And it looks at the severity of the episodes that did occur.

The median number of loose stools did not differ, but you can see the maximum number of loose stools were higher in a placebo group versus BEZLO.

As I mentioned, the time to resolution of the new episode resolved within 2 days in 59 percent of the patients on BEZLO as opposed to 48 percent of the patients on placebo. There were no differences necessarily, so slightly higher within placebo with regard to having severe CDI.

Another way to look at this would be to look at the length of stay the patients had. You mentioned their length of stay. And we did do a separate analysis as well. And if it's okay, I'll call Dr. Guris up to speak to the length of stay analysis that we performed.

DR. GUIS: Slide up, please. So this is a forest plot by risk groups. And here what we calculated is the length of stay, hospital stay throughout the 84-day period. This includes the initial hospital stay that the patients had as well.

As you can see, overall and in each risk group, there is a reduction in hospital stay. Overall, it is 2 days. That's the first column that you see where it was 14.2 percent in the placebo -- 2 days in the placebo group versus 12 days in the BEZLO group. So there's two days' reduction in overall length of stay in the BEZLO group compared to placebo.

DR. KARTSONIS: Thank you. Just to add to the last part about the colectomy, we didn't have a

lot of patients who went on to develop or need a colectomy. It was really just a handful and there were no differences in those groups.

DR. GREEN: I have one more. And then my next question is in response to a comment that Dr. Wilcox made about the potential of BEZLO to impact secondary spread of disease. And I'm not 100 percent certain whether that would or would not happen. So you are impacting the toxin, you're not eradicating the recurrent organism.

On the other hand, it might be more easily spread if you have diarrhea versus if you simply have colonization without diarrhea. And getting at these data would have probably been challenging because you probably would have had to ask hospitals for their nosocomial C. diff rates affiliated with patients in your study. But I wondered if you tried in any effort to get at that inference that Dr. Wilcox made.

DR. KARTSONIS: We did not. We didn't really have a mechanism to do so, so we didn't ask any hospitals if they were centers of excellence

for C. diff or anything of that sort. So we don't have that information necessarily with regard to that.

I will tell you the one thing we did look at is we did look at did we have any impact on colonization. And we did that as part of an extension phase of our study that followed patients out to a year, and there really were no differences in terms of colonization over time.

But that may not necessarily be a marker because, you know you would imagine that to spread, you'd probably have to do so in a setting of diarrhea or a loose stool. So we don't have that information to be able to share with you today.

DR. BADEN: As it is now 10:46, I know we all have many more questions, including myself, but I think we should take our break. We'll have the FDA presentation and we will have time to delve in deeper to many of the issues that we still need to understand. So we'll take a break for 15 minutes.

While we take the 15-minute break, panel members please remember there should be no

discussion of the meeting topic during the break amongst yourselves or with any other member of the audience. We will resume promptly at 11:00 a.m.

(Whereupon, at 10:48 a.m., a recess was taken.)

DR. BADEN: It is now 11:03. We will resume the next session. There are still many of the panel members who have mentioned that they have questions, clarifying questions for the sponsor. I encourage panel members to continue to let Lauren and myself know if you have questions and we will make sure all questions are addressed.

But in the process I want to make sure we have a chance to get through the meat of the agenda so that we have all of the information on the table to be discussing. So we'll proceed to the FDA's presentations, clarifications with the agency, depending on the time, more questions or more likely have lunch. And then, after lunch, we will resume further discussion.

So we'll now proceed with the agency's presentations. And I think Dr. Dixon will be

presenting first.

FDA Presentation - Cheryl Dixon

DR. DIXON: Yes. Good morning. I am Cheryl Dixon, the statistical reviewer for the bezlotoxumab BLA submission. I will be presenting the division's assessment of the clinical efficacy of bezlotoxumab for the prevention of Clostridium difficile infection recurrence.

As you will see from my presentation, we are in general agreement with most of the results as presented by the applicant earlier this morning, however we differ in the ability to interpret those results and the final conclusions drawn.

In my presentation, I will be discussing the regulatory history of the clinical development program. I will provide an overview of the design of the phase 3 trials, P001 and P002, focusing on the endpoints used to assess the efficacy of bezlotoxumab.

I will then briefly summarize patient disposition and patient demographics and characteristics, followed by a discussion of the

efficacy results for the main endpoints and then with a summary and conclusions.

The IND for which bezlotoxumab was studied under was submitted in November of 2005. The phase 2 trials were conducted between 2005 and 2008. The first phase 2 trial, P018, was designed to evaluate the efficacy and safety of actoxumab, the antitoxin A antibody.

This trial was stopped early when emerging preclinical data suggested the need for inclusion of antibodies directed against toxin B as well in the monoclonal antibody regimen.

P017 was then designed to evaluate the efficacy and safety of the combined monoclonal antibodies actoxumab plus bezlotoxumab. This trial was considered the proof of concept trial for the clinical development of the combination monoclonal antibody regimen. As the focus of the clinical development program became the combination monoclonal antibody regimen, no phase 2 trials which evaluated bezlotoxumab alone were conducted.

In October of 2009, an end-of-phase-2

meeting was held with the applicant. At this meeting, the applicant proposed to conduct two pivotal phase 3 trials of identical design to evaluate the combination of actoxumab plus bezlotoxumab administered in combination with standard of care antibiotics in patients with CDI.

The proposed primary endpoint was CDI recurrence during the study period, where CDI recurrence was defined as the development of a new episode of diarrhea associated with a positive stool test for C. difficile following clinical cure of the initial CDI episode.

The division concurred with the definition of CDI recurrence, but indicated that the CDI recurrence rate should be based on all randomized patients and not based on the subset of clinical cures.

The division also advised that a 4-arm factorial design, which included actoxumab alone, bezlotoxumab alone, the combination of actoxumab plus bezlotoxumab, and placebo be implemented in one of the phase 3 trials in order to address the

combination drug rule.

In July of 2010, a special protocol assessment was requested for P001. The submitted protocol incorporated the factorial design and the calculation of the CDI recurrence rate as recommended at the end of phase 2 meeting and also incorporated an interim analysis to allow for dropping of an individual monoclonal antibody arm if the results were favorable to do so. In December of 2010, an SPA agreement for P001 was made.

The protocol for P002 was reviewed in 2012. At this time, after further evaluation by the statistical review team, it became apparent that there were scientific concerns with the primary endpoint of CDI recurrence as defined.

The CDI recurrence endpoint essentially treats subjects who failed treatment of the initial CDI episode as not having a recurrence since they are included in the denominator of the recurrence rate. This does not seem intuitively appropriate since the clinical failures cannot be evaluated for

recurrence as one has to be cured first in order to develop recurrence.

The ability to interpret this endpoint is of most concern, however, if there is an imbalance in the proportion of subjects with initial clinical cure between the treatment groups, particularly if the monoclonal antibody group has a lower initial clinical cure rate than the placebo group, because this results in a smaller number of subjects in the monoclonal antibody arm that can potentially develop recurrence, but a larger number of subjects who by default are considered as not having a recurrence in the analysis.

Given these concerns, the more relevant endpoint for assessing the efficacy of the monoclonal antibody regimen would be global cure, which is defined as clinical cure of the initial CDI episode and no CDI recurrence. Therefore, it was requested that the primary endpoint for P002 be changed to global cure.

The applicant did not expect the monoclonal antibodies to have an impact on clinical cure and

indicated their preference for both trials to have the same primary endpoint. The division further pointed out that if there was no difference in clinical cure, then the difference between the treatment arms for global cure should be similar to the difference between treatment arms for the recurrence endpoint.

The applicant still maintained that CDI recurrence was the appropriate primary endpoint for P002, in part that the power of the trial for achieving success was not planned based on global cure. They proposed to conduct a pooled analysis of the two phase 3 trials in order to address this concern.

In the end, the division acknowledged the applicant's intent to retain CDI recurrence as a primary endpoint in P002, again reiterated our concerns with this endpoint, and disagreed with the proposed pooled analysis for assessing global cure just to ensure substantial power.

As we would want confirmatory evidence from separate trials the division intended to base our

assessment of global cure, as well as all efficacy endpoints, on the analyses from the trials individually.

I will try to illustrate our concerns with the choice of endpoint a little further in the next few slides. The intended role of the monoclonal antibody is for the prevention of CDI recurrence. The applicant believed, based on the assumed activity of the monoclonal antibody, that it was best to treat the patient with the monoclonal antibody while the patient was receiving standard of care treatment for the initial CDI episode rather than waiting until treatment with standard of care was complete and the patient was considered successfully treated.

Typically, the recurrence rate would be the number of patients with a recurrence divided by the number of patients with clinical cure. However, due to the study design, patients with clinical cure is a post-randomization and post-treatment subgroup. Therefore, the recurrence rate was defined in the protocol as the number of patients

with a recurrence divided by the number of patients treated regardless of initial clinical response.

However, there are concerns with this definition which may best be seen when looking at the complement of the recurrence rate in which subjects who maintained clinical response and did not have a recurrence are grouped with those who were clinical failures of the initial CDI episode. This intuitively does not seem appropriate.

Additionally, the clinical failures are not evaluated for recurrence but are treated by default as not having a recurrence. So a larger number of clinical failures will lead to an underestimate of the actual recurrence rate. This would be of most concern in the assessment of the monoclonal antibody if the monoclonal antibody group had more clinical failures than the placebo group.

Therefore, the more relevant endpoint for assessing the efficacy of the monoclonal antibody would be global cure in which those who are not clinical cures are grouped with those who had recurrence and are more appropriately treated as

failures in the analysis. The global cure endpoint will capture the full effect of the monoclonal antibody. In other words, its effect, if any, on initial cure as well as the effect on recurrence.

The next two slides include very simplistic hypothetical examples to support our preference of the global cure endpoint. In this hypothetical example, no difference in the initial clinical cure is assumed, as was the assumption by the applicant for the monoclonal antibody. In both arms, there are 100 total patients of which 80 were clinical cures. In arm 1, 10 of the 80 developed recurrence, whereas in arm 2, 25 of the 80 developed recurrence.

Therefore, the recurrence rate, based on the protocol definition, would be 10 percent for arm 1 and 25 percent for arm 2, with an absolute difference of 15 percent. The global cure rate would be 70 percent for arm 1 and 55 percent for arm 2, and also has an absolute difference of 15 percent. Therefore, if there was no difference in initial clinical cure, then the global cure

endpoint would allow for the same assessment of treatment effect as the recurrence endpoint.

In this hypothetical example, it is assumed that there is a difference in the initial clinical cure between arms and the clinical cure rate for arm 1 is lower than that for arm 2. The recurrence rate is assumed to be the same as was observed in the previous example, with arm 1 having a lower recurrence rate than arm 2.

However, when looking at global cure in this example, there is no difference between the arms observed. So unless it can be proven that the differences observed for initial clinical cure was not due to any effect of treatment but solely a random occurrence, then treatment effect would be most appropriately assessed by the global cure endpoint, as it captures the effect on initial cure as well as recurrence, whereas just considering recurrence ignores the possible effect treatment may have on clinical cure.

I will now return to a discussion of the phase 3 trials. Both trials were randomized,

multi-center, double-blind, placebo-controlled trials conducted in subjects 18 years or older who were receiving standard of care antibiotic treatment for an episode of CDI.

In P001, subjects were randomized in a 1 to 1 to 1 to 1 ratio to receive a single infusion of actoxumab, bezlotoxumab, the combination, or placebo. In P002, subjects were randomized in a 1 to 1 to 1 ratio to receive a single infusion of bezlotoxumab, actoxumab plus bezlotoxumab, or placebo.

The infusion could occur at any time during treatment with standard of care, and the patient did not need to be experiencing diarrhea at the time they entered the trial. Randomization was stratified by oral standard of care therapy, which included metronidazole, vancomycin or fidaxomicin, and by hospitalization status, which was inpatient or outpatient.

The design for P001 also included an interim analysis which allowed for the halting of further enrollment into one or both of the individual

monoclonal antibody treatment groups if there was sufficient evidence of superiority of the combination over the individual monoclonal antibody.

Based on the results of the interim analysis, which showed low efficacy, an observed increase in the number of deaths and serious adverse events in the actoxumab arm compared to placebo, enrollment in the actoxumab arm was stopped following the recommendation of an independent data monitoring committee. Enrollment in the remaining three treatment groups continued until trial completion.

The protocol-specified primary endpoint was CDI recurrence. As previously mentioned, CDI recurrence was defined as the development of a new episode of diarrhea associated with a positive stool test for toxigenic C. difficile following clinical cure of the baseline CDI episode.

Clinical cure of the baseline CDI episode required the subject to have received standard of care treatment for less than or equal to 14 days,

and not have diarrhea on the 2 days immediately following the last day of standard of care antibiotic treatment.

Global cure was a secondary endpoint and was defined as clinical cure of the baseline episode and no CDI recurrence. Clinical cure as an endpoint on its own was considered an exploratory endpoint.

The primary analysis population was the full analysis set or FAS. The FAS population was a subset of all randomized subjects excluding those who did not receive an infusion of study medication, did not have a positive stool test for toxigenic C. difficile at study entry, or did not receive a protocol defined standard of care therapy within a one day window of the infusion.

Additionally, in P001, subjects from a single investigative site found by the applicant to have serious good clinical practice non-compliance issues were excluded from the FAS.

The primary analysis of the efficacy endpoints was a comparison of treatment groups in

the proportion of subjects with CDI recurrence, global cure, or clinical cure using the FAS population. Adjusted differences in the rate and corresponding 95 percent confidence interval stratified by oral standard of care therapy and hospitalization status were also calculated.

To control type 1 error rate due to multiple treatment comparisons, a sequential testing approach was used. In both studies, the order of the testing was the combined monoclonal antibody versus placebo comparison and, if significant, followed by the bezlotoxumab versus placebo comparison.

In addition, P001 adjusted the alpha level to control for the interim analysis as well as the second primary objective to compare the combined monoclonal antibody arm to each of the individual monoclonal antibody arms.

As previously indicated, the division's assessment of efficacy is based on the results of the individual studies. Therefore, no efficacy results of the studies pooled will be presented.

Approximately 400 subjects per treatment arm were randomized into the trials with the exception of the actoxumab-alone arm of P001 for which enrollment was halted after the interim analysis. Overall, 96 percent of the randomized patients in both trials were included in the FAS, and most of the patients excluded from the FAS were due to not receiving study infusion.

Demographic and baseline characteristics of the FAS population were generally balanced among treatment groups in both trials. Overall, the mean age of patients was 62 years in P001 and 64 years in P002. Approximately 56 to 57 percent were female, and the majority of the subjects were white. A similar proportion of patients received metronidazole or vancomycin as their oral standard of care, and only 3 percent received fidaxomicin as their standard of care.

Approximately 53 percent of the patients in P001 and 41 percent in P002 were enrolled at sites from the United States or Canada, and a slightly larger percentage of patients from Asian sites were

enrolled in P001 than P002.

The majority, 67 to 69 percent, of the patients were hospitalized at the time of enrollment. Only approximately 34 percent of the patients had a prior history of CDI ever, although most of those events had been in the 6 months prior to enrollment.

A hyper-virulent strain of C. difficile, defined as ribotypes 027, 078, or 244, was detected in approximately 12 percent of patients in P001 and 14 percent of the patients in P002 overall. However, in P002, slightly more placebo patients had a hyper-virulent strain of C. difficile as compared to the other two treatment arms.

The median duration of standard of care prior to the infusion was 3 days in both studies and ranged from 14 days before study infusion to the day after study infusion was received. Overall, 28 percent of the patients in P001 experienced diarrhea on the day of the study infusion.

While in P002 23 percent of the patients

overall experienced diarrhea on the day of the study infusion, the bezlotoxumab arm had a slightly lower percentage of patients experiencing diarrhea on the day of infusion, 18 percent as compared to 26 percent in the other 2 arms.

Given the median duration of standard of care prior to the infusion was 3 days, and typically antibiotic treatment is having an effect by then, the fairly large percentage of patients not experiencing diarrhea on the day of study infusion would be anticipated.

This table presents the results for initial cure, CDI recurrence, and global cure in the FAS population of P001. Since enrollment in the actoxumab arm in P001 was halted following the interim analysis, these results have not been presented. Please note that I have presented two-sided rather than one-sided p-values for ease in interpretation due to situations where the placebo arm was better than the monoclonal antibody arm.

In P001, there was a significantly lower

proportion of subjects with CDI recurrence in both the combined monoclonal antibody arm and the bezlotoxumab arm as compared to placebo. The adjusted differences in CDI recurrence were at least 10 percent in favor of the monoclonal antibody arms as compared to placebo. A slightly lower proportion of subjects had CDI recurrence in the combination monoclonal antibody group as compared to bezlotoxumab, but the difference was not statistically significant.

Clinical cure of the initial CDI episode was lower for both the monoclonal antibody, which was significantly lower, and the bezlotoxumab, which was numerically lower, as compared to placebo. Due to this negative imbalance in initial clinical cure, the interpretation of the CDI recurrence endpoint is complicated.

Thus, global cure, which captures the overall effect of the treatment, would be the more appropriate endpoint to consider. Although the proportions of subjects with global cure were numerically in favor of the combined monoclonal

antibody group and bezlotoxumab in comparison to placebo, the differences were not statistically significant.

This table presents the results for P002. In P002, the results for CDI recurrence were similar to those seen in P001. There was a significantly lower proportion of subjects with CDI recurrence in both the combined monoclonal antibody group and the bezlotoxumab group as compared to placebo. And the adjusted differences in CDI recurrence were approximately 10 percent in favor of the monoclonal antibody arms compared to placebo.

A slightly lower proportion of subjects had CDI recurrence in the combined monoclonal antibody group as compared to bezlotoxumab, but again, the difference was not statistically significant.

As seen in P001, clinical cure of the initial CDI episode was numerically lower for the combined monoclonal antibody group compared to placebo. However, clinical cure was numerically higher for the bezlotoxumab as compared to placebo.

Neither of these comparisons were statistically significant.

Although the proportion of subjects with global cure was numerically in favor of the combined monoclonal antibody group compared to placebo, the adjusted difference of 5.2 percent was not statistically significant. The proportion of subjects with global cure in the bezlotoxumab group was significantly higher than placebo with an adjusted difference of 14.6 percent.

However, the significance of this difference should be interpreted with caution given the predefined testing strategy in which the combined monoclonal antibody group versus placebo comparison was to be tested first.

Given the results shown in the previous slides, there is a concern that bezlotoxumab alone and in combination with actoxumab may have a negative effect on initial clinical cure. Therefore, in order to explain the unanticipated differences observed for clinical cure, the reasons for failure to achieve clinical cure were further

investigated.

In both trials, the most common reasons for failure were evidence of diarrhea during at least 1 of 2 days after standard of care was completed or the standard of care was received for greater than 14 days. Most of the subjects who received greater than 14 days of standard of care did so because of continued loose stools, although some subjects received continued standard of care even though their diarrhea had resolved.

The proportion of subjects who had missing stool information or discontinued prior to the end of standard of care was generally balanced across the treatment groups. Therefore, the difference in clinical cure rates observed can primarily be attributed to continued loose stools or evidence of diarrhea, which was higher for the combined monoclonal antibody group in both trials, and for the bezlotoxumab group in P001 as compared to placebo.

Various sensitivity analyses were conducted by the applicant and the division. The results of

most of these analyses were fairly consistent to the results observed for the primary analysis.

In the primary analysis, the assessment of CDI recurrence was based on the last available information for a subject. Therefore, subjects with incomplete information to assess recurrence, such as those having a new episode of diarrhea but for whom a stool sample was not collected for toxin testing, those who died prior to week 12, or those whose last stool information was collected prior to day 80, were treated as not having a recurrence.

Treating incomplete information in this way could lead to an underestimate of the CDI recurrence rate. Additionally, it was noted that some subjects received a concomitant medication or procedure potentially useful in the treatment of CDI during the follow-up period, which can confound the assessment of recurrence.

Therefore, one of the sensitivity analyses conducted by the division imputed subjects with incomplete information on their stool or as well as those who received a concomitant medication or

procedure potentially useful in the treatment of CDI during the follow-up period as a recurrence or failure.

The results of the sensitivity analysis for P001 are presented in this slide. As you can see from the bottom of this table, a similar proportion of subjects did not have a stool sample of a new episode of diarrhea collected for toxin testing, died before week 12, or did not have stool information past day 80.

A slightly higher proportion of placebo subjects received an active concomitant medication or procedure for CDI during follow-up as compared to the combined monoclonal antibody group or the bezlotoxumab group. Thus, a slightly higher proportion of placebo subjects were imputed as a CDI recurrence in this sensitivity analysis.

For P001, the overall conclusions are the same based on the sensitivity analysis as the primary analysis, although with the sensitivity analysis a slightly larger treatment difference for CDI recurrence and for global cure is observed.

The results of the sensitivity analysis for P002 are presented in this slide. As you can see from the bottom of the table, there is an imbalance between the monoclonal antibody groups and placebo in the number of subjects who did not have a stool sample of a new episode of diarrhea collected for toxin testing. There was also a slightly larger proportion of bezlotoxumab subjects who received an active concomitant medication or procedure for CDI during the follow-up.

Thus, the overall imbalance impacts the conclusions drawn for the CDI recurrence endpoint in which bezlotoxumab versus placebo comparison is no longer significant. Although the difference in global cure is statistically significant for the bezlotoxumab versus placebo comparison, but again should be interpreted as so with caution, the difference is less than that observed for the primary analysis and is driven as much by the difference that was observed in clinical cure of the initial CDI episode as the difference in CDI recurrence.

Numerous subgroup analyses were also conducted. In general, the results of most subgroups were consistent and the treatment differences trended in the same direction as the overall population. Exceptioned were those of gender and age where the treatment differences of CDI recurrence and global cure observed for males and for subjects less than 65 were not as large as those observed for females and for those 65 years or older respectively.

In summary, there appears to be a decrease in CDI recurrence with the use of bezlotoxumab. However, the CDI recurrence endpoint is difficult to interpret since subjects without clinical cure of the initial CDI episode are treated as not having a recurrence in the calculation of the recurrence rate and also due to the imbalance noted in the proportion of subjects with initial clinical cure between treatment groups.

Recall that, in P001, the difference in initial clinical cure was in favor of placebo compared to bezlotoxumab, but in P002 the

difference in initial clinical cure was the reverse. A difference in clinical cure was also noted for the combined monoclonal antibody group compared to placebo, where in both trials the difference is in favor of placebo. Therefore, a negative effect of bezlotoxumab on clinical cure of the initial CDI episode cannot be ruled out.

Due to these concerns, global cure would be the more relevant endpoint to assess the efficacy of bezlotoxumab as it captures the overall effect of the treatment. The results for global cure are only significant for one of the two trials, and the significance observed in P002 needs to be interpreted with caution for two reasons.

The first is the non-significant result of global cure observed for the actoxumab plus bezlotoxumab arm versus placebo comparison, which was to be conducted prior to the bezlotoxumab versus placebo comparison based on the hierarchal ordering of the prespecified testing strategy.

The second reason, and possibly more clinically relevant, is the discordant results

observed for clinical cure for bezlotoxumab between the two trials as I mentioned in the previous slide. The results observed for the actoxumab plus bezlotoxumab arm were consistent across both trials, and the results for bezlotoxumab in P001 are more similar to these results.

So in conclusion, while there appears to be a decrease in CDI recurrence with the use of bezlotoxumab, there is concern as to whether the efficacy of bezlotoxumab for the prevention of CDI recurrence has been adequately demonstrated and whether a negative effect of bezlotoxumab on clinical cure of the initial CDI episode can be ruled out.

I will now turn the presentation over to Dr. Hiwot Hiruy, who will be presenting the division's assessment of the clinical safety of bezlotoxumab.

FDA Presentation - Hiwot Hiruy

DR. HIRUY: Thank you, Dr. Dixon. My name is Hiwot Hiruy. I will present the clinical safety review for bezlotoxumab. I'll start the safety presentation with methodology used for safety

analysis then present the overall exposure to bezlotoxumab, death, serious adverse events and treatment emergent adverse events that occurred in the safety population. I will also discuss our analysis of infusion related adverse reactions, and finish with results of some of our subgroup analyses.

Before starting my presentation I want to cover the definitions of treatment-emergent adverse events and serious adverse events used for the analysis. Treatment-emergent adverse event is defined as any adverse event that occurred during or after infusion of the study drug. Definition of serious adverse event included adverse event terms per ICH-E2A and are listed below the serious adverse event bullet point there.

In addition, the sponsor included two additional adverse event terms, adverse events that result in cancer, and adverse events associated with overdose in the serious adverse event reporting. The sponsor's definition of serious adverse events were used in the safety analysis.

Because the design of the two pivotal studies P001 and P002 were similar, including adverse event reporting schema, data for the two studies were pooled together. In both studies, treatment-emergent adverse events were reported for the first 4 weeks of the studies and serious adverse events were reported throughout the 12 weeks of the study period.

The two studies, however, did have some differences. Study P001 followed an adaptive design with 4 arms; BEZLO alone, ACTO alone, combination arm, and the placebo arm with planned interim analysis. The actoxumab-only arm was dropped after the interim analysis and is not included in the safety population.

Study P002, on the other hand, was designed with 3 study arms, BEZLO alone, combination arm, and placebo arm, and had an extension cohort of 300 subjects that were followed for additional 9 months beyond the 12-week study period.

This diagram just illustrates that the arms that received similar study infusions were pooled

together for the safety population. For example, data for the subjects that received bezlotoxumab in study P001 were combined with data for the subjects that received bezlotoxumab in study P002.

The 4 study arms marked by the red boxes made up the safety population. Any subjects that received partial or full infusion of the study drugs was included in the safety population. The placebo arms for each of the studies were combined together to make up the comparator arm. As mentioned earlier, the fourth arm in P001, denoted by the gray box in the diagram, the actoxumab arm, is not included in the safety population.

Looking at the overall exposure to bezlotoxumab, a total of 1790 subjects were exposed to bezlotoxumab alone or in combination with actoxumab. Of these, 816 received BEZLO alone, and 974 received BEZLO in combination with actoxumab. About 126 of these subjects were healthy volunteers participating in phase 1 studies, and the remaining were subjects in phase 2 and 3 trials.

Of note, with exception of 30 subjects in

one phase 1 study who received 2 doses of BEZLO infusion at 10 milligram per kilogram, the remaining 1760 subjects received BEZLO as a single 10 milligram per kilogram of body weight infusion. Those in the ACTO plus BEZLO, the combination arm, received additional 10 milligram per kilogram of the actoxumab infusion.

Looking at the mortality rate in the safety population, a total of 56 subjects died in the BEZLO arm with a mortality rate of 7.1 percent in the BEZLO arm. Fifty-one subjects died in the combination arm with a mortality rate of 6.6 percent. And 59 subjects died in the placebo arm with a mortality rate of 7.5 percent over the 12-week study period.

The any BEZLO column included in this table includes subjects that received bezlotoxumab either alone or in combination with actoxumab. From that group, 107 subjects who received any BEZLO died with a total mortality rate of 6.8 percent. Overall, there was no major imbalance in the mortality rate among the three study arms.

I also included in the last row the deaths that occurred in the extension arm of study P002. In addition to the deaths that I reported, there were additional 28 deaths in study P001 in the actoxumab arm, with a mortality rate of 11.9 percent, which was significantly higher than the other study arms. As mentioned earlier, the actoxumab alone arm is not included in the safety population.

Looking at the serious adverse events, 29.4 percent of subjects in the BEZLO arm, 27.3 percent of subjects in the combination arm, and 32.7 subjects in the placebo arm experienced at least one serious adverse event.

Slightly more subjects in the placebo arm experienced serious adverse events but there was no major imbalance in the proportion of subjects that experienced serious adverse events among the three treatment arms.

The infection, and infestation, and gastrointestinal system organ class accounted for the majority of serious adverse events reported.

Cardiac failure, diarrhea, and abdominal pain occurred more frequently in the BEZLO arm compared to placebo.

Looking at treatment-emergent adverse events, 61.7 percent of subjects in the BEZLO arm, 58.6 percent of subjects in combination arm, and 61.2 of subjects in the placebo arm experienced at least 1 treatment-emergent adverse event.

Most common treatment adverse event in the BEZLO arm was nausea followed by diarrhea, pyrexia, headache and vomiting. Again, there was no imbalance in the proportion of subjects that experienced treatment-emergent adverse events among the 3 study arms.

Since bezlotoxumab is an immunoglobulin, we looked at possible infusion-related adverse reactions. To do so, we first looked broadly at all the treatment-emergent adverse events within the first 24 hours after infusion, which included day 1 and day 2 of the study. We then looked for combination of sign and symptoms involving two or more organ systems that may be attributed to

infusion related reactions.

Infusion-related reactions search criteria was adapted from Sampson's criteria and included 2 or more sign and symptoms for mucocutaneous symptoms, respiratory, cardiac, gastrointestinal and any general sign and symptoms including pyrexia, diaphoresis, chills, fatigue and asthenia. Also, a reduction in systolic blood pressure to less than 90 millimeters of mercury or drop in systolic blood pressure by more than 30 percent was considered sign and symptom of infusion-related reaction.

Overall, 18.8 percent of subjects in the BEZLO arm, 15.4 of subjects in the combination arm, and 14.6 of subjects in the placebo arm experienced at least 1 treatment-emergent adverse event during the first 2 days of the study.

But looking specifically at the combination of sign and symptoms outlined earlier for infusion related reactions, 4 subjects in the BEZLO arm warranted an additional look. One subject developed ventricular tachycardia 30 minutes into

the infusion and the sign and symptoms necessitated permanent discontinuation of the infusion. The details of these subjects are presented in the next couple of slides.

Additionally, 2 subjects were reported to have hypotension during infusion, but neither of these patients had systolic blood pressure less than 90 or had dropped by more 30 percent. One subject did have a drop in systolic blood pressure by more than 30 percent from baseline at 30 minutes after start of infusion and at the end of infusion.

The subject that had permanent discontinuation of the bezlotoxumab infusion was a 32-year-old male with HIV/AIDS, pneumocystis pneumonia, and history of hyponatremia and hypokalemia, but no history of arrhythmia with normal pre-infusion electrocardiogram with atrial and ventricular rate of 103 beats per minute.

As mentioned earlier, he developed ventricular tachycardia with a heart rate of 200 beats per minute, chills, dizziness approximately 36 minutes after the start of the infusion.

His pre-infusion vital signs showed sinus tachycardia of 110 beats per minute, blood pressure 110/70, temperature of 38.3, respiratory rate of 20. Thirty minutes after the start of the infusion, his vital signs showed a heart rate of 200, blood pressure 120/80, temperature of 38.5, and respiratory rate of 20.

His pre-infusion labs were notable for potassium of 5.3 mL equivalence per liter, low calcium of 8.2 milligram per deciliter. He had multiple concomitant medications, which included pentamidine, potassium, pantoprazole, and prednisone.

Shortly after the symptoms developed, the bezlotoxumab infusion was discontinued and the subject was treated with steroids and histamine blockers intravenously. The chills and ventricular tachyarrhythmia resolved within 5 minutes after discontinuation of the infusion.

The dizziness resolved within 90 minutes. The electrocardiogram performed 30 minutes after discontinuation of the infusion showed atrial and

ventricular rate of 99 beats per minute. The sponsor considered the event as infusion related.

Because congestive heart failure was the most common serious adverse event experienced in the bezlotoxumab-containing arms, we carried out a subgroup analysis to evaluate whether there was a difference in outcome in relation to a baseline CHF. Of note, information about the stage of CHF for subjects was not provided, and CHF was taken as a dichotomous variable.

We compared the occurrence of serious adverse events and death among subjects with baseline CHF compared to those without baseline CHF.

Not surprisingly, those with baseline CHF experienced more serious adverse events compared to those without baseline CHF, 48.9 percent versus 26.7 percent respectively. The proportion of death was also higher for those with baseline CHF.

When looking at the 325 subjects with baseline CHF by treatment arm, those in the BEZLO arm had numerically higher number of treatment-

emergent adverse events, serious adverse events, death compared to the placebo. Of note, the baseline characteristics including the median age, CHF severity, Charlson Comorbidity scores were comparable among the three treatment arms.

Looking at the serious adverse events experienced in the bezlotoxumab-treated subjects with baseline CHF, infection and infestation accounted for 30 percent of the serious adverse events, followed by cardiac 21 percent of the serious adverse events, and respiratory accounted for 10 percent of serious adverse events.

Looking at the placebo arm, the top three organ system classes that accounted for the majority of serious adverse events were again infection and infestation about 41 percent, cardiac 10 percent, and gastrointestinal is another 10 percent.

Looking at the serious adverse events that occurred in more than 2 subjects in the bezlotoxumab arm, cardiac failure occurred in 15 subjects in the BEZLO arm compared to 5 subjects in

the placebo arm.

This table summarizes briefly the causes of death noted in the subjects with baseline CHF. CHF, cardiac arrest and respiratory failure were the top 3 causes of death in the bezlotoxumab arm.

We also carried out additional subgroup analyses by age, sex, race, and body weight, and there were no significant differences in treatment-emergent adverse events, serious adverse events, and deaths among the study arms.

In summary, 1,790 subjects have been exposed to bezlotoxumab alone or in combination with actoxumab. Overall, the proportion of treatment-emergent adverse events, serious adverse events and death were similar in the bezlotoxumab-containing arms and the placebo arm.

There was one infusion reaction that led to discontinuation of bezlotoxumab infusion. There were higher number of subjects who experienced congestive heart failure in bezlotoxumab containing arms, 17 in the BEZLO arm, 17 in the combination arm, compared to 7 in the placebo arm. There were

higher number of serious adverse events and death in bezlotoxumab-treated subjects with baseline congestive heart failure as compared to placebo.

This concludes the safety review presentation.

Clarifying Questions to the Presenters

DR. BADEN: Thank you both for extensive presentations and analyses of these complex datasets. Are there any clarifying questions for the FDA from the committee? Dr. Moore?

DR. MOORE: So, yes thank you. Dr. Hilton and I were actually looking at page 10. That would be slides 19 and 20, where the serious adverse event, there was, sorry, discordance between the consistency, inconsistency between the two slides where the colors are off.

I just want to make sure that those were labeled all correctly. So for example, respiratory is light green, but then GI is light green in the next slide. Do you know what I mean? You can't make a direct comparison, so I just want to make sure that those are actually labeled correctly.

DR. BADEN: Please use your microphone when responding.

DR. HIRUY: Yes, you are right. The color coding is not congruent in the two.

DR. MOORE: Thank you.

DR. BADEN: Dr. Goetz?

DR. GOETZ: Yes, I had a question about the mortality data. If you look at slide 17 in the safety, my understanding is this analysis looks at people on ACTO and BEZLO, and BEZLO alone. So the mortality -- actually, I've seen where I'm reading that. We have broken those out and see the same trends. I'm sorry. I misread the slide for a moment.

DR. HIRUY: Okay.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: I had a question regarding the efficacy analysis and I wanted to thank you for including actual numbers in the breakdown, looking at the slides that start with 7. Certainly, as a clinician, I appreciate the focus on global cure rate because I think that's what we as physicians

and that's what patients want, both of those good things. But I also see the question of focusing solely on recurrence as also having some merit.

I was curious in looking at these variables, if it would be at all valid to look at sort of like a true recurrence rate of N -- let's see, I feel like, as I'm getting older, maybe I start to need glasses -- N with the sub R with the denominator as the clinical cure rather than big N. Would that be a valid way to look solely at recurrence and separating out the cure question?

DR. DIXON: The applicant presented those results earlier this morning.

DR. SCHAENMAN: But do you feel that that's valid?

DR. DIXON: Given the design of the study, since that was a post-treatment and post-randomized subgroup, we felt that that was not the appropriate way to look at the data.

DR. BADEN: Dr. Follmann, did you have a clarifying question on that point?

DR. FOLLMANN: No, I was just going to

say -- I was just going agree with the FDA that that's basically not comparing two fair groups because they're identified based on cure, yes or no. And so it's not, in my mind, a very good analysis. It destroys randomization.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you. This is for Dr. Dixon. And I think you had sort of hinted this yourself. So you talked about one of the concerns with looking at the BEZLO alone independent of the combined BEZLO/ACTO arm as not following the original statistical plan, and therefore it maybe doesn't make sense.

But having found, through the work that the ACTO alone may have a negative effect, do you think from a clinical perspective -- I think you maybe hinted at that -- that that's probably not something that we should really focus too much on and really look at the BEZLO alone independently, as that is what's being considered for approval?

DR. DIXON: Since that's really a clinical question, I'll defer to the clinical colleagues to

answer that part of the question.

DR. MISHRA: Sorry, can you clarify your question?

DR. GREEN: Yes. Again, so one of the rationale in Dr. Dixon's statistical presentation to us for downplaying a benefit in a study where BEZLO alone had a benefit but the combined didn't have a benefit, or had a lesser benefit, was that the original design was look at the combination and then look at the product individually.

But we know that as they went through the evolution of their evaluation of these, both products in the combination, that it looked like ACTO alone may have had -- well, it was stopped because it appeared to have a negative impact, at least I think, on clinical cure.

So knowing that, is there still a need to sort of follow their original pathway when it looks like a premise was wrong, that is to say that ACTO alone may have been bad, and therefore the combination potentially could be worse than an individual drug? Or biologic actually.

DR. MISHRA: Right. I mean, I can't speak to whether you should still follow that sort of statistical pathway, but in terms of, could the antitoxin A drug be sort of driving some of the results that you're seeing? It's certainly possible. And I think that's sort of one of the underlying questions, is what is driving that?

Is that sort of a random occurrence that this is -- that what you're seeing is all because of what's happening with actoxumab? Or is this an actual negative effect that you're seeing from toxin B? So we don't really know.

DR. GREEN: Right. Again, I was just raising the question because, both in the stuff we received before coming here and in the oral presentation, it was the rationale for considering that the data didn't demonstrate as much endpoint accomplishment as the sponsors might want because they didn't sort of accomplish it in both. But you've answered the question for me.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: I just have a couple of

clarifying questions on the case of the ventricular arrhythmia. First, the pentamidine is associated with ventricular tachyarrhythmia if it's infused quickly. Is there any evidence that there was a use of the pentamidine fluid as flush accidentally before, number one? And number two, azithromycin is not listed on the patient's medications. Just wondering if that's he really was not on azithro or if he was.

DR. HIRUY: So in regards to the pentamidine question. So the data I received was from the case report forms, so I know that he has been on pentamidine but I don't know exactly the timing of infusion. He had had multiple concomitant medications, so I'm pretty sure he may have been on macrolide as well.

DR. BADEN: Do you know if it was inhaled or intravenous pentamidine?

DR. HIRUY: It's IV. It's for treatment. He's cotrimoxazole sensitive.

DR. COX: We could also check and see if the sponsor has any additional information on that

case.

DR. KARTSONIS: Thank you, Dr. Cox. We did look at this case obviously very carefully. As you heard, the patient had a number of concomitant underlying conditions obviously, including HIV and significant immunocompromise from that as you mentioned with the PCP, for which the patient was getting IV pentamidine.

We didn't see anything unusual with regard to the IV pentamidine. We'll go back and double check that issue. The patient, to our knowledge, we did look very closely at all their concomitant medications and we do not recall the patient being on a macrolide or azithromycin in particular.

I will, however, note several important factors about this case. Besides being on pentamidine and obviously being an ill patient, I mean, the patient already had sinus tachycardia when the patient entered into the study. And a second point to keep in mind is that in particular that he also had a known history, as Dr. Hiruy mentioned, of electrolyte abnormalities, and

obviously was on both sodium and potassium replacement as a result of that.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Thanks. I wanted to sort of elaborate on the comment Dr. Schaenman made. It seems like the fundamental issue here is how to count the cures. The FDA doesn't like to count the cures as successes, which makes sense. The sponsor doesn't really like to count the cures as failures because this is happening during the period of time when the drug should have no effect, and so why should we be focusing on that endpoint then.

You pointed out, why don't we just throw them away and that's sort of appealing except it destroys randomization, so I don't think that's really quite viable. But we could just ignore it and say, let's start the clock at day 28 or sometime like that. It's a fair starting line for everyone. And then just see who has one day of more than three stools, yes or no, and just count as endpoint like late diarrheal success.

So this is a fair comparison of all the

groups. It gets at what the sponsor wants, which is a delayed benefit of their treatment, which is fair. And I think it also has the benefit of -- let's suppose someone's not cured early, but then is diarrhea free from day 28 until the end of the study. They're counted as a success under this metric, but not under any of the other ones that have been proposed.

So I would like to see that kind of analysis. To me, that sort of gets at what I think is most informative and kind of fair and balances the issues. And then I guess also, as a sensitivity analysis on that, I would like to count people as failure if you have diarrhea or die, and then see. Those two analyses would be very informative for me, I think.

DR. BADEN: So then, I guess Dr. Baden. Dr. Dixon, you included in your analysis both the ACTO and the BEZLO, yet this says, spinning off of Dr. Green's comment, this is all about BEZLO. Why shouldn't we just throw out that analysis since it's about other compounds and not the one of

interest?

DR. DIXON: Because BEZLO is included in that arm, it provides some additional information as to what BEZLO might be contributing. You can't just say that the results are driven by the ACTO in that arm. They're possibly also driven by the BEZLO in that arm. So that's additional BEZLO information to consider.

DR. BADEN: Thank you. And the sponsor mentioned earlier the issue of the definition of clinical cure, and that if one recast that definition based upon better information, they provided new information that wasn't in the briefing documents.

What is your impression of if one alters the definition of clinical cure, one may make more sense of these data?

DR. DIXON: We haven't had the chance to fully review those analyses, so it's hard for me to make a decision about what those results are saying.

DR. MISHRA: I would just point out, again,

first of all, that's a post hoc analysis. I mean, that obviously needs to be taken into account. The other thing is that it was a blinded study and you're still seeing sort of these differences in the duration of standard of care therapy and failures for patients who had diarrhea after standard of care.

I'll tell you that we have -- we're sort of in a process of looking at all these failure cases and just trying to get a better handle on it. And it's sort of all over the place. It's true. There are some patients who, I think as the sponsor noted, were very immunosuppressed, so they may have a longer duration of therapy even if their diarrhea had resolved.

But there were certainly other cases where you look at where say a patient gets the standard of care regimen of whatever, 10, 11 days, and the infusion was given sometime during that period, and then they still have lingering diarrhea for several days after that. Now, in some cases, that may be treated. In some cases, it wasn't treated and it

just sort of resolved.

So it's a little bit of a mixed bag in terms of again how to interpret, I guess, the question of the significance of these failures. And so I think that's something that we're going to be taking a look at more.

DR. BADEN: Dr. Follmann, did you have a follow-up question on this theme?

DR. FOLLMANN: Well, yes, it was just sort of the comment about a post hoc analysis. You know I'm not a real big fan of post hoc analyses, but I think what happened here is that, originally, there was an endpoint recurrence which has problems. And so they couldn't really agree on what the proper endpoint should be, should it be global cure or recurrence.

So I think the distain I have, or the distaste I have for general post hoc analysis is really ameliorated here because I think, fundamentally, there was sort of an agreed upon endpoint which I don't really like, and so I think we're free and open to make our best judgment now

without sort of the negative, necessarily usual negative consequence about a post hoc analysis.

DR. BADEN: Interesting. Dr. Andrews?

DR. ANDREWS: Thanks. I guess some of my questions have been answered, but I am intrigued by the possibility that you can't rule out that the drug had a negative effect on cure rate as defined one way. And so I'm wondering if there is any plausible theory about how that could have happened? Is there any reason for us to trust that?

Can you -- this is a very naïve, very stupid question probably -- but can you give the drug after people are cured? Can you give it to them after 12 days and stop the recurrence? Can you give it to them later than right when they're in the middle of needing therapy, needing treatment?

I like the idea, I love the idea, of looking at a cure as diarrhea and death would be the not cured and just put away all these questions of infection versus not and how do you test it, because I think those are the things that are

really relevant to people. And I think, given the adverse events data, which is small but looks also concerning, I think those kinds of patient centered outcomes are really important to look at.

DR. MISHRA: So I'm not sure exactly what the question was there, but I'll try and answer. I mean, I think the question of mechanism of action is still uncertain, right? So I mean, the one thing that we can say is that it would sort of assume that the mechanism of action of a monoclonal antibody binding to the toxin wasn't going to have an effect on clinical care.

But, early in the development program, sort of the idea that the antitoxin A sort of quickly -- that that would work, you quickly saw the data come that it did have a negative impact. So clearly, there's potentially something there that we don't understand. And I think, from our standpoint, we really don't know what the mechanism of action is.

We sort of try to theorize and I think the sponsor I think has talked about how it could have

to do with quickly allowing the gut to repopulate and all this stuff. But we honestly, we don't know. But I think you can't rule out that a negative impact is possible.

DR. BADEN: Dr. Hilton?

DR. HILTON: I believe the way this treatment would be given to patients is as was done in these trials. That is that, once the infection is identified, the treatments would be given. And so conditioning on whether a clinical cure occurred or not doesn't make sense in terms of evaluating the outcome.

To me, only the global cure outcome makes sense because the CDI recurrence outcome, those who do not have it include those who did not have a recurrence and those who failed the clinical cure. Sorry. That's hard to explain.

DR. BADEN: At this point, it's clarifying questions, and we'll have more time for discussion amongst us.

DR. HILTON: Okay. Just one more point, then, regarding the analysis method, following up

on Dr. Green's point, is that typically a factorial design, such as P001 used, would analyze -- I forget how the drug is called -- BEZLO, plus or minus ACTO, versus placebo plus or minus ACTO?

That wasn't part of the plan, but that would be typical. Then both comparators, the BEZLO and the placebo, would pay the penalty of some patients having ACTO exposure. That's the more traditional way to analyze a factorial design.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: My question may not be considered a clarifying question.

DR. BADEN: Clarifying, please, Dr. Daskalakis.

DR. DASKALAKIS: So I just wanted to ask a theoretical question about the signal in congestive heart failure. So it's a small volume of fluid, 250 ccs, so not very much fluid. Is there a biologic theory about why that could be? I mean, I don't think of monoclonal antibodies, unless they're doing something in terms of volume or in terms of osmolarity, creating like a big fluid load

that could do something like that. Any idea about what that could be about?

DR. HIRUY: So clearly, as you mentioned, the volume is not -- I don't think is the question. And we didn't think it was oncotic pressure either because the CHFs that were observed were, the median was like on day 30. So unless it had some kind of immune-mediated something, because this is a novel therapy and we don't know what the off-target events might be. So other than that, I don't have a clear mechanistic --

DR. DASKALAKIS: Could I ask a follow-up? Any sort of in vitro data about cross -- I think you may have mentioned it, but I can't remember, about interaction of this antibody with cardiac tissue?

DR. KARTSONIS: Thank you for the clarifying question. So as you know, it is an exogenous target. It's a fully human monoclonal antibody, so the fact that it would have an effect on any tissue is diminished as a result of that.

We did do cross reactivity studies in

tissues. In fact, we looked at 38 different tissues in both mouse and human, including the aorta and heart in both of those species, and we did not see an effect. We also did preclinical toxicology of repeated dose of administration of bezlotoxumab in mice and also again saw no histopathological effects on the heart, as well as no hemodynamic effects on the heart as well. So from a preclinical standpoint, there is no data to support that finding.

As we mentioned earlier this morning, a lot of the events that are occurring, that we're seeing, tend to occur very late, at a point when the exposure of the drug is actually less. Remember, single administration, most of the cardiac events that we did see, both in the 41 patients who had serious CHF reported as a serious AE, as well as in the CHF subset at baseline, tended to occur late. And we have no mechanistic explanation for it and we maintain that the data support that there's no negative effect on the heart.

DR. BADEN: Any speculation on why?

DR. KARTSONIS: Yes, sure, I'd be happy to go into that. I mean, if it's okay, can I have slide 74 up again? 74 was from our base presentation. Yes, please, slide up please. Remember, this is the CHF subset of patients that were included, the 325 patients that were reported.

It's important to remember this is not a stratified group, so we're doing an analysis of safety based on a non-stratified group. Not only numerically are there more patients in the bezlotoxumab, but it's not entirely balanced with regard to baseline factors. The proportion of patients who had Charlson Comorbidity Indexes of greater than 5, so that means they have five different conditions that they had at baseline that were considered significant was higher, as well as there were more patients on diuretics, which would be a potential sign that the patients potentially were getting treated for their CHF differently.

So if we then go to the next slide, slide 75, please, we carefully looked at all of this

data. We want to start by looking at the data from week 4 because, if there was going to be an effect, we figure that it would occur at a time when the exposures were the highest.

As you can see, the number of patients with any cardiac AE within the first 4 weeks did not differ between the groups. And particularly, the number of patients with a cardiac SAE were numerically higher, but there were no differences in the number of cardiac failures in between bezlotoxumab and placebo. In fact, the lowest rate of cardiac SAEs occurred in the ACTO plus BEZLO groups. So ACTO plus BEZLO is the lowest, placebo is in the middle, and BEZLO is the highest. That doesn't really suggest a potential pattern with regard to those particular findings.

Then with regard to the deaths where there is a numerical difference there, I think you saw from the FDA's presentation that most of these deaths were not due to cardiac. We looked at every single one of these deaths and, in fact, the deaths were mostly attributed to neoplasms, renal and

urinary events, and infections or other characteristics.

Specifically, I think the real way to look at these cases is to delve into each one of them and to look at them. And we've done that. In fact, I don't want to bore the committee. I've already done that to the FDA at our late cycle meeting. But we've looked at each one of these different cases and, in each one of the cases that we see, especially the SAEs, for example, the 11 cases that occurred early, each one of them has a reason.

There were 3 patients who had cardiac arrest. All of them were 88 years of age or older. There were patients with CHF that were reported. In the 3 patients that led to death due to CHF, 2 of them were in the setting of either endocarditis or Enterobacter bacteremia. And the third patient was a patient who had stage 4 CHF, had an AICD in place, developed an arrhythmia, and then went into CHF, and subsequently died.

So we believe that it's really a sign of the

underlying pathology and the sicknesses of these patients. It's really not attributed to the actual drug itself. We're not disputing the numerical imbalances, but we do believe there's explanations to explain it and we don't believe it's due to BEZLO.

DR. BADEN: Thank you. Dr. Goetz?

DR. GOETZ: I'm not gainsaying anything the sponsor has said. If I recollect properly the half-life of the drug is approximately 14 days, and thus the timing of adverse events such as drug administration, if there's a cumulative tissue effect, is, I think, perhaps a little bit different.

But also, you've talked about histological studies looking at tissue cross reactivity. If I remember right, those are in mice and there are none in any human tissue that I heard. Is that correct?

DR. KARTSONIS: They were done in both mice and human tissues.

DR. GOETZ: Okay, I missed you saying that.

My apologies.

DR. KARTSONIS: So I'm sorry about that, but we did look at the in vitro data in mice and human tissues, including both human and mice heart and aorta. And there were no effects there. The half-life of the drug is 19 days. But still, you're going to have your peaks very early and the drug is going to decrease over time.

Interestingly, when we did an analysis of all adverse experiences, not just cardiac but all, we didn't really see a time to event. So if there's some late immunological finding, we sure didn't see it because most of the SAEs tended to occur within the first 30 days, in fact, 60 percent of them, and half the deaths occurred in the first 4 weeks. So we haven't been able to identify any sort of immunological or autoimmune phenomenon that might explain this, so that's where we are at this point.

DR. GOETZ: Thank you. (Off mic).

DR. BADEN: Any other clarifying questions for the FDA presentation? Dr. Honegger?

DR. HONEGGER: This is again regarding the design and the statistical analysis. I'm sorry, Jonathan Honegger. So my understanding is actually the FDA changed its recommendation from -- there was the design of the first phase 3 trial, and then as the second one was being assessed, the FDA changed its recommendation at that point for what the primary endpoint should be. Is there a reason that they didn't pick it up the first time they prepared the phase 3 trial?

DR. DIXON: I was not the reviewer of the protocol for P001, but I was the reviewer for the protocol of P002. And I guess I have different experience regarding trials of this and I picked that up at that time. And I think the focus of -- when the first protocol was being reviewed, they were focusing on other issues of that design rather than how the recurrence rate was defined.

DR. HONEGGER: Can I follow that up? So there's a change in the primary endpoint recommendation before the second trial is my understanding. I guess a big question in my mind

is, do we need to really look at these A plus B studies or can we just look at the BEZLO alone. And if there's already a change in the primary endpoint, I guess you recognize that there's a problem with clinical cure being a possibility.

My question is, for the second one, had the sponsor changed his hypothesis that A could be damaging for clinical cure based upon ACTO plus BEZLO, had impaired clinical cure that was statistically significant in P001 and A alone had impaired clinical cure that was statistically significant in the first trial? Did they change their hypothesis for the second trial suggesting that BEZLO alone might actually be superior than the combination? And if so, can we just take that hypothesis and focus on BEZLO alone?

DR. DIXON: The initial program development was based on the combination. And since it wasn't until the results of the trials came out that showed that maybe BEZLO alone was sufficient, I can't ignore the fact that the trials were designed with the combination as the primary focus.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: So now I'm curious. Was the discussion about the primary endpoint and changing it made before any data came out or was it made after the results of the first trial came out?

DR. DIXON: It was prior to the conduct of the interim analysis for P001. There were no results at the time. Right.

DR. FOLLMANN: So no results, and so both of you adopted those positions, you not liking recurrence, them continuing to like recurrence, before you saw any data?

DR. BADEN: Dr. Surawicz?

DR. SURAWICZ: Chris Surawicz, University of Washington. Can I ask a question about the data that you sent but that wasn't presented about the septic shock and the table 8 in the document that we got? It says, was the negative effect of the ACTO, was that the 33 percent due to deaths?

Because in the previous sentence it looks as though sepsis and septic shock were actually lower in the BEZLO and the combo group compared to the

placebo group, which made we wonder whether it had some actual benefit in terms of preventing sepsis. It's page 25 of what we were sent on May 23rd.

DR. BADEN: Twenty-five of 29 of the FDA document.

DR. SURAWICZ: Yes, table 8. Because we heard that the ACTO was discontinued because it wasn't efficacious and actually had it poorer outcomes. Was that sepsis? Was that the reason for the poorer outcomes?

DR. HIRUY: Are you talking about ACTO?

DR. SURAWICZ: The ACTO-alone segment.

DR. HIRUY: I don't actually remember exactly what --

DR. SURAWICZ: Okay.

DR. HIRUY: -- was the main driving for -- yes.

DR. SURAWICZ: Okay. But then the --

DR. BADEN: Shall we ask the sponsor to clarify that point?

DR. KARTSONIS: So we obviously carefully looked at the data from the interim analysis with

regard to ACTO and the potential effect that might have. And if I could actually have slide 684 to start, if that's possible, this is a summary of the data. Actually, if you could, put the slide up, please.

This is the summary of how the data looked at the time of the interim analysis, which would have been about 160 patients in each of the 4 arms, 40 percent per group. And what you can see here is that there were more serious AEs in the ACTO group as opposed to any of the other groups that you can see there. And particularly, there were more adverse events that led to death in the ACTO group proportionately relative to the other groups.

Keep in mind that at this point, the DMC also knew that there was also no difference with regard to efficacy for ACTO alone relative to the combination. In fact, at that point, the p value for difference in terms of recurrence was 0.008. And so taking this data as well as the efficacy data into hand, they were concerned about continuing with the ACTO-alone arm.

Now, I will say, we've gone back and looked all of the deaths that occurred in the ACTO-alone group, and we've done that with all the data that we have. In fact, if I could have 673, please, perfect. If you could, please, slide up, please. These are the AEs that were reported that led to death in the ACTO-alone group. You really can see that there's no clustering around any particular event except potentially for sepsis and septic shock where you can see that there were large numbers.

Now, I will also point out that, when we look at the total number of deaths, whether it be in the BEZLO group, the ACTO plus BEZLO, placebo group, sepsis is also the leading cause of death in all those groups. So again, we're dealing with an ill, elderly patient population. We've carefully looked at all of the septic and septic shock deaths that occurred in the ACTO group. And if you go to the next slide, 674 - please; slide up, please.

Here is a sort of patient by patient description of the different septic shock deaths

that occurred in this group. I think there's some interesting patterns that you see, which is that the different types of infections are all over the place. There are gram-positives, there are gram-negatives, there are CDI included in these.

The sites of infection also varied from UTI leading to sepsis to other, just plain bacteremia, leg ulcers leading to development of a sepsis. And you can see that the time frame also varied with regard to all of them. Only one of them was reported as C. difficile-related sepsis, which you can see in the third row there.

I would also point out the last row, which was the investigator's assessment of death. And you can see that none of these events were considered related by the investigator. So I mean, we still are a little puzzled about what happened with regard to the ACTO-alone arm in the interim analysis, but when you take into consideration that there was no efficacy seen, particularly with the p-value as I mentioned before, and there was this trend toward safety findings, the decision was made

obviously to discontinue the ACTO-alone arm.

DR. BADEN: So did it cross a stopping rule?

DR. KARTSONIS: In terms of efficacy.

DR. BADEN: Was the DMC's decision based on futility or based upon a safety signal? And was there a stopping rule that they applied?

DR. KARTSONIS: Sure. So the predefined efficacy stopping rule was a p-value of 0.001. Oh, 3 zeros. Sorry about that. 0.0001 is called Haybittle-Peto if you ever want to know. It's taken years for me to learn how to say that term. So it did not go below that in that regard, but it was awfully close at 0.008. And keeping in mind also that the safety findings we're seeing, we think the DMC actually made the right decision.

In fact, we have now more data that Dalya shared with you in her presentation. Because remember, this was done when 160 patients had reached week 12. There were also additional patients that had been enrolled in the ACTO arm before the interim analysis.

We've looked at all of that data, which

really was the 242 patients that were shown. And it shows the same trend, both in terms of lack of efficacy as well as the safety finding. So the decision made by the DMC was the correct one, even if it didn't necessarily meet the predefined efficacy rule.

DR. BADEN: But it was an integration of both features?

DR. KARTSONIS: And that's how the letter was written to -- when the trial was unblinded and we looked at the data from the interim report, those were the two factors that drove the decision by the DMC.

DR. BADEN: Thank you. Dr. Surawicz?

DR. SURAWICZ: Thank you. Then it looks as though, when you then go back, both the BEZLO and the combo group had less sepsis and septic shock than placebo. So was that statistically significant? It was 23.7 for placebo, 12.5 for BEZLO, and 13.7 for the combo.

DR. KARTSONIS: I will call on -- I can't remember that number if it was --

DR. SURAWICZ: I was actually asking the --

DR. BADEN: It's an FDA question.

DR. KARTSONIS: I'm sorry. I apologize.

DR. SURAWICZ: It's for them.

DR. BADEN: It would be the agency.

DR. SURAWICZ: Yes. And again, it's that table 8. It just made me wonder whether it was actually helping or whether it was the fact that the patients had responded to therapy, and they were less sick and therefore less likely to get sick.

DR. IARIKOV: Could you please tell what document you're referring to?

DR. SURAWICZ: So table 8 of the document that was sent May 23rd.

DR. IARIKOV: What table? Sorry.

DR. SURAWICZ: It says table 8 summarizes the deaths that occurred in the phase 3 trials. The rates of death were comparable, but the highest proportion of deaths in all study arms was due to sepsis and septic shock.

Deaths due to sepsis and septic shock were

observed at a higher rate in the placebo arm, 14 of 59 or 23.7 percent, as compared to BEZLO, 7 over 56 or 12.5 percent, or the combo 7 of 51 and 13.7 percent.

DR. BADEN: I don't know if --

DR. HIRUY: I'm sorry. Can you rephrase the question for us?

DR. SURAWICZ: Well, I just wondered if we should pay attention or if it was significant that there was fewer deaths from sepsis and septic shock with the treatment compared to placebo. Or if that's a small difference that we shouldn't pay any attention to.

DR. IARIKOV: I would call it -- sorry -- a numerical imbalance. There was no formal statistical analysis associated with these numbers. And this is what's reflected and this is what data showed.

DR. SURAWICZ: So not something we should pay attention to?

DR. IARIKOV: It's up to advisory committee members.

DR. SURAWICZ: It's descriptive not statistically -- it's not significant is what you're saying.

DR. IARIKOV: Right. And it was not analyzed formally. There was no hypothesis associated with these numbers. It was observed.

DR. SURAWICZ: Thank you.

DR. BADEN: Last question from Dr. Goetz, and then we will get to lunch.

DR. GOETZ: I'll pass on my question.

DR. BADEN: Then we will get to lunch one minute early. So we will break for lunch. We'll reconvene again in this room in one hour at 1:30. Please take any personal belongings you may want with you at this time.

Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you. See you here at 1:30 prompt.

(Whereupon, at 12:29 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:34 p.m.)

Clarifying Questions (continued)

DR. BADEN: So we should resume the meeting. And I know some of the panel members have flights to catch, so we will keep things moving and hopefully be done by 4:00. The discussion was ongoing and we had gone through the list of questions, but I think there was one more question that Dr. Weina wanted to raise. And I think he had a graphic to help him ask the question.

STAFF MEMBER: You need to say slide up.

DR. WEINA: Slide up, I guess.

(Laughter).

DR. WEINA: Beam me up, Scotty. All right. There was a big discussion about whether this -- if the mechanism of action makes sense or doesn't make sense. And if it does make sense, shouldn't it have some influence on the initial infection. And I was just sketching this out and thinking through it.

So my clarifying question becomes, if you

look at the upper right -- and a picture is worth a thousand words. And please correct any errors in my thought process here, and maybe this will help us. So if you look at the upper right here, in the initial infection, you have the antibiotic present and you've given the BEZLO. So because of the antibiotics, the bacteria die. The toxin B is bound, but the toxin A is just continuing there and continuing to work.

In the case of a recurrence, what is happening is that there is no antibiotics present because basically -- and hopefully the BEZLO is still present because you've shown that it sticks around for quite a long period of time. And as a matter of fact there are some varying -- I mean half-life is very different than when you can still detect it and everything else. But let's say that BEZLO is still around.

So the bacteria has to grow, because that's what happens in a recurrence. Otherwise, the toxin B isn't there to be bound, so the idea is that the bacteria is growing, and the toxin B may be bound

if the BEZLO is present, and the toxin A just keeps working.

Why this becomes important in trying to figure this out is because, if you look at the timeline the microbiota is disrupted, the antibiotic treatment of whatever is there to treat it, C. diff is -- some other infection causes the microbiota to be disrupted, C. diff grows. You have an illness secondary to the toxins A and B. Antibiotic treatment is started for the C. diff. And the BEZLO is added and B is bound.

But the bacteria are killed by the antibiotic and the toxin A is still working and somehow 70 percent of them are cured. Of the individuals are cured, 30 percent recur because the bacteria are back, and the toxin B is still bound, and the toxin A is still working. So we're trying to, I think, work out in our head what's wrong with that thinking?

DR. KARTSONIS: Your schematic is very intriguing because we -- I'm going to call one of my colleagues, Dr. Therien, back up to show a

schematic we've generated, which I think might show similar kind of viewpoints.

DR. THERIEN: Yes, I just sketched this down in the last 30 seconds while you were speaking. No, 1128.

DR. WEINA: We got to figure out how you guys do it so quick, because it took us the entire break to just figure out how to send it to their computer. Okay?

(Laughter.)

DR. THERIEN: No, I cheated. I made this a while back. Slide up, please. So this is a representation of I think what you were trying to show. And what this schematic diagram shows essentially is how the healthy -- or the gut microbiota changes over time in the context of a primary and recurrent CDI episode and also how the C. difficile burden changes over time in the lumen of the gut.

So the blue line represents the gut biota. A blue line at the top of the diagram means that the gut biota is healthy and normal. A blue line

at the bottom means that it has been disrupted by antibiotics.

So a patient comes into the hospital in this particular representation with a healthy gut biota and is put on antibiotic therapy for whatever reason, another infection or surgery, scheduled for surgery. And that will impact the gut biota and you'll see the blue line start to go down. At some point this patient comes into contact with toxigenic C. difficile spores form the environment.

As long as antibiotic therapy is on board, nothing will happen. The biota will continue to be disrupted. The spores will not germinate. But as soon as the antibiotic therapy is completed, the course of antibiotic is completed, then essentially a race begins between Clostridium difficile and the gut biota.

The gut biota will start to recover but toxigenic C. difficile spores may germinate, colonize the gut, and start producing toxin which will lead to the clinical manifestations or symptoms of disease, which is what is represented

here by the red color that you see. And that patient would then become diagnosed, following a positive stool test, will become diagnosed with an episode of CDI.

The patient would then be put on standard of care antibiotics, the gray box at the bottom in the middle there. And for that duration, what you'll see is the C. difficile burden will start to come down, as will the levels of toxins. But also the gut biota, which had begun to recover, now begins to be disrupted again, and you see the blue line going down as well.

Essentially, the same story starts again. Once the standard of care antibiotics are completed, the race begins anew and if C. diff wins that race, you get a recurrent episode of CDI, more symptomatology shown by the red color. And that patient again, without any other options, will begin standard of care antibiotics and you get this recurrent cycle that we talk about, where each new episode brings about a higher risk of a further recurrent episode.

In this diagram as well, at the very top, you'll see I've highlighted what we consider to be the at risk window. This is essentially the window following successful cure of the initial episode, where the gut microbiota has not yet recovered and where the patient is at risk for CDI recurrence. And you see that the window is limited in time by the start of the recovery of the gut microbiota.

So this is what happens in the absence of bezlotoxumab. If we now go to the next slide, you will see what happens in the presence of bezlotoxumab. Slide up. And essentially, what has changed here is that red area for the recurrent CDI has now turned green. And the reason for that is because bezlotoxumab is administered concurrently with standard of care antibiotics. You can see the blue bezlotoxumab at the bottom.

We know that bezlotoxumab remains in circulation, because of its long half-life, throughout the at-risk window. And because it's able to bind the toxin that is produced during the recurrent episode of C. difficile, it does not

impact the growth of C. difficile, but it prevents the symptoms of the infection.

What you've done here is you've eliminated the need for standard of care antibiotics to treat that recurrent episode. You've eliminated the recurrent cycle and you're now allowing the gut microbiota to revert back to essentially a healthy level, which now provides that long-term protection against further recurrent episodes of CDI.

There was a question previously about whether we know whether bezlotoxumab has an impact on the microbiota. We do not have clinical data, but we do have limited preclinical data in the hamster showing that this recovery of the microbiota does happen and that bezlotoxumab does not prevent it from happening.

Of course, the whole notion of an at-risk window and of the fact that that at-risk window is associated with disruption of the gut microbiota, and the fact that the at-risk window eventually ends because the microbiota recovers is a well-validated idea in the literature, both in

human patients and in animals. And so that part of it has really been demonstrated quite convincingly.

Does that clarify things?

DR. WEINA: It helps ignoring toxin A.

DR. THERIEN: Right, okay. You did talk about toxin A. So the whole question, I now that Dr. Kartsonis replied to, a similar question earlier. Unfortunately, I don't have that much additional data to share.

What I can tell you is that there appears to be a dependence on the nature of the host species in terms of what the roles of toxin A and B are in disease. We know that in rodent models, in the hamster and the mouse, you do need both actoxumab and bezlotoxumab. You need to neutralize both toxins to get full efficacy.

On the other hand, in the piglet model, that looks a lot like humans, where you only need the bezlotoxumab to get the full efficacy.

So there is some sort of a dependence on the host species. I think if you ask some experts, they will tell you that that may have to do with

the fact that the receptors for the toxins, the cellular receptors for the toxins on the epithelium are expressed in certain species and not in others, and that that would be the determinant of what the individual roles of toxins A and B are in disease.

So I think our data really contributes to the debate that's ongoing in the literature currently about what the roles of toxins A and B are, contributes to that debate arguing that toxin B is the key pathogenic determinant, at least in human recurrent CDI.

DR. BADEN: Thank you. Dr. Schaenman?

DR. SCHAENMAN: Could you put your slide up again?

DR. THERIEN: Certainly.

DR. SCHAENMAN: As was said, a picture's worth a thousand words. And I think Dr. Weina and I were really trying to see this from a microbial pathogenesis point of view. But the way you guys are framing the mechanism, what you're really doing is preventing the clinician from retreating the patient by suppressing symptoms.

DR. THERIEN: Essentially, that is true, yes. We are essentially preventing the need for that next course of antibiotics.

DR. SCHAENMAN: Right. And just to play devil's advocate for a moment, you could do the same with over-the-counter Imodium arguably, that by suppressing symptoms and that need for retreatment, that's one way to break the cycle. And I've actually heard some C. diff experts recommend that we try to avoid retreating, and maybe that's kind of what the vancomycin taper does in a way. It slowly separates the prescribing physician from the patient.

DR. THERIEN: I am happy to deflect that question to our clinician, my clinician colleague.

DR. KARTSONIS: Sure. And I can't speak to the potential value of using an Imodium or a Lomotil to do that. But I will tell you, when you look at the totality of the data that we've shown, it's not just preventing loose stools.

We've shown that, if you look at the adverse experience, the proportion of patients who actually

had serious CDI that was reported as an adverse event was higher in the placebo group versus BEZLO. The severity of the infections, the number of patients who had been treated with a subsequent FMT, the rehospitalization data, the length of stay data, all of that data, we think, does speak to the clinical value of the product that goes beyond just the efficacy endpoint that we mentioned.

So I can't directly answer your question because I haven't done that study, but we believe that what we offer with bezlotoxumab as a single infusion over 60 minutes is clearly an advance in a situation where currently there's nothing else. So I'll just stop there and we'll go from there.

DR. BADEN: Thank you. Dr. Moore, you have a question?

DR. MOORE: Yes, just a quick couple of points. I can't endorse, just as a side note, the use of Imodium in this setting because of the reduction of motility and the increase in time of exposure, but that's a separate issue.

DR. BADEN: But it's a different topic.

DR. MOORE: Yes, indeed, it's completely different. So moving on, I lost my train of thought. No. The main thing is, the reason that there's a significant recurrence is there continues to be recurrence despite binding of toxin B, is I think the fact that, in the process of doing this particular study, the sponsor sort of stumbled upon or waded into the morass of the unknown about the gut microbiome, as we all have. We've sort of stumbled into it knee deep.

The fact of the matter is that it's not just the binding of toxin B which will prevent disease, it's the restoration of gut health. And that's why, although toxin B, binding of toxin B clearly is important, as you see in the data, restoration of gut health with restoration of the microbiome is probably the key factor.

Frankly, you're right. Indirectly by reducing or eliminating the possibility of the physician adding on additional antimicrobial treatments, it goes a long way to facilitating that. And what the impact will be with fecal

transplant is not clear, but I think that the slide that was shown by the sponsor, and they were sort of wading into the discussion regarding the question to the committee, is that -- I think it's the slide that was shown by the sponsor showing that those that require fecal transplant was significantly less than those who had the placebo really speaks volumes.

DR. BADEN: Sorry, I don't think there were statistics on that.

DR. MOORE: You're correct, there were not.

DR. BADEN: Any other questions or discussion from the committee?

DR. SURAWICZ: A quick question. In the people who had no risk factors, was the efficacy different?

DR. KARTSONIS: As you know, we only predefined five risk factors in this particular study. And when we look at that subgroup who had no risks -- if you look at the group who had 1 or more risk factors, the difference was 30 percent versus 17 percent, which was over a 50 percent

relative-risk reduction, or close to a 50 percent, I should say, relative-risk reduction.

In the subgroup that had no risk factors, the difference was 2 percentage points in favor of bezlotoxumab, but the 95 percent confidence intervals do indeed overlap here. But keep in mind that this is the risk factors that we had pre-identified. It doesn't include other risk factors that patients may have, such as renal failure or surgery or concomitant antibiotic use or other things that might also potentially be evaluated.

It obviously also doesn't take into consideration that there are some people you may treat even in the setting of no risk factor because they can't have CDI recurrence, they're about to get married, they're about to go on a trip.

There's different factors that we're ultimately trying to ensure that the prescribers have access to this medication for all patients in the event of -- you know, based on their judgment if it was the appropriate therapy to give in that

setting.

Questions to the Committee and Discussion

DR. BADEN: Thank you. So then if there are no more questions or discussion from committee members, then we'll now proceed with the questions to the committee and panel discussion.

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.

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. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll

go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We'll continue in the same manner until all questions have been answered or discussed.

I'd now like to ask Dr. Nambiar to present the question and the charge to the committee.

DR. NAMBIAR: Thank you, Dr. Baden. Today's meeting we've discussed the benefits and risks of bezlotoxumab for the prevention of C. difficile recurrence. As we've stated earlier, the applicant is seeing approval of bezlotoxumab for the prevention of recurrence of Clostridium difficile infection in patients older than 18 years of age.

You've heard presentations from the FDA and the applicant regarding the safety and efficacy of this product for the proposed indication and heard the comments submitted to the open public hearing. Based on the information provided to you in the briefing documents, the presentations, and discussions today, we seek your input on one voting

question.

From an efficacy standpoint, as you've heard, there are differences in assessment between the applicant and the agency.

You've heard a lot of discussion about the considerations for appropriate endpoint and analysis populations, and the observed differences in cure rates for the initial CDI episode between the antibody arms and the placebo arm, and the potential impact of these findings on the efficacy assessment of bezlotoxumab in the prevention of CDI recurrence.

We would appreciate receiving your advice on these issues and any other aspects of the efficacy assessment that you consider important.

From a safety standpoint, while there are no major safety concerns identified so far, you've heard discussions regarding the observed imbalance in serious adverse reactions in a subgroup of patients with congestive heart failure. So as always, in addition to your votes, we greatly value and benefit from the rationale you provide to

support your decision and any recommendations that you might have regarding this application.

So the single question we have for the committee is, has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of C. difficile infection recurrence in patients aged 18 years and older?

If yes, please discuss your rationale and provide any recommendations concerning labeling. If no, please discuss your rationale and what additional studies or analyses are needed. Thank you.

DR. BADEN: Any clarifying questions from the committee about the question to us that we can ask the agency to clarify for us?

(No response).

DR. BADEN: Seeing none, then, if there are no questions or comments regarding the wording of the question, we'll now open the question to discussion. I realize we've had hours of discussion. And I see --

UNIDENTIFIED PANEL MEMBER: (Inaudible – off mic) -- discussion amongst ourselves.

DR. BADEN: Just amongst the committee about the question. Dr. Follmann?

DR. FOLLMANN: Well, in the space of two minutes, I've gone from abstain to -- well I won't tell you what I'm going to do actually. I suppose that's not right. But anyway, so what I'm looking at is, has the applicant provided substantial evidence of the safety and effectiveness?

I was interested in an analysis where we'd start at, say, day 28, look at whether or not you had 3 loose stools or not in a day, count that as a failure, count deaths as a failure additionally as a sensitivity analysis. To me, that's a very important analysis and it hasn't been presented today. So I would mention that.

The other thing has to do I guess with the recurrence. That word to me means, and I think it would to most people, gee I'm cured of whatever, now I'm at risk for it coming back. And if it does come back, then I've recurred. But in fact that's

really not the design of this study. And so to me, to say the word recurrence would be a study like you suggested where you basically randomize those who are cured, maybe start giving the antibody at day 13 or so. So anyway, those are the points that I'm thinking about.

DR. BADEN: Your point is well taken that we have to weigh the data that are before us, not the data we hope to have.

DR. FOLLMANN: Or what we think it might look like.

DR. BADEN: Dr. Weina?

DR. WEINA: Pete Weina, Walter Reed. Just one question for the agency. Did you specifically mean to say effectiveness versus efficacy, or is that not a distinction in your mind?

DR. COX: It's safety and efficacy, but it's oftentimes a question of effectiveness. So yes, we're talking about efficacy. And just to clarify what we're talking about, oftentimes people refer to effectiveness as how a drug works in the real world. And I'm assuming that's what you mean when

you say effectiveness.

DR. WEINA: That's exactly what I mean.

DR. COX: Yes. We're talking more safety and efficacy, the traditional use of the words as we use it. Sometimes we use effectiveness almost synonymously with efficacy.

DR. BADEN: Dr. Andrews?

DR. ANDREWS: Ellen Andrews from the Connecticut Health Policy Project. I guess, to your point about effectiveness, when I think of effectiveness for patients, it's getting well and being able to go to that wedding, or whatever. And the adverse events, even though they were meant to talk about safety, I would have expected to see some reduction in not just deaths, but also diarrhea, and nausea, and some of those other kinds of problems.

I didn't see that and I know that that wasn't a study done to look for that kind of effectiveness, but that's what I see there and it's troubling.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: Since we're just talking amongst ourselves, I think they did show a reduction in diarrhea because they talked about all-cause diarrhea and not just C. diff specific diarrhea.

DR. BADEN: Dr. Green?

DR. GREEN: I'm a little troubled by the full question which includes looking at prevention in patients aged 18 or older. I didn't actually hear any data or discussion about patients 18, or 19, or 25, or 30.

I'm a pediatrician and I suspect that, if this gets FDA approval, our clinicians will use it before it's studied and FDA approved in kids. We often have to do that because studies in kids lag far behind.

But I don't really know how well it works in this age group. I don't really know how well it works in individuals who are not so severely affected or do not have such risk factors. It does seem that there's a population that gets benefit from it. And I have -- as someone who longs to see

more anti-infectious agents available, but also just --

DR. BADEN: Dr. Green, I think the question now is understanding the question and discussion of the evidence, not our rationale. We take a vote and, after we vote, we provide rationale and advice to the agency. So this is more, do we understand the question, do we understand the data?

DR. GREEN: Okay.

DR. BADEN: Hence the effectiveness versus efficacy to make sure, and then we will have a chance after we vote to explain pros and cons of our opinions. So other clarifying questions or discussion that will help inform understanding the data and the question?

(No response).

DR. BADEN: Okay. If there's no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your

selection, the light may continue to flash. If you are unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

So I guess the voting may now begin. So please all make sure you vote. And we now have the sign, so the voting is now complete.

(Vote taken.)

DR. TESH: For the record, the voting result is 10 yes, 5 no, and 1 abstention.

DR. BADEN: Now that the voting is complete, we will go around the table and have everyone who voted state their name, vote, and, if you want to, you can state the reason why you voted as you did into the record. We'll start with Dr. Surawicz in the right.

DR. SURAWICZ: Thank you. I voted yes. I think these were well done studies that were very detailed. They provided us with a tremendous amount of data. We know the severity of recurrent C. diff and its impact. I believe that the sponsor showed that it was efficacious and overall very

safe. I would hope that it would be used for high-risk patients and not for everyone. And I would hope that the safety data would continue to be collected after its use if it is approved.

DR. BADEN: Dr. Goetz?

DR. GOETZ: Yes, I'm Dr. Goetz from the VA and David Geffen School. I also affirm my vote as yes. And I was, as Dr. Surawicz was, impressed by the quality of the study, the depth of the analyses performed by the sponsor, as well as by the FDA whose analyses I very greatly appreciate.

Thinking about this as a whole, the word substantial is an important word to me, always means not without a shadow of a doubt, but really the overwhelming body of data supported this. I voted yes, although I have some concerns about the word recurrence because I think that what's more important to the clinician, and as well as to the patient, is what might best be termed as sustained clinical response.

Cure is a hard word to use because relapses occur in funny ways. But sustained clinical

response is a better phrase, in my view, recognizing that the sustained clinical response is likely driven by a lower recurrence rate. But because of the nature of the study design, it makes it a little bit more challenging just to look at it in terms of recurrence.

As is Dr. Surawicz, I'm concerned about identification of populations who will most benefit because of the value equation of the medication more than the safety and risk profile of the medication.

If I heard the sponsor properly a few moments ago, in the approximately 25 percent of patients who had zero of the -- none of the five identified risk factors. The delta between the 2 arms, the BEZLO arm, placebo arm, is 2 percent and the confidence interval is less clearly crossing zero.

So I think there is a value judgment that will need to be made. And while I would not necessarily restrict the package label to people who have a risk factor, I think it's an item that

merits consideration here.

I applaud the sponsor for the data they are collecting to allow them to evaluate some of the nuances and looking at the microbiome is an important factor here to substantiate some of the data. I think there are questions that need to be looked at in sub-analyses regarding timing of the therapy. Repeat dosing wasn't addressed. It's an important issue that will come up clinically most certainly. I think those cover my primary issues here. Thank you.

DR. BADEN: Dr. Hilton?

DR. HILTON: I'm Joan Hilton, a biostatistician from UCSF. I voted yes in spite of a number of study design weaknesses. For example, it would have been nice to randomize after the initial infection was resolved to see if that would delay recurrence.

I agree with Dr. Goetz's comment that sustained response would be a nice definition to pursue. I was also concerned about the roughly 60 percent of subjects with at least one treatment-

emergent adverse event. But when I looked across the types of individual events, the most common was less than 7 percent. So I think that these are very sick patients, and they're having a lot of symptoms in the setting that they're in, and probably those cannot be avoided and will resolve relatively quickly.

So I think, given the environment of strong medical need for treatments for C. difficile, in spite of the weaknesses, I decided to vote in favor of this.

DR. BADEN: Dr. Moore?

DR. MOORE: I voted yes, of course, as you see in the table. But I won't reiterate most of the -- most of my concerns have been previously stated.

The only thing I would say, it's a difficult question to answer properly because the safety and effectiveness were lumped into the same question and not separated and that raised its own issues. So the only thing I would say regarding safety is, this drug I think might have to -- you might have

to stipulate, the FDA might want to stipulate that if the drug is going -- that it should be used with caution in patients who have heart problems. That said, it's about the only thing I would recommend. Beyond that, I didn't see any overriding significant safety concerns.

With regard to effectiveness, I think the data were -- no matter how you slice it, I mean, I really want to thank the FDA for their very thorough dissection and interpretation of the data, as well as the sponsor for the heavy lifting that was done.

It's a difficult spot to be in as an advisory committee member to walk into a disagreement between the sponsor and the FDA, but I think it's an amicable disagreement. And I think, largely, the difficulties were resolved to my satisfaction, I guess, is what I'm trying to say for the purpose of this voting.

DR. BADEN: Dr. Gea-Banacloche?

DR. GEA-BANACLOCHE: I voted yes. I think that the description, the analyses of the FDA, it

says everything really. I think that they were right saying that the most important endpoint should have been the global cure and not the recurrence. And I think it's unfortunate how things develop. But I think that the FDA is also right when they say that it does seem like there is a decrease in recurrence of C. difficile when you use this drug.

I think it's a big concern that by approving this drug we're going probably to multiply by a factor of I don't know how many hundreds the cost of treatment of C. difficile and probably the cost of preventing 1 recurrence is going to be I don't know how much. So that's a big concern in terms of how the FDA is going to phrase the approval and in which patients these drugs could be used.

I think that the immediate tendency of start treatment and give your monoclonal antibody is going to exist there. But I cannot see anything in these data that says these drugs should not be made available. I think that there should be a place for it and that's the reason I voted yes.

DR. BADEN: Ms. Thomas?

MS. THOMAS: Jeanine Thomas, MRSA Survivors Network. In my opinion, this therapy is not significantly better than the placebo. Sponsor has not proven efficacy and the side effects and mortality rates are too high. As a C. diff survivor myself, I am very concerned about the gut microbiome being compromised. I believe further studies would not improve the effectiveness of this therapy. We need superior therapies.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: Jonathan Honegger. I voted yes. I recognize the concerns and appreciate the concerns of the FDA about the endpoint. These were well-done studies and large studies in appropriate populations. And I was driven particularly just by the urgent need for targeted therapy for C. diff.

I also hope these are used primarily in high-risk. I hope that follow-up studies are done to help further clarify its role in people who are not high-risk people, safety effects in CHF and other cardiac disease, repeat dosing, and then of

course in children looking at PK and eventually efficacy. I don't know -- I'll just stop at that point. Thank you.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: Joanna Schaenman, UCLA. I also voted yes. Although I still have some questions about what the mechanism truly is, I think there's no question that it is a novel mechanism. And as I think was mentioned earlier, we haven't had any new drugs in our armamentarium for C. diff for some time, so I think there's definitely room for something like this, which is so novel.

I also appreciated the sort of the statistical dialogue between the sponsor and the FDA. I thought it was very elucidating. And I want to echo some of the comments mentioned previously that if approval is given, attention should be given to the wording in terms of what this drug is actually doing in terms of global cure. And I would also encourage FDA to include some of Dr. Follmann's requested analyses in the

package labeling if it does come to that point.

I also want to echo what's been said previously regarding targeted therapy. As Dr. Goetz mentioned, the impact seemed most minor in those least at risk patients. And because although the study concerns didn't reach the burden, to me, that seemed to prevent approval.

Certainly, there was some safety signal in the CHF patients, and so because we're always balancing risk-benefit, I think the role for this drug would be in high-risk patients, in patients at risk of recurrence. In those patients, the risk for potential heart effects would potentially outweigh -- the benefit would outweigh the risk. And so again, targeted therapy I think would be the best utilization.

I would also encourage the sponsor to continue looking at the time of use as it relates to standard of therapy because maybe there is the right niche between balancing all these different things, restoration of microbiome, active antibacterial therapy, and addition of a biologic

where we could orchestrate best the use of these different therapies.

DR. BADEN: Dr. Weina?

DR. WEINA: I voted yes. Has the applicant provided substantial, yes but not conclusive evidence of safety and efficacy, especially given the 2011 data and the unmet medical need, we're probably preventing possibly up to 8000 cases a year, and possibly up to 3000 deaths a year. So given the unmet medical need, I think that there's a reason to -- that there's substantial but not conclusive.

I do have concerns about that maybe there should be a warning, not necessarily a black box warning, but some sort of warning on CHF, maybe a phase 4 trial suggesting looking at the isolates. And actually focusing on -- I mean, given the mechanism of action that's been discussed, you would expect something better than a 10 percent improvement. You would expect something much more substantial. So maybe there are isolates that it works better for and not other isolates, and that's

why we're seeing the difference. And maybe get a closer look at that.

I would also encourage the agency to really look more closely at the issue of cross-reactivity even though BEZLO doesn't really have "an endogenous target" that's been identified because toxin B is the target. It doesn't really rule out cross reactivity. And really looking at the tissues that are used and potentially looking for other potential reasons why you may be seeing some of the concerning, quote/unquote, "safety signals" could be found by looking at that for cross-reactivity.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. I'm Barb Gripshover, and I voted yes also. And I really appreciated the FDA's concerns of the primary endpoint of the study. I agree that it seemed like not the best choice, but I think the sponsor did a really good job of looking at other data. And I think I might have been most moved by looking at the cure rate when you expanded your cure rate and showed that,

at all time points, it was making a difference.

So I think that it does seem that the drug is effective for preventing recurrence for a significant number of people, so that's why I voted yes. I do think that we want to go with high-risk populations because I think that the benefit may not be there for people that don't. And that's it.

DR. BADEN: Lindsey Baden. I voted no, but I suspect my views are not that divergent from others. It's just how to weigh the evidence. I think that the question is substantial evidence, not preponderance of evidence, and not evidence that we're not able to evaluate but can be shown as supportive. I find that potentially tricky.

This is not a rare disease. Five hundred thousand cases a year in the U.S. alone. And we have 800 patients in total treated with the therapy of interest. And based on that, we make conclusions of safety, and based on that we're making conclusions of efficacy that getting to third base is substantial, getting to third base or getting to home base. Not being a sports person,

it's dangerous to make analogies.

I think there is a preponderance of evidence, but the issue of substantial evidence, to me, is a very high bar for a first-in-class, novel therapy for which we have no experience and which we have a lot of hope, and desire, and need, and I want my patients to have this. But the data that we have to date, in my view, are conflicting.

I think both the sponsor and the FDA did a fabulous job at presenting a lot of data from many different sides. Many aspects of the data were incomplete and we wanted more, but in part there is time limitations as to how much we could discuss. But I'm leery of data that I want to see tomorrow versus the data we have today that we're able to scrutinize and evaluate. And I think some of the discussion alluded to data that will be generated from this dataset that will be informative. When we have those data, then they can be evaluated and incorporated.

Then there is the question of how to look at the global cure. And if one looks, the 3 out of

the 4 groups that received the antibody did worse in clinical cure. And 1 group did better. And then with recurrence, I think there was clear signal of benefit. That's a complicated analysis to interpret.

Then redefining the goalpost of what clinical cure is and being able to evaluate those data only from a few slides presented today makes it very hard to have confidence in understanding those data. So I'm torn by the data that we have versus the data that I want and that this is not a rare disease.

So the ability to do studies should not be difficult in larger populations, so we have the data we need to make a decision about substantial efficacy in the right population versus the hope and implication that it should work the way we think it should. And I'm leery of it should versus we have the data in humans that demonstrate the activity as we expect.

So I think there is a cloud in my mind over the efficacy that I think the sponsor has an

analysis that makes sense. To me, this seems like they jumped from a phase 2 to two phase 3s. And really, the two phase 3s, in my mind, are the 2bs that design the endpoints that should be the endpoints that get confirmed because we're now changing the primary endpoints of the study.

I don't think that it's wrong. I think we learned. We learned a lot from this study about the biology of C. diff that we didn't expect. But I'm uncomfortable declaring conclusions of substantial efficacy and safety based upon data from 800 with analyses that are fluid for very good reason, but are still fluid.

So I think the discrepancies in the data on the clinical cure, the issues in the change of endpoint, additional analyses that are not available, the additional studies that many of us have mentioned, the safety signal with CHF, all in the setting of 800 total treated for a first-in-class do not reach the bar for me of substantial efficacy.

It's a preponderance. It is a very

intriguing and encouraging intervention, but the level of proof is not there yet in my view.

Dr. Green?

DR. GREEN: Michael Green, University of Pittsburgh, Children's Hospital, Pittsburgh. I voted yes. First off, I want to thank both the sponsor and also the FDA for their analysis, their presentation, their ability to respond to our questions. I want to thank my fellow committee members because I think your questions really helped me to further understand what we were seeing and to try to put it into context.

I voted yes as a pediatrician when this study was really done primarily in a geriatric population, and my yes is probably not an unconditional yes, but we didn't get to limit our recommendation other than to say how we might like to see it used or what might be on the product recommendation.

I think there is evidence that there is a role in a particular population. I think that the fact that those with risk factors and those with

more important or severe disease seem to have the greatest benefit. And they're also probably the ones that are at greatest risk from this disease, although I don't take care of those individuals on a day-to-day basis, suggest that there is a role for them.

I would hope that this product would not be used in individuals who did not really have those risk factors or have severe disease. And in fact, the company's own presentation suggested that they did not show a statistical benefit in that group. I have no idea of how well it works in an 18-year-old, even though we're talking about an indication down to 18, in particular an 18-year-old without risk factors.

I know, although I wasn't allowed to say this before -- I can say it now -- that my intensivist in my ICU at the Children's Hospital of Pittsburgh will be thinking that they should use this because more is better. And I fear that and I do fear the cost.

Yet, I do really believe that there is a

population for whom this should be targeted and is likely to show some benefit, in part because there is not a lot of good alternatives. I urge and beg the sponsor to do additional studies, particularly in the pediatric population, and to take what we've learned by our input, your input, the FDA's input, and try to perfect those studies, and to do additional phase 4 studies.

I also would echo the previous comments about caution in those with underlying heart disease since we don't really understand exactly what that signal is representing or why it's occurring. Thank you very much.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis, New York City Department of Health. I wanted to start off again by echoing the thanks that you've heard, both to the agency and the sponsor for really great presentations and very detailed analyses.

I will the reveal that I have trained under Dr. Baden, so I'm going to sound just like Dr. Baden right now, which is that we have had a very

limited experience with this drug purely in these studies. There are about less than 800 experiences of people on this drug alone, and that makes me very concerned from the perspective of this data being convincing.

I think that it both confounds the safety signal and also potentially confounds the efficacy signal. I am concerned that we have a mixed signal on the effect of this drug on treatment.

So we talk about recurrence being an issue and what I fear is that, as this drug rolls out, more being better than less, that more and more people who potentially would just get treated and be fine will be exposed to this agent. And if there is an adverse effect on treatment, that could be a significant impact both on the healthcare system and the health of individuals.

So I think it's really critical, if this does sort of proceed, that there are more phase 4 studies done to really see what's happening with the drug from the perspective of it looked in isolation rather than in the context of other

agents.

From the perspective of safety, the CHF and death signal, I think, is actually significant. And the reason that I say that is because of this very good conversation we've had in the context of this committee that people are saying, "I hope this is used for people with risk factors." Well, that also means that you're going to be using it in people who have CHF. So if you look at the definition of CHF, it's really permissive. Pretty much if you have a little bit of failure, you're going to qualify as a CHF patient in this study.

So I am concerned that we don't really have a sense of the safety. We haven't had enough experience with 800 people on the drug to be able to proceed in this way. Which is one of the reasons that I voted no.

I think, otherwise, a lot of what I've said has been said before. And like I think that Dr. Baden said, it's in the eye of the beholder. I think that much of my thoughts are similar to the people who said yes, but I am concerned that we

need more experience.

DR. BADEN: Thank you. Dr. Andrews?

DR. ANDREWS: Ellen Andrews for the Connecticut Health Policy Project. I also agree, I'm probably in agreement with everybody around the table, but I voted no. I think it has enormous potential.

I especially want to thank the sponsor, for I think this might be the first time I've ever voted no on anything, because we need more tools in the toolbox. We absolutely do, so I'm very happy that you're working on this.

But this is given to very fragile people, which I get is why it makes looking at the safety data that's concerning me so much problematic. But it also means that you're giving this to fragile people. And if there's any chance that it interferes with a cure, that's a real concern.

I think that really needs to be sorted out before we give it to people who are fragile and looking at a pretty serious infection.

Why we can't give -- I've still not heard a

great explanation for why we can't give this drug after the cure at day 14. So I'm worried about that. I'm worried about changing the definition of cure. I am worried about people with heart failure. I think, if it is approved, it should be limited to people, especially to people it worked the best for, people who have had infections in the past. They are going to be at risk and it's more likely to work for them. I just don't think it's quite ready yet, but I think it has enormous potential. Thank you.

DR. BADEN: Dr. Corbett?

DR. CORBETT: So I abstained from voting, which like Ellen I've been to many of these meetings, never abstained, and I don't think I've ever voted no. And I would say I also agree with pretty much what everyone is saying, and that was really my difficulty in truly at this very moment saying yes or no, because I think all these things are true.

Still, my biggest challenge is really not -- I know we've approved drugs before; we don't

know exactly the mechanism. I can name several of those. But I'm still really struggling, especially that we're trying to really focus in on how drugs are best used for individuals that I just feel uncomfortable that we don't have more information on that.

I am truly grateful for Merck for looking at this type of therapy in individuals, especially a non-antimicrobial approach for someone with an infection. This is huge. It's wonderful. So I commend you on that, also for the FDA for being very mindful of the data and how the data was analyzed and how it was looked at.

So I do think eventually this will be a very, very promising drug. I think it is already. I just don't feel currently that I felt very strongly that it should be approved immediately.

DR. BADEN: Thank you. Dr. Follmann?

DR. FOLLMANN: I'm Dean Follmann. I voted no. I think I agree with a lot of what's been said so far. And I'd like to -- I thought the sponsor did a great job, and the FDA did a great job, and

the committee had a lot of great discussion also.

I was interested in a particular kind of analysis that I think will show benefit for both studies but it wasn't done, and so for that reason I voted no largely. I think if the analysis for the late diarrheal success endpoint I had talked about showed success, I probably would have voted yes.

The chair talked about some trepidation about changing endpoints going on in a study and that's something I agree with should be done with caution. But in my mind, in this setting, the primary endpoint, I thought, was deeply flawed as the FDA pointed out, where non-cures were called successes.

So that leaves open a new world where I think we have more license to use our thinking about what kind of endpoints we would view as convincing and we're not beholden to the thinking of other people. And so that's why I feel I have a little more license here to go with that endpoint.

So anyway, I did vote no. I probably would

have voted yes if I'd seen that analysis that I liked. As I mentioned earlier, I'm wary of the word recurrence because I think it means you've done a different study than you have done. I would prefer something that's more neutral that doesn't suggest that you're cured when you start this therapy because you're not.

The only other thing I would mention is there's been talk about risk and how the treatment might vary with baseline risk and, including the subgroup that had no risk factors at baseline, I imagine that's a pretty small group.

So if we're just seeing whether it's beneficial, if there's a benefit in that group, the study wasn't powered for that or anything, I think the proper thing to do would be to look at whether the treatment effect in that group differs from the other group, do formally a statistical test of interaction.

The statisticians will know what I'm talking about, but be prudent about carving out rare subgroups and saying, oh, it doesn't work here.

And that's all I have to say.

DR. BADEN: Thank you. Before we adjourn, are there any last comments from the FDA?

DR. NAMBIAR: Thank you, Dr. Baden. I just wanted to take this opportunity to extend my thanks and sincere appreciation to the committee members for all the advice provided and the discussions were very helpful. They're certainly very beneficial to us as we continue to evaluate the application further.

I also want to extend our thanks to the applicant for their presentations and all the hard work with this application. And I also want to thanks the speaker at the open public hearing for their comment. Wish you all safe travels. Thank you again.

Adjournment

DR. BADEN: We will now adjourn the meeting. Panel members, please take all your personal belongings with you as the room is cleaned. All material left on the table will be disposed of. Please remember to drop off your name badge at

registration so they may be recycled. Thank you all for your attendance and participation.

(Whereupon, at 2:30 p.m., the meeting was adjourned.)