FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Virtual Meeting

Tuesday, January 24, 2023

9:05 a.m. to 3:56 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Frimpong, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

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

Professor of Medicine, Harvard Medical School

Boston, Massachusetts

Michael D. Green, MD, MPH

Professor of Pediatrics, Surgery and Clinical & Translational Science
University of Pittsburgh School of Medicine
Division of Infectious Diseases
Director, Antimicrobial Stewardship & Infection Prevention
Co-Director, Transplant Infectious Diseases
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

W. David Hardy, MD, AAHIVS

Attending, Rand Schrader (HIV) Clinic
Adjunct Clinical Professor of Medicine
Division of Infectious Diseases
Keck School of Medicine of University of Southern California
Los Angeles, California

Sally A. Hunsberger, PhD

Mathematical Statistician

Biometrics Research Branch

National Institute of Allergy and Infectious Diseases (NIAID)

National Institutes of Health (NIH)

Rockville, Maryland

Richard A. Murphy, MD, MPH

Chief, Infectious Diseases

Veterans Affairs White River Junction Medical Center

Medicine Service

White River Junction, Vermont

Nimish Patel, PharmD, PhD

Professor of Clinical Pharmacy

Skaggs School of Pharmacy and Pharmaceutical Sciences

University of California San Diego, Division of Clinical Pharmacy

La Jolla, California

Federico Perez, MD, MS

Infectious Disease Physician

Louis Stokes Cleveland VA Medical Center

Associate Professor of Medicine

Case Western Reserve University

Cleveland, Ohio

George K. Siberry, MD, MPH

Medical Officer, Adult Clinical Branch

Office of HIV/AIDS

Bureau of Global Health

United States Agency for International Development

Washington, District of Columbia

Sankar Swaminathan, MD

Don Merrill Rees Presidential Endowed Chair

Professor and Chief

Division of Infectious Diseases

Department of Internal Medicine

University of Utah School of Medicine

Salt Lake City, Utah

Roblena E. Walker, PhD

(Consumer Representative)

Chief Executive Officer

EMAGAHA, INC.

Mableton, Georgia

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Richa S. Chandra, MD, MBA

(Industry Representative)

Clinical Development Head

Communicable Diseases

Global Health Development Unit

Novartis Pharmaceuticals

East Hanover, New Jersey

TEMPORARY MEMBERS (Voting)

John E. Bennett, MD

Senior Investigator, Laboratory of Clinical Immunology and Microbiology

NIAID, NIH

Bethesda, Maryland

Nina Clark, MD

Professor of Medicine

Division Director, Infectious Diseases

Co-Director, Infectious Disease & Immunology Research Institute

Loyola University Stritch School of Medicine

Maywood, Illinois

Arthur Flatau

(Patient Representative)

Austin, Texas

Joan F. Hilton, ScD, MPH

Professor, Biostatistics

Department of Epidemiology & Biostatistics

University of California

San Francisco, California

Stacey R. Rose, MD, FACP, FIDSA

Associate Director, Center for Professionalism

Associate Professor of Medicine, Infectious Diseases

Baylor College of Medicine

Houston, Texas

FDA PARTICIPANTS (Non-Voting)

John Farley, MD, MPH
Director
Office of Infectious Diseases (OID)
Office of New Drugs (OND), CDER, FDA

Peter Kim, MD, MS
Director
Division of Anti-Infectives (DAI)
OID, OND, CDER, FDA

Heidi Smith, MD, PhD
Clinical Team Leader
DAI, OID, OND, CDER, FDA

Shrimant Mishra, MD, MPH
Medical Officer
DAI, OID, OND, CDER, FDA

Jalal Sheikh, PhD
Clinical Microbiology Reviewer
DAI, OID, OND, CDER, FDA

Owen McMaster, PhD

Pharmacology-Toxicology Reviewer

Division of Pharmacology/Toxicology-Infectious Diseases

OID, OND, CDER, FDA

Xianbin Li, PhD

Statistical Reviewer

Division of Biometrics IV

Office of Biostatistics

Office of Translational Sciences (OTS)

CDER, FDA

Timothy Bensman, PharmD, PhD

Clinical Pharmacology Reviewer

Division of Infectious Disease Pharmacology

Office of Clinical Pharmacology

OTS, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:05 a.m.)

Call to Order

DR. BADEN: Good morning and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently being displayed.

My name is Lindsey Baden, and I will be chairing this meeting. I will now call the January 24, 2023 Antimicrobial Drugs Advisory Committee meeting to order. Dr. Joyce Frimpong is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. FRIMPONG: Good morning. My name is Joyce Frimpong, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Lindsey Baden?

DR. BADEN: I'm Dr. Lindsey Baden. I'm an infectious diseases specialist at Brigham and Women's Hospital in Boston, Dana-Farber Cancer Institute, and Harvard Medical School. Thank you.

DR. FRIMPONG: Dr. Richa Chandra?

DR. CHANDRA: Hello. I am Richa Chandra. I'm representing the pharma industry at this meeting, and I currently head anti-infective drug development at Novartis Pharmaceuticals. Thank you.

DR. FRIMPONG: Dr. Michael Green?

DR. GREEN: Good morning. This is Michael Green. I'm a pediatric infectious disease specialist and transplant infectious disease specialist at UPMC Children's Hospital Pittsburgh and the University of Pittsburgh School of Medicine. Thank you.

DR. FRIMPONG: Dr. W. David Hardy?

DR. HARDY: Good morning. This is Dr. Hardy. I'm an infectious disease physician, and I work in the LA County USC Rand Schrader Clinic in Los Angeles, and I'm an adjunct clinical

professor at the Keck School of Medicine at USC.

DR. FRIMPONG: Dr. Sally Hunsberger?

DR. HUNSBERGER: Yes. I'm Sally Hunsberger. I work at NIAID. I'm a biostatistician in the biostatistics research branch. Thank you.

DR. FRIMPONG: Dr. Richard Murphy?

(No response.)

DR. FRIMPONG: Dr. Richard Murphy?

(No response.)

DR. FRIMPONG: Dr. Richard Murphy?

(No response.)

DR. FRIMPONG: Dr. Nimish Patel?

DR. PATEL: Good morning. I'm Nimish Patel, and I'm a pharmacist and epidemiologist at Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California San Diego.

DR. FRIMPONG: Dr. Federico Perez?

DR. PEREZ: I am Federico Perez, infectious diseases physician at Case Western Reserve University and the Cleveland VA in Cleveland, Ohio.

DR. FRIMPONG: Dr. George Siberry?

DR. SIBERRY: Good morning. I'm George

Siberry, pediatric infectious disease physician and medical officer at the Office of HIV/AIDS at USAID. Thank you.

DR. FRIMPONG: Dr. Swaminathan?

DR. SWAMINATHAN: Yes. Hi. This is Sankar Swaminathan. I'm the chief of infectious diseases division at the University of Utah School of Medicine in Salt Lake City.

DR. FRIMPONG: Dr. Roblena Walker?

DR. WALKER: Good morning. I am Dr. Roblena Walker, consumer rep, as well as the chief executive officer for EMAGAHA, INC.

DR. FRIMPONG: Dr. John Bennett?

DR. BENNETT: Good morning. I'm John Bennett, an infectious disease physician at the National Institutes of Health in Bethesda, Maryland.

DR. FRIMPONG: Nina Clark?

DR. CLARK: Hi. This is Nina Clark. I'm an infectious diseases physician at Loyola University Medical Center and Stritch School of Medicine in Maywood, Illinois. Thanks.

DR. FRIMPONG: Arthur Flatau?

MR. FLATAU: Good morning. This is Arthur Flatau. I'm the patient representative from Austin, Texas.

DR. FRIMPONG: Dr. Joan Hilton?

DR. HILTON: Good morning. I'm Joan Hilton, professor of biostatistics at University of California San Francisco.

DR. FRIMPONG: Dr. Stacey Rose?

DR. ROSE: Good morning. I'm Stacey Rose. I'm an infectious disease physician at Baylor College of Medicine in Houston, Texas.

DR. FRIMPONG: For FDA participants, Dr. John Farley?

DR. FARLEY: Good morning. John Farley, director of the Office of Infectious Diseases, CDER, FDA.

DR. FRIMPONG: Dr. Peter Kim?

DR. KIM: Good morning. This is Peter Kim, director of Division of Anti-Infectives in the Office of Infectious Diseases, CDER, FDA.

DR. FRIMPONG: Dr. Heidi Smith?

(No response.)

DR. FRIMPONG: Dr. Heidi Smith?

DR. SMITH: Good morning, clinical team leader, Division of Anti-Infectives.

DR. FRIMPONG: Dr. Shrimant Mishra?

DR. MISHRA: Good morning. This is Dr. Shrimant Mishra, a clinical reviewer in the Division of Anti-Infectives.

DR. FRIMPONG: Dr. Jalal Sheikh?

DR. SHEIKH: Hi. This is Jalal Sheikh, clinical microbiology reviewer in the Division of Anti-Infectives.

DR. FRIMPONG: Dr. Owen McMaster?

DR. McMASTER: Good morning. This is Owen McMaster, pharmacology/toxicology reviewer in the Division of Pharmacology-Toxicology for Infectious Diseases at FDA.

DR. FRIMPONG: Dr. Xianbin Li?

DR. LI: Good morning. I'm Xianbin Li, a statistical reviewer for the Division of Biometrics IV, in the Office of Biostatistics.

DR. FRIMPONG: Dr. Timothy Bensman?

DR. BENSMAN: Good morning. I'm a clinical pharmacology reviewer in the Division of Infectious Disease Pharmacology, Office of Clinical Pharmacology, FDA.

DR. FRIMPONG: I would like to give a chance for Dr. Richard Murphy.

(No response.)

DR. FRIMPONG: Alright. Dr. Murphy still may not be connected.

Alright. Dr. Baden, I'll hand it off to you.

DR. BADEN: Thank you, Dr. Frimpong.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will only be allowed to speak into the record 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 advisory committees 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.

Dr. Frimpong will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. FRIMPONG: 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 this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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

which the government may expect from the employee.

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

Today's agenda involves a discussion of new drug application 217417, for rezafungin lyophilized powder for injection, submitted by Cidara Therapeutics, Incorporated, for treatment of candidemia and invasive candidiasis in adults.

This is a particular matters meeting during which specific matters related to Cidara's new drug application 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 the FDA's invited industry representative, we would like to disclose that Dr. Richa Chandra is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Chandra's role at this meeting is to represent industry in general and not any particular company. Dr. Chandra is employed by Novartis Pharmaceuticals Corporation.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs 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 proceed with FDA opening remarks from Dr. Peter Kim.

Dr. Kim?

FDA Opening Remarks - Peter Kim

DR. KIM: Thank you, Dr. Baden.

Good morning and welcome. My name is Peter Kim, director of the Division of Anti-Infectives in the Office of Infectious Diseases, Office of New Drugs, Center for Drug Evaluation and Research, FDA. I will be providing some introductory comments regarding the NDA, which we presented here at this advisory committee meeting, NDA 217417, for rezafungin.

The applicant, Cidara Therapeutics Incorporated, has submitted this NDA for rezafungin for injection. Rezafungin is a member of the echinocandin class of antifungals. The proposed indication is treatment of candidemia and invasive candidiasis in patients 18 years of age and older.

The proposed dosing regimen is once-weekly administration by IV infusion, with an initial 400-milligram loading dose, followed by 200 milligrams once weekly thereafter.

(Pause.)

DR. KIM: We appear to be having a slight delay on the slide change.

Okay, there we go. Thank you.

Rezafungin has been granted orphan drug, qualified infectious disease product, and fast-track designations for the treatment of candidemia/invasive candidiasis caused by susceptible *candida* species. The NDA contains clinical data from one adequate and well-controlled phase 3 noninferiority trial in adults with candidemia and invasive candidiasis; one exploratory dose-finding phase 2 study enrolling a similar population with candidemia/invasive candidiasis; and an integrated phase 2/3 safety database consisting of 151 patients with candidemia and invasive candidiasis receiving the proposed rezafungin clinical dosing regimen, as well as an

additional 81 patients with candidemia/invasive candidiasis receiving a higher rezafungin dose for up to 28 days.

Drugs to Treat Serious Diseases in Patients with an Unmet Need. For antibacterial drugs with the potential to treat serious infections in patients with few or no available treatment options, FDA may consider a more flexible development program. This is aligned with 21 CFR part 312, subpart E, which we will discuss further in the next slide. We believe it may be appropriate to utilize a flexible development program in the antifungal space for select products, but we seek the committee's input.

21 CFR part 312, subpart E notes that the Food and Drug Administration has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side

effects from products that treat life-threatening and severely debilitating illnesses than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.

For drugs to treat serious diseases in patients with an unmet need, there must be adequate data to demonstrate the drug is safe and effective and the statutory standards for approval are met. A drug's effectiveness must be established by substantial evidence defined as, "evidence consisting of adequate and well-controlled investigations, including clinical investigations."

This is generally interpreted as requiring two adequate and well-controlled trials, each convincing on its own. The Food and Drug Administration Modernization Act amended the provision to add that FDA may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence."

Adequate and Well-Controlled trials/ The purpose of these trials is to distinguish the effect of the drug from other influences such as spontaneous change, placebo effect, and observational biases. 21 CFR 314.126 describes the trial design elements intended to minimize bias and permit a valid comparison with a control to assess the drug's effect.

Characteristics of adequate and well controlled trials include a clear statement of objectives and proposed methods of analysis; permits valid comparison with a control to provide quantitative assessment of drug effect; the method of selecting patients provides assurance they have the disease being studied or evidence of susceptibility and exposure to the disease to be prevented; the method of assignment to study arm minimizes bias and is intended to ensure comparability between groups; measures to minimize bias on the part of the subject, observers, analysts of the trials; method of assessing treatment response is well defined and reliable;

and analysis of the results is adequate to assess the drug's effects, the analytic methods used, comparability of test and control groups, and effects of any interim analyses.

Now, for some considerations for flexible development programs, if the flexible development program involves smaller, shorter, or fewer clinical trials, there may be less clinical safety data, and nonclinical toxicology studies may play a greater role in safety evaluations. There may be smaller sample sizes and greater uncertainty in efficacy trials, leading to greater reliance on nonclinical data such as activity of the drug at therapeutically relevant exposures in vitro and in animal models.

Regarding labeling considerations, for anti-infective drugs developed under a flexible program, the labeling should include the known risks and benefits, as well as a description of the limitations of the data available to support approval. The indication should identify the approved patient population for which FDA has

determined the benefits of the drug outweigh the risks so that the healthcare community is informed of how to use the drug appropriately.

The following is example wording for an indication based on use of a flexible development program for patients with a serious infection in the setting of limited or no alternative treatment options, what we will refer to as a limited use indication. "Drug-X is indicated for the treatment of Infection-Y in patients who have limited or no alternative treatment options. Approval of this indication is based on limited clinical safety and efficacy data."

Now for an overview of the day, first we will hear presentations by the applicant, Cidara Therapeutics Incorporated, followed by presentations by FDA, including the efficacy assessment by Dr. Li; nonclinical safety assessment by Dr. McMaster; clinical safety assessment by Dr. Mishra; clinical microbiology assessment by Dr. Sheikh; clinical pharmacology assessment by Dr. Bensman; and summary comments by Dr. Smith.

This will be followed by lunch, the open public hearing, the charge to the committee, and committee discussion. That concludes the presentation. Thank you.

DR. BADEN: Thank you, Dr. Kim.

Before we move to the applicant presentation, I'd like Dr. Murphy to introduce himself now that we've overcome some technical challenges.

Dr. Murphy?

DR. MURPHY: Thanks, Dr. Baden.

Richard Murphy, White River Junction, VA Medical Center and Dartmouth School of Medicine; infectious disease physician. Thanks.

DR. BADEN: Thank you.

Now we will move to the applicant's presentation.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to

understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, 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 such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentation from Cidara Therapeutics.

Dr. Waldo?

Applicant Presentation - Carol Waldo

DR. WALDO: Good morning. I am Carol Waldo,

senior vice president of Regulatory Affairs and Quality at Cidara Therapeutics. I want to thank the chair, members of the panel, and the FDA for the opportunity to present our data, which support rezafungin for the treatment of candidemia and invasive candidiasis.

Rezafungin is an antifungal and part of the well-established echinocandin class with over 20 years of use. The active ingredient, rezafungin acetate, is derived from anidulafungin and retains the safety profile of the class, while improving the molecular stability and pharmacokinetics profile.

These structural adaptations differentiate rezafungin from other echinocandins by allowing for once-weekly dosing with high front-load plasma drug exposures. According to guidelines established by IDSA, echinocandins are a first-line standard-of-care treatment for *candida* infections due to the improved survival benefit observed in anidulafungin clinical trials.

Let me briefly review the regulatory

history. Rezafungin was developed under FDA's guidance for flexible development of antibacterial therapies for patients with unmet medical need in the treatment of serious disease. In offering this pathway, the agency applies statutory standards with flexibility while preserving appropriate guarantees for safety and effectiveness in order to address the urgent need for new drugs. In the setting of unmet medical need, a safety database should have at least 300 subjects exposed to the proposed dose or higher.

A single phase 3 trial with a larger noninferiority margin can be acceptable in the context of a limited use indication. Clinical data should be supported by a robust nonclinical program, demonstrating in vitro activity with MIC data from a range of pathogens, efficacy in animal models, PK/PD relationships using modern pharmacometrics, and nonclinical safety studies.

Rezafungin addresses unmet medical need in a serious illness for patients with limited treatment options. Rezafungin efficacy and safety

demonstrated comparability to caspofungin. PK/PD data show that exposure levels achieve concentration-dependent killing and target attainment with activity against *candida* isolates with reduced susceptibility. There are no clinically meaningful drug-drug interactions.

Importantly, once-weekly IV dosing allows for IV catheter management, including earlier removal, and allows for outpatient treatment for patients unable to maintain IV access and for whom oral therapy may be inappropriate. The FDA has designated rezafungin as a qualified infectious disease product. This designation was created to spur the development of drugs for serious or life-threatening infections.

Rezafungin also has fast-track and orphan status. Beginning with a pre-IND meeting in 2015, we met with FDA over 15 times to discuss rezafungin development. The phase 2 study, STRIVE, initiated in 2016 and enrolled 207 patients over three years at 68 clinical sites in 10 countries. In mid-2018, we aligned with FDA on the phase 3 pivotal study

design and NI margin. The phase 3 ReSTORE study enrolled 199 patients over three years and 137 clinical sites in 18 countries. In a pre-NDA interaction early last year, the division agreed it was reasonable to proceed with an NDA based on STRIVE and ReSTORE for a treatment indication.

The safety and efficacy of rezafungin continues to be assessed. A small phase 3 treatment study is ongoing in China. Phase 3 ReSPECT for the prophylaxis of *candida* infections is also ongoing, and Cidara's expanded access program provides rezafungin to patients in the community in need of a treatment option.

We have conducted two global randomized clinical studies comparing rezafungin to caspofungin in patients with candidemia and/or invasive candidiasis. Over 300 subjects were enrolled at the proposed dose or higher across the clinical development program.

Consistent with a flexible development pathway, a single phase 3 study with a data-driven NI margin of 20 percent, comparing rezafungin to

caspofungin, supports a limited use indication for treatment. The primary endpoint of all-cause mortality at day 30 is a first for an echinocandins development program and was supported by a secondary endpoint of global response at day 14. It is important to note that global response, which directly assesses the drug's ability to treat a *candida* infection, was the primary endpoint supporting approval for the first three echinocandins. Phase 2 STRIVE provides supportive data.

In a flexible development program, the importance of nonclinical data is elevated in its role supporting a streamlined clinical program. Our robust microbiology package includes susceptibility testing against over 7,000 isolates, representing over 20 *candida* species, most of which are MIC data through the SENTRY International Antifungal Surveillance program.

Rezafungin's mechanism of action was thoroughly characterized, as well as its potential for and mechanisms of resistance. In vivo efficacy

was assessed in a variety of animal models. Our comprehensive nonclinical safety package includes toxicology studies up to 6 months duration, which is 6 times longer than the maximum duration studied in our clinical program for a treatment indication.

Notably, because rezafungin dosing is not limited by liver toxicity, we were able to study exposure levels significantly higher and for a longer duration compared to studies conducted for other echinocandin programs. We also conducted a full battery of genotoxicity, reproductive developmental, local tolerance, and photo toxicity studies.

The rezafungin development program outcomes support an overall positive benefit-risk assessment. The pivotal phase 3 study is supported by a phase 2 study. Phase 3 ReSTORE achieved noninferiority for the primary endpoint of all-cause mortality. Both studies demonstrated comparable rates of global cure and overall success. Integrated safety data show that rezafungin's safety profile is comparable to the

class.

Rezafungin demonstrates broad coverage against *candida* species with high-target attainment, including for strains that are typically less susceptible or resistant, such as *C. glabrata* and *C. auris*. Rezafungin also demonstrated faster clearance of candidemia in both clinical studies. The PK/PD profile demonstrates extensive tissue penetration, a lack of drug-drug interactions, and supports once-weekly dosing. Robust nonclinical data further characterizes and supports the clinical safety and efficacy profile of rezafungin.

In our presentation today, we will show that the totality of nonclinical and clinical data supports treatment of patients with candidemia and invasive candidiasis as a limited use indication. We acknowledge that this is a change from that proposed in the briefing book. We do support a limited use indication.

There are areas of unmet need where patients could benefit from rezafungin; for example,

patients who need echinocandins, but are unable to receive a once-daily IV dosing; patients who are unable to receive oral azole therapy, a common step-down treatment; patients infected with *candida* pathogens with reduced susceptibility to current treatment options; patients with deep tissue infections; or patients who have failed other antifungal therapies.

With this information in mind, here is our agenda for the remainder of the presentation. Dr. Vazquez will describe the unmet medical need; Dr. Flanagan will review the pharmacology and microbiology; Dr. Das will review efficacy data and Dr. Sandison will review the safety data; and finally, Dr. Clancy will conclude with his clinical perspective on why rezafungin would be a valuable addition for patients with these difficult-to-treat infections. We also have additional responders with us today to answer your questions. All outside experts have been compensated for their time.

Thank you. I'll now turn the presentation

to Dr. Vazquez.

Applicant Presentation - Jose Vazquez

DR. VAZQUEZ: Good morning. Thank you, Ms. Waldo.

I'm Jose Vazquez, Chief of Infectious Disease and Professor of Medicine at the Medical College of Georgia at Augusta University. I've been treating patients with candidemia and invasive candidiasis for decades. I've also been involved in clinical mycology for more than 30 years, evaluating all antifungals approved, going back to 1991 with fluconazole. From my experience, I can tell you that there is an urgent need for a new antifungal to treat these serious and often fatal infections.

Let me start with a brief background. Candidemia is a bloodstream infection, but in at least a third of cases, it also involves deep or visceral tissue. We can also see invasive candidiasis without candidemia. It's sometimes difficult to identify the exact location of the infection, however, if the tissue is involved in

addition to the bloodstream, it requires a longer course of therapy.

The risk factors for candidemia and invasive candidiasis are quite common. Infections are often caused by the presence of central venous catheters, use a broad-spectrum of antimicrobials, or major surgeries. Patients who become infected are usually hospitalized and quite ill by the time they are diagnosed with this opportunistic infection. It can be diagnosed with solid-organ tumors, hematologic malignancies, and uncontrolled diabetes.

Candidemia and invasive candidiasis are serious and life-threatening infections. In fact, they are considered to be among the most serious fungal infections in the United States. According to the CDC, the average rate of new infection is approximately 9 per 100,000 people, and there are approximately 25,000 cases documented every year.

Candida species were the second leading pathogens among bloodstream infections, according to a 2015 CDC survey of acute care hospitals in the

United States. Furthermore, *candida* species and invasive candidiasis are on the CDC threat list. These infections are associated with high morbidity and mortality. Patients with *candida* infections can suffer from a wide range of symptoms, including fever and septic shock, in addition to their underlying condition. Candidemia and invasive candidiasis are also associated with a prolonged length of hospital stay, adding an estimated 3 to 13 days of hospitalization after diagnosis, demonstrating crude mortality rates of over 40 percent.

In addition, mortality rates also vary by *candida* species. In fact, *Candida krusei* and *Candida glabrata* have the highest attributable deaths and are also some of the most antifungal resistant species that we encounter.

It is very important that we treat these infections early and with appropriate therapy. It is also important to control the source of underlying infection. However, in many cases, the source of infection is the catheter, which is used

to administer the therapy. Removing the catheter as part of the source control will therefore challenge the use of daily IV therapy.

As recommended by the Infectious Disease Society of America, echinocandins are currently the first-line antifungal agents for the treatment of candidemia and invasive candidiasis, except when infecting the central nervous system, the eyes, or the urinary tract. Echinocandins such as anidulafungin, caspofungin, and micafungin have a well-established efficacy and safety profile, and these antifungals have documented fungicidal activity.

In addition, echinocandins have improved outcomes, including survival benefits, as demonstrated in the clinical trial comparing anidulafungin versus fluconazole, which was published in the New England Journal of Medicine by Annette Reboli, et al., in 2007. This pivotal study laid the foundation for echinocandins to be considered the standard of care. In fact, several studies indicate improved outcome for echinocandins

versus other antifungals.

Azoles are generally considered step-down therapy. The rising threat of resistance challenges current treatment options. Rates of azole resistance are increasing, especially among the five non-albican species, as seen here, specifically in *Candida glabrata* and *Candida auris*. *Candida krusei* is seen primarily in hematology-oncology patients and has some intrinsic multidrug resistance as well. In fact, azole antifungal resistance across the different species, in comparison to *Candida albicans*, has contributed to the recommendation of initiating echinocandins as frontline therapy.

The increasing azole resistance across the common *candida* species also limits physicians' ability to choose an appropriate oral step-down therapy. This also increases the need for outpatient echinocandins. Though less prevalent than azole resistance, the increasing echinocandin resistance seen in *Candida glabrata* and *Candida auris* underscore the need for additional therapies

in these critically ill patients.

While echinocandins are the current first-line therapy, treatment gaps continue to exist, particularly for those patients with the highest unmet needs. Not all patients can be appropriately treated with the current echinocandins. All of the first generation echinocandins were developed more than 20 years, and modern pharmacometrics were not widely used, leaving gaps in standard dosing and therapeutic exposure. Today we have specific concerns about underdosing in some populations such as the critically ill.

Additionally, a recent study examined target attainment of echinocandins to investigate the likelihood of achieving clinical success. It determined that while wild-type organisms may be covered with the current dosing, *candida* isolates with elevated MIC values are unlikely to attain therapeutic exposure. This is especially concerning, given the increasing rates of reduced susceptibility to all antifungals that have been

observed across the different *candida* species. There are also concerns regarding the ability of the marketed echinocandins to reach deep tissue infections.

These observations suggest the need for higher therapeutic exposure to the echinocandins. Moreover, intravenous catheters are required for current echinocandins, but are a common source of candidemia. Thus, the need for daily IV therapy can undermine a physician's ability to clear the infection and may result in persisted candidemia. Furthermore, when echinocandins are required for outpatients, this necessitates PICC line placement and daily healthcare touch points that increase the risk of medical complications and the acquisition of healthcare associated infections.

In summary, candidemia and invasive candidiasis are serious life-threatening infections. While echinocandins are the current first-line therapy, gaps in treatment continue to exist, particularly for those with the highest unmet need. We need antifungal agents that treat

deep tissue infections. We need an antifungal agent that acts quickly at well-studied doses without the associated side effects or drug-drug interactions observed with current treatment options.

The emerging threats of *Candida auris* and azole-resistant *Candida glabrata* have increased the urgent need for new therapeutic solutions; yet, new antifungal agents have not been approved for these infections since 2007. It's time.

Thank you. I will now turn the presentation over to Dr. Flanagan.

Applicant Presentation - Shawn Flanagan

DR. FLANAGAN: Thank you, Dr. Vazquez.

I'm Shawn Flanagan, vice president, Clinical Pharmacology and Early Development at Cidara Therapeutics. I am pleased to briefly share some important aspects of rezafungin's pharmacology and microbiology.

Rezafungin was discovered in an attempt to improve the pharmacokinetic properties of currently available echinocandins. The addition of the

choline moiety on the ring, shown on the left, yielded improved chemical and biological properties. Increased stability was the key. Other echinocandins undergo non-enzymatic degradation to an open ring form with hepatotoxic potential. Rezafungin avoids this.

Stability in terms of both reduced metabolism and degradation, relative to other echinocandins, resulted in a long half-life, which allows for once-weekly dosing in the clinic. This infrequent dosing schedule, where an entire week of drug can be given with each dose, generates a front-loaded exposure, allowing its therapeutic benefits to be maximized, such as improved cidality and tissue distribution.

It is widely accepted from a PK/PD standpoint that drugs that exhibit concentration-dependent killing are most effective when higher dose levels are administered infrequently. This has been demonstrated for other anti-infectives, both antibacterial and antifungals, and has been shown to be the case for

rezafungin as well.

As was seen with other echinocandins, both AUC over MIC and Cmax over MIC were predictive of efficacy with rezafungin in dose fractionation studies designed primarily by Paul Ambrose at ICPD. Neutropenic mice infected with *Candida albicans* were evaluated in a 7-day study. Each dose level was divided into daily, twice-weekly, or once-weekly fractions, providing different shapes of the plasma concentration time profiles.

Shown here at the mid-dose level of 2 milligram per kilogram, the single-dose regimen in green provides high front-loaded drug exposure early in therapy, with smaller peaks shown in yellow for twice weekly, or red for daily dosing, which had the lowest peak concentrations. All regimens provided approximately the same weekly AUC for each dose level. The shape of the AUC impacted efficacy.

Here we show the log change in colony-forming units with more than 2 log kill seen, where the entire weekly dose was given as a

single dose as compared to net fungal stasis when divided twice weekly, and no effect when further divided into daily doses. Front-loaded dosing, which optimizes both AUC and Cmax, was shown to have improved efficacy over multiple lower doses. Fortunately, due to its long half-life, rezafungin can be administered at its optimal strategy that maximizes both AUC and Cmax.

Shown here are the mean rezafungin function concentration time profiles in healthy subjects for a 400-milligram first dose, followed by a 200-milligram dose a week later. The higher first dose allows for rapid distribution in the tissues and steady-state extent of exposure without having to wait for accumulation with time. The AUC is relatively unchanged from the first 400-milligram dose to each subsequent week of 200 milligram once weekly.

A few key results from our clinical pharmacology findings are highlighted here. Rezafungin has no potential for clinically meaningful drug-drug interactions. Further, we do

not anticipate that any dose adjustments will be needed, as rezafungin's pharmacokinetics are consistent across subgroups. Rezafungin does not prolong or shorten the QT interval at doses up to the maximum tested dose of 1400 milligrams.

Rezafungin protein binding is high like other echinocandins. The overall volume of distribution is about 40 liters, which is similar to anidulafungin and is about twice that of other echinocandins. Rezafungin, like other echinocandins, distributes rapidly in the tissues, with greater amounts in highly perfused tissues relative to plasma, except the brain. Echinocandins are relatively large polar molecules that do not readily pass the blood-brain barrier.

We need to interpret distribution data cautiously. Concentrations in bulk tissue do not reveal where within the tissue that drug is found. As most distribution studies are conducted using radiolabeled drugs, results may be misleading for compounds that are metabolized or degraded into inactive forms, and then there's the unfortunate

example of daptomycin that reached the lung, only to be rendered inactive by pulmonary surfactant.

What can be done to improve our understanding? Well, in developing our approach, we worked with researchers who had developed quantitative imaging methodologies to assess concentrations in an abdominal infection model. What the research team at Rutgers under Dr. Perlin, as well as Dr. Clancy from University of Pittsburgh, who is speaking with us today, found is that rezafungin function could reach infection sites better than micafungin.

The study compared a single dose of micafungin of 5 milligrams per kilogram, approximating its human exposure, to 2-dose levels of rezafungin in a mouse intra-abdominal abscess model. At the same 5-milligram-per-kilogram dose level, increased concentrations of rezafungin could be noted in lesion and surrounding liver, especially at 24 hours post-dose.

Due to its enhanced stability, we know that we can give higher doses less frequently than

micafungin, and as expected, at the dose of 20 milligrams per kilogram, markedly higher concentrations could be seen in the liver and abscess. The 400-milligram rezafungin weekly dose in the clinic is 4 times the 100-milligram daily dose of micafungin, so this is a relevant multiple for comparison. A more accurate adjustment, based on AUC exposure, would equate to a dose of around about 1400 milligrams per kilogram in mice.

Continuing on, for subsequent days of the study on this slide, tissue levels at 48 and 72 hours in the abscess and surrounding liver tissue show that the single dose of 20-milligram-per-kilogram rezafungin penetrated the abscess better at higher more sustained levels than continued daily dosing of micafungin. Again, note that the human equivalent dose of rezafungin is about two-thirds of this dose, but even accounting for this, rezafungin levels in lesions would still be expected to exceed the mutant prevention concentrations against *Candida albicans* and *Candida glabrata*, indicated by the dotted line on

this plot. This study demonstrated increased penetration to the site of infection of intact active drug.

In vitro, rezafungin has a similar spectrum of activity and potency against *candida* species as other echinocandins, particularly anidulafungin, as was demonstrated in MIC values generated against over 5,000 isolates collected in the 2014-2021 SENTRY annual international surveillance. Forty-three of these strains possessed *fks* hotspot mutations, and rezafungin activity was in line with that of anidulafungin and micafungin and slightly improved over caspofungin.

Resistance mechanisms impacting susceptibility to existing echinocandins also affect rezafungin. However, based on rezafungin's front-loaded exposure in vivo, it may be able to provide therapeutic benefit against a subset of mutant strains with elevated echinocandin MIC values. This can perhaps best be illustrated by showing some of our PK/PD target attainment results.

As background, PK/PD target attainment analyses are widely accepted as predictive for anti-infectives, where activity is directed at the infective organism. The target is from efficacy studies in neutropenic mouse model of disseminated candidiasis. Echinocandins were largely developed prior to these methodologies, but they have all been studied now, and many of these studies were conducted at the University of Wisconsin by Dr. Andes and colleagues.

Rezafungin was independently studied by Dr. Andes for several *candida* species, using strains that had been characterized for other echinocandins and selected across a range of rezafungin MICs, including some *fks* mutants. Rezafungin PK/PD modeling has been used to set doses for phase 2 and confirm that targets in patients could be reached prior to phase 3. PK/PD results are part of the overall breakpoint determination, along with clinical outcomes and the epidemiological MIC data.

Rezafungin has a high probability of target

attainment by design. Shown here is the distribution of rezafungin *candida* MICs from the surveillance results described a couple slides earlier for *albicans* in gray and *glabrata* in red. These two species account for over 60 percent of all candidemia and invasive candidiasis, and in the case of *Candida glabrata*, represents a species with a higher predisposition to develop antifungal resistance.

Monte Carlo simulation was used to generate tens of thousands of clinical exposures, reflecting the variability from the population PK model. Plotted here is the probability of achieving the nonclinical PK/PD efficacy targets required for stasis, shown in the solid lines, or 1 log reduction in fungal burden, shown in the dotted lines, in the clinical population relative to the MIC of the infecting organisms.

As the MICs increase, a high probability of target attainment is maintained by rezafungin for multiple dilutions past the observed MIC 90s. This level of target attainment is not common for

echinocandins for severe *candida* infections, and especially for those caused by *glabrata*. Following review of rezafungin's nonclinical and phase 1/2 clinical data, the CLSI subcommittee on antifungal susceptibility tests proposed and approved a provisional susceptible breakpoint of 0.5 microgram per mL for Candida glabrata. This value is 4-to-8 fold higher than susceptible breakpoint values for the approved echinocandins, reflective of rezafungin's higher probability of target attainment for this species.

In summary, pharmacology studies demonstrated that the structural modifications yield improved chemical and biological properties that differentiate rezafungin from the other echinocandins. Although in vitro activity is similar to other echinocandins, rezafungin's long half-life, allowing for infrequent dosing with front-loaded exposure and extensive distribution and lesion penetration, could reduce the potential for resistance development; and importantly, rezafungin maintains a high probability of target

attainment across a wide range of MICs, suggesting the potential to treat those *candida* infections from less susceptible strains.

Thank you. Dr. Das will now review the clinical efficacy data.

Applicant Presentation - Anita Das

DR. DAS: Thank you, Dr. Flanagan.

I'm Anita Das, consultant statistician to Cidara. I served as the primary statistician for both STRIVE and ReSTORE studies. I will share the efficacy data showing that rezafungin is noninferior to caspofungin for all-cause mortality, and that it consistently demonstrated comparable clinical and mycological outcomes in each of the two global randomized clinical studies.

Let me begin with the STRIVE study design. STRIVE was a phase 2, multicenter, randomized, double-blind study that assessed the appropriate dosing regimen of rezafungin and provides supportive of efficacy. Patients 18 years and older with established mycological diagnosis of candidemia and/or invasive candidiasis were

enrolled. Patients also had to have at least one attributable systemic sign a baseline.

Key exclusion criteria are shown here. These criteria were implemented because of poor echinocandin penetration in the central nervous system, prolonged dosing required for treatment, or safety considerations. The study was conducted in three parts, part A, B1, and B2. In part A, patients were randomized 1 to 1 to 1 to IV rezafungin 400/400 milligrams, IV rezafungin 400/200 milligrams, or IV caspofungin.

In part B1, patients were randomized 2 to 1 to IV rezafungin 400/400 or IV caspofungin. After the review of unblinded part A data, part B1 was closed, and part B2 was started with patients randomized 2 to 1 to IV rezafungin 400/200 or IV caspofungin. Since STRIVE provides supportive rather than confirmatory data, results presented here are pooled across part A and B.

Rezafungin was given once on days 1 and 8, with optional dosing on days 15 and 22, and caspofungin was given daily. To maintain the

blind, patients randomized to rezafungin also received daily saline placebo. After at least 3 days of treatment, patients in the caspofungin group could be switched to oral fluconazole, and to maintain the blind, rezafungin patients could be switched to oral placebo. Patients were followed through day 59.

The primary efficacy endpoint was overall success at day 14 in the microbiologic intent to treat or mITT population. Overall success was defined as mycological success plus resolution of attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline. The mITT population was defined as all patients who received at least one dose of study drug and had documented *candida* infection based on a blood culture or a specimen from another sterile site within 96 hours prior to randomization. Secondary endpoints included mycological response, and the investigator's assessment of clinical response at each visit. All-cause mortality at day 30 was an additional endpoint.

Patients were on average 60 years of age, mostly male, and white. The majority of patients were enrolled in Europe and the United States. About three-quarters of patients were diagnosed with candidemia only, and 25 percent with invasive candidiasis. The majority of patients with invasive candidiasis had intra-abdominal or peritoneal disease.

Patients enrolled in this study were ill with background comorbidities, as reflected by the APACHE II score and the high percentage in the ICU at the time of dosing. The median APACHE II score was similar between treatment groups, and 20 percent of rezafungin and 15 percent of caspofungin patients had an APACHE II score of 20 or greater. All patients were hospitalized at the time of enrollment, and more than one-third were in the ICU at the first dose of study drug. Moderate to severe renal impairment was seen in 22 percent of the rezafungin 400/400 group and about 38 percent in both the rezafungin 400/200 and caspofungin groups.

Turning now to the efficacy results, the two rezafungin treatment arms achieved overall success rates of 61 percent and 76 percent at day 14, compared with 67 percent of patients on caspofungin. Secondary endpoints aligned with these findings as well. We also assessed 30-day all-cause mortality and considered patients with an unknown survival status as deceased. The all-cause mortality rate at day 30 in the mITT population was approximately 24 percent in the rezafungin 400/400 group, 9 percent in the rezafungin 400/200 group, and 16 percent in the caspofungin group. Based on the target attainment data and positive and similar efficacy data of the two rezafungin doses, 400/200 was selected as the dose for the phase 3 study.

Turning now to the ReSTORE study, ReSTORE was a pivotal phase 3, global, randomized, double-blind study. Enrollment and exclusion criteria were similar to the STRIVE study with one notable difference; patients with severe neutropenia were eligible in ReSTORE.

Patients were randomized 1 to 1 to

IV rezafungin 400/200 or IV caspofungin. Patients randomized to rezafungin were dosed at days 1 and 8, with optional dosing at days 15 and 22. Caspofungin patients were dosed daily. After at least 3 days of treatment, patients randomized to caspofungin could switch to oral fluconazole. To maintain the blind, patients randomized to rezafungin were given daily IV saline, and after 3 days of IV treatment could receive oral placebo. This is the same dosing schedule that was followed in the STRIVE study. Patients were followed through day 59.

The analysis population for the efficacy endpoints was the modified intent to treat. This was defined as all randomized patients who received at least one dose of study drug and had a documented *candida* infection from a blood culture, or a positive culture from another normally sterile site within 96 hours before randomization. The primary endpoint was all-cause mortality at day 30. This was defined as patients who died on or before day 30 or with unknown survival status. Patients

who discontinued the study prior to day 30 were followed for survival status.

Global cure at day 14, as assessed by an independent data review committee, was considered a key secondary endpoint. Global cure is a composite endpoint requiring clinical cure and mycological eradication, and for those invasive candidiasis patients diagnosed by radiology, radiologic cure.

Other secondary endpoints included mycological eradication at days 5 and 14 and global cure and mycological eradication at other visits. Mycological eradication required clearance of the baseline positive blood culture or positive sterile site culture, with no change of antifungal therapy for the treatment of candidemia and/or invasive candidiasis. These secondary endpoints are clinically relevant, as they provide a direct measurement of drug activity.

The sample size of 184 patients in the mITT population provided 90 percent power to show noninferiority using a 20 percent noninferiority margin, which was deemed acceptable to support a

limited use indication. The sample size calculation assumed a 20 percent all-cause mortality rate in both treatment groups and a one-sided alpha of 0.025.

Now let's look at the results of the ReSTORE study. The patient population was similar to that in the STRIVE study. Patients were around 60 years of age and mostly male. The majority of patients were white; however, we also had a large Asian enrollment because the study was conducted in several sites in the Asia-Pacific region. About 70 percent of patients were diagnosed with candidemia and 30 percent with invasive candidiasis. The majority of invasive candidiasis patients had intra-abdominal or peritoneal infection. Thirty-nine percent of patients in both groups had moderate to severe renal impairment.

As with STRIVE, the patients enrolled in this study had significant underlying conditions. All patients were hospitalized at study enrollment, however, fewer rezafungin patients were in the ICU at the time of dosing or were on mechanical

ventilation, 31 percent and 17 percent, compared with caspofungin patients at 39 percent and 30 percent. Thirteen percent of rezafungin patients and 18 percent of caspofungin patients had an APACHE II score of greater than or equal to 20. Baseline pathogens were comparable between groups. The most common pathogens were *Candida albicans*, *glabrata*, *tropicalis*, and *parapsilosis*; 99.5 percent of pathogens were susceptible to rezafungin and caspofungin.

Turning now to the primary endpoint results, rezafungin was shown to be noninferior to caspofungin for the primary endpoint of all-cause mortality at day 30 in the mITT population. Twenty-four percent of rezafungin patients were either known to be deceased or had an unknown survival status versus 21 percent of caspofungin patients, with a treatment difference of 2.4 percent and upper limit of the 95 percent confidence interval for the difference of 14.4, which is below the noninferiority margin of 20 percent. Unknown survival status was low,

3 percent in both treatment groups.

Moving to secondary endpoints, an analysis of the key secondary endpoint, global response, provides supportive evidence of efficacy. At day 14, about 60 percent of patients in both groups achieved global cure. Rates of indeterminate outcome were relatively high, at 11 percent and 9 percent in the rezafungin and caspofungin groups. The primary reason for an indeterminate outcome was lost to follow-up or withdrawal of consent. Global cure rates were similar between treatment groups at each of the other study visits.

Now looking at other secondary endpoints, the rate of mycological eradication at days 5 and 14 was also high and comparable between groups. At day 5, 69 percent of patients in the rezafungin group and 62 percent in the caspofungin group achieved mycological eradication, and at day 14, 68 percent and 66 percent of patients achieved eradication.

This slide shows global cure and mycological eradication at day 14 for the four most common

candida species. Cure and eradication rates are similar between treatment groups for patients with *Candida albicans*. For *Candida glabrata, parapsilosis,* and *tropicalis*, the global cure and mycological eradication rates range from 67 to 83 percent in the rezafungin group compared with 56 to 82 percent in the caspofungin group.

For analyses of subgroups, data for the STRIVE and ReSTORE studies were pooled. Here I show subgroup analyses of all-cause mortality. All-cause mortality differed between the treatment groups with respect to age and renal impairment. In North/South America, which primarily represents the United States, as only one patient was enrolled from South America, all-cause mortality was 14 percent in the rezafungin group and 9 percent in the caspofungin group.

All-cause mortality was higher in patients with candidemia only compared with invasive candidiasis, but the rates were similar between treatment groups. In patients with a modified APACHE II score greater than or equal to 20,

all-cause mortality was lower in the rezafungin group, although the number of patients in this group are small.

We also conducted an exploratory analysis of time to negative blood culture in the subgroup of patients diagnosed with a positive blood culture before randomization. At 24 hours, the probability of a negative blood culture in the rezafungin group is 0.6 compared with 0.49 in the caspofungin group. Looking at the Kaplan-Meier curves, we see that the curve separate at 24 hours and the difference between groups is maintained. These data suggest rezafungin may provide earlier clearance of the *candida* pathogen, consistent with front-loading dosing.

In conclusion, both the STRIVE and ReSTORE studies demonstrated that rezafungin was efficacious in the treatment of candidemia and invasive candidiasis. Specifically, in ReSTORE, rezafungin was noninferior to caspofungin for the primary efficacy outcome of 30-day all-cause mortality. The upper bound of the 95 percent

confidence interval was 14.4, which is below the noninferiority margin of 20 percent. Rates of global cure at day 14, a key secondary endpoint, were high and comparable between treatment groups.

Similar outcome rates were also shown between the treatment groups for the secondary endpoints of global cure at other visits and mycological eradication in ReSTORE, as well as the endpoints of overall cure, all-cause mortality, and mycological eradication in STRIVE. These secondary and exploratory endpoints provide supportive evidence of the efficacy of rezafungin.

Thank you. I'd now like to turn the presentation to Dr. Sandison to review the safety data.

Applicant Presentation - Taylor Sandison

DR. SANDISON: Thank you, Dr. Das.

I'm Taylor Sandison, chief medical officer at Cidara. I'm pleased to be here today to present the safety data that demonstrate that rezafungin's safety profile aligns with the well-characterized class of echinocandins and with the severity of the

underlying disease in the patients enrolled in our program.

Let me start by defining our key safety population. Across our clinical development program, a total of 312 individuals received rezafungin at the proposed dose of 400 milligrams, followed by 200 milligrams or higher, administered for at least 2 weeks, meeting FDA's minimum recommended safety database for a flexible development program.

Given the similar study designs and enrolled patients, and in agreement with the agency, we pooled our phase 2 and 3 data to better inform the safety profile. The safety data for rezafungin we will present today will focus on the 53 patients from STRIVE and 98 patients from ReSTORE who received the 400/200 dose. These 151 patients dosed with rezafungin and the 166 caspofungin patients will make up the populations for our pooled safety analyses.

Among the pooled safety population, the median duration of therapy, IV and oral combined in

both treatment groups, was 14 days with a range of 1 to 28 days. About 32 percent of patients in either group received oral therapy after their initial IV treatment. As expected in the seriously ill hospitalized population, nearly all patients in both groups experienced at least one adverse event.

Severe adverse events, those grade 3 or greater, and serious adverse events occurred in approximately half of patients in each group. Few patients had adverse events that led to interruption of drug, and 9 percent of patients in both groups experienced adverse events leading to discontinuation. Similar percentages of patients died in each treatment group.

Turning now to the most common adverse events, here are the common adverse events reported in at least 5 percent of treated patients. For brevity, we have not included adverse events that occurred in at least 5 percent of patients in the caspofungin arm, but occurred less frequently in the rezafungin arm.

In general, these are the adverse events

we'd expect to find in a hospitalized population. There were some imbalances in a couple of preferred terms, but there is no clear pathophysiologic reason that rezafungin or caspofungin would cause most of these events. As expected, electrolyte disturbance was the most commonly observed adverse event among both echinocandins, and these are typically easily managed.

Turning to severe adverse events, the most common severe adverse event in both groups was septic shock. Except for pneumonia, percentages of patients with severe adverse events were similar between treatment groups. In terms of pneumonia, about half of these adverse events occurred after completion of study drug in both study arms.

The same risk factors that predispose patients to candidemia and invasive candidiasis also predispose patients to development of other infections such as pneumonia. The underlying comorbidities for these patients included COVID, influenza, leukemia, transplantation, and other types of immunosuppression. Fifty-five percent of

patients on rezafungin and 49 percent on caspofungin reported a serious adverse event. As expected, the most common serious adverse event was septic shock, occurring in 6 percent of patients in both treatment groups.

For completeness, here's a list of serious adverse events by system organ class. You can see most are balanced between groups and limited to few patients. There are also imbalances in both arms across various system organ classes with no predominating patterns.

Adverse events leading to discontinuation of study drug occurred in 9 percent of patients in both treatment groups. Most adverse events were reported by single patients across preferred terms. In the rezafungin-treated group, only infusion-related reaction was reported in 2 patients. In the caspofungin group, chorioretinitis and endophthalmitis occurred in 2 patients each. Although not fully captured on the slide, four of the adverse events leading to discontinuation of study drug for rezafungin were

temporarily associated with placebo administration. These were infusion-related reaction, wheezing, adverse drug reaction, and urticaria.

The incidence of serious adverse events resulting in death was similar in both treatment groups, 23 percent of patients in the rezafungin group and 24 percent of patients in the caspofungin group. Shown here are adverse events leading to deaths occurring in more than one patient. The most common adverse event leading to death was septic shock, followed by multi-organ dysfunction syndrome and sepsis. All of these occurred in a similar percentage across groups. The mortality rate observed here is not unusual for this vulnerable population and is similar to what has been reported in previous clinical trials for this indication.

Let me now turn to adverse events of special interest, which included photosensitivity; neurological events, including tremor and neuropathy; and infusion-related reactions. These events were chosen as they are either known class

effects or a potential risk was identified through earlier nonclinical or phase 1 clinical trials. We did not see any events of photosensitivity in the phase 2 or phase 3 studies, so this will not be addressed further in subsequent slides.

Before looking at the neurologic adverse events of special interest, I'm presenting the most relevant findings from our toxicology studies. This overall interpretation of the results is based on independent outside expert review across all studies. There were no toxicological findings in the 4-week cynomolgus monkey toxicology study at exposures of up to 9-fold above the clinical exposure at our proposed dose. The doses were increased in the 13-week studies in an effort to evaluate toxic effects of the drug, as is the goal of toxicology testing.

Animals in the 60 milligrams per kilogram high-dose group exhibited tremors, hunched posture, and poor conditioning after several weeks of dosing, and were determined to have exceeded the maximum tolerated dose by the study director, and

the dose was reduced to 45 milligrams per kilogram for the duration of the study. Animals in the 60/45-milligram-per-kilogram dose group had exposures of approximately 15-fold above clinical exposures at the end of this study.

Because of the clinical observations noted in the high-dose group, we added detailed neurobehavioral assessments and comprehensive neuropathological evaluations to this in subsequent toxicology studies. At tolerated doses several fold above the proposed clinical exposure, there were no organ toxicities. These exposures are at or above the exposures where liver toxicity was observed for the other echinocandins in subchronic toxicology studies.

Dose groups of 30 milligrams per kilogram, which was about 9-fold the clinical exposure and lower, were well tolerated with no adverse effects. Non-adverse Schwann cell phospholipidosis, confirmed by electron microscopy, was noted at all rezafungin doses. Of note, phospholipidosis is known to be caused by a variety of approved drugs,

including other antimicrobials, and according to FDA, has an unknown clinical significance. Non-adverse Schwann cell hyperplasia was also noted at higher doses. There was no definitive evidence of rezafungin axonal/nerve fiber degeneration or myelinopathy up to the highest tolerated dose, which was 9-fold higher than the clinical exposure.

To support the prophylaxis program, a 6-month non-human primate study, which included blinded neurobehavioral observations, was also performed. This is a 6-fold longer duration than our clinical treatment trials. In this study, non-adverse Schwann cell phospholipidosis and, at high dose, hyperplasia were again noted. These findings show evidence of reversal with recovery.

There was no definitive evidence of rezafungin-related tremors or neurodegenerative changes following a detailed evaluation of the neurobehavior and central nervous system and peripheral nervous system pathology in the study. The overall nonclinical conclusions were that the risk of neurological toxicity with rezafungin is

low. Nevertheless, this was considered to be a potential adverse event of special interest and evaluated clinically in our phase 2 and 3 treatment studies.

Moving to the clinical findings, tremors are known adverse effects for many antifungal agents, including caspofungin and anidulafungin. In our trials, 4 patients treated with rezafungin experienced tremor. All four of these events were of mild severity and resolved. An independent neurologist assessed these 4 adverse events. Two were considered not related to drug due to other underlying causes. One event was deemed possibly related. This patient was already out of the hospital and experienced fluid shifts due to diuretic use. This may have contributed to unreported electrolyte abnormalities. Finally, one event of tremor was considered related to study drug through hypokalemia and resolved after replacement of potassium.

Given the known effects with other echinocandins and these clinical findings, we

expect that tremor will be a labeled event for rezafungin, and we will continue to monitor for tremor in our ongoing clinical trials.

Due to earlier findings in animal studies, we looked further into events of neuropathy in the clinical studies. There was a low incidence of neuropathy in both treatment groups, with two patients in the rezafungin group and four in the caspofungin group. As with tremor, we are continuing to monitor for neuropathy in our ongoing clinical trials.

Infusion-related reactions are a known adverse effect of echinocandins that are associated with the rate of drug infusion. If these events occur, they can be easily managed by reducing the infusion rate or stopping the infusion altogether. Overall, infusion-related reactions occurred in four rezafungin-treated patients and one caspofungin treated patient. The infusion-related hypersensitivity reaction was reported as rash and significant wheezing during the study drug infusion in a patient while receiving saline placebo on

day 3. The adverse drug reaction was a rash that occurred during saline placebo infusion in the same patient on day 4. One additional rezafungin patient with infusion-related reaction experienced the event during a day 3 placebo infusion.

If only adverse events occurring while active study drug is being infused are considered, then the pooled groups -- 2 patients in the rezafungin group and 1 patient in the caspofungin group -- had infusion reactions that can be appropriately attributed to an active study treatment.

In summary, the safety profile of rezafungin appears to be similar to that of caspofungin and aligns with the well-characterized class of echinocandins. Nearly all patients experienced an adverse event, however, the prevalence of overall adverse events, as well as the incidence of serious adverse events, are reflective of the severity of the disease, which is expected due to the underlying comorbidities in this ill hospitalized population.

There was a similar incidence of deaths between the treatment groups which aligns with background rates in this population. Adverse events of special interest were generally rare across both studies, and finally, few neurological adverse events were reported, and they were mostly mild, transient, and reversible.

Thank you. I'll now turn the presentation to Dr. Clancy to share his clinical perspective.

Applicant Presentation - Cornelius Clancy

DR. CLANCY: Well, thank you, Dr. Sandison.

I'm Neil Clancy. I'm professor of medicine and associate chief of the Division of Infectious Diseases at the University of Pittsburgh. I've been researching and treating patients with fungal infections for more than 25 years, with a particular focus on infections in immunosuppressed and other vulnerable populations, and on infections by *candida* species. I'm very pleased to be here today to share my clinical perspective on the data just presented, given the morbidity and mortality associated with candidemia and invasive

candidiasis.

As you heard today, candidemia and invasive candidiasis are serious medical conditions with high mortality. The CDC have identified *candida* species as the second leading cause of bloodstream infections, and the World Health Organization has identified *candida* as a global threat that can only be met by continued medical advances, including the development of new treatments.

Echinocandins are our primary first-line treatment for candidiasis. We know and trust in their efficacy and safety profiles. But we also know that current options given once daily can be improved upon, so let's look at how rezafungin may help to fulfill our unmet needs.

The pharmacokinetic profile of rezafungin includes a long half life which allows for once-weekly administration. This potentially reduces the need for inpatient management and indwelling catheters, thereby reducing potential infusion-related complications. The front-loaded pharmacokinetic profile provides potential for

faster microbial clearance and allows for sustained therapeutic exposures of rezafungin. Thereby, it maximizes anti-*candida* activity over time while minimizing the potential for underdosing, which is a concern in critically ill patients and other difficult-to-treat cohorts.

Nonclinical animal models have shown rezafungin's ability to penetrate deep tissue to a greater extent than micafungin and to attain higher tissue concentrations. Based on comprehensive in vitro and clinical studies, rezafungin has no or low risk of meaningful drug-drug interactions, which is particularly important for patients at risk for these events such as transplant recipients.

Turning to potential microbiologic advantages, rezafungin's improved target attainment has potential to better manage infections caused by resistant pathogens. These would include infections by *Candida glabrata* and other species that may carry *fks* mutations that confer elevated echinocandin MIC values. Rezafungin has achieved

multiple successful clinical outcomes against *fks* mutant *Candida glabrata* infections, and it has demonstrated efficacy against multidrug resistant *Candida auris* in vitro and in animal models. At present, rezafungin is the only antifungal with the CLSI provisional breakpoint against *Candida auris*.

Rezafungin is also associated with earlier mycologic clearance of blood cultures, which may be associated with more rapid resolution of infections. And finally, there's less potential for resistance development with rezafungin due to its high initial drug exposure and less potential for underdosing. These pharmacologic and microbiologic benefits of rezafungin may afford advantages to physicians treating patients with these highly complex and often fatal infections.

Moving on to safety considerations, echinocandins have a well-established safety profile and, in general, are well tolerated. The safety data observed for rezafungin aligned with my experience with the currently approved echinocandins. In clinical studies, adverse events

were mostly mild and transient, resolving while patients remained on treatment. Serious adverse events and adverse events leading to death occurred at comparable rates between groups in the studies; and again, they were the types of events one can expect in this very sick, mostly hospitalized population. A limited number of neurological adverse events were observed and were mostly mild and reversible.

So in my opinion, the clinical benefits and potential pharmacologic and microbiologic benefits of rezafungin outweigh potential risks in patient populations with limited treatment options for candidiasis.

Now let me share two published cases from the rezafungin expanded access program, which highlight clinical settings in which the drug afforded advantages over existing treatments. In the first case I'll describe, rezafungin was used to treat a patient with multidrug resistant *Candida glabrata* vascular graft infection. Over 3 years prior to receiving rezafungin, the patient had

exhausted treatment options within all antifungal drug classes, including micafungin, multiple azoles, and amphotericin B.

The patient required continuous antifungal treatment due to the presence of the infected graft and no coils in the sternum, which provided foci for ongoing multidrug resistant *Candida glabrata* infection. This *Candida glabrata* had an *fks* D666Y mutation, conferring resistance to all approved echinocandins. Rezafungin was requested, and it was subsequently used for more than 2 years. There were no significant adverse events, including no neurologic adverse events, and the infection was successfully suppressed.

Another expanded access case involved a liver transplant recipient with fluconazole-resistant *Candida krusei* peritonitis and multiple abdominal abscesses. These infections were first treated with micafungin, which failed as evident by the presence of more abscesses. The physician requested rezafungin because of its potential for improved distribution and higher

levels at the site of infection. The patient cleared the peritonitis and abdominal abscesses after 12 weeks of rezafungin therapy dosed once weekly in an outpatient transplant clinic. Notably, the patient tolerated the medication with no neurologic or rezafungin-related adverse events.

Other cases from the expanded access program also demonstrate rezafungin's utility, and they attest to the real-world challenges and unmet needs facing clinicians and patients in the care of invasive candidiasis.

Let me now share two recent clinical scenarios where rezafungin, if available, may have been useful in my own clinical practice. The first patient is a 32-year-old man with active injection drug use and a past history of *Candida glabrata* and *Staphylococcus aureus* vertebral osteomyelitis. Two years prior to his present admission, he received 8 weeks of micafungin followed by fluconazole. He is now readmitted with azole-resistant *Candida glabrata* bloodstream infection and native aortic valve endocarditis. He's being cared for by

a multidisciplinary endovascular infection team comprised of infectious diseases clinicians, cardiothoracic surgeons, and other healthcare professionals.

He had been treated with micafungin, and he underwent aortic valve replacement. Echinocandin treatment was planned for at least 6 weeks postoperatively, and the team is currently trying to place this gentleman in an outpatient program that can address his drug use while treating his infection. This scenario highlights the need for an active antifungal that does not require a PICC line or port placement. This case is an example of a patient who could derive clinical benefit from having once-weekly rezafungin as a treatment option.

The second patient from my clinical practice is a 54-year-old woman with multiple sclerosis, who was admitted to the hospital twice previously with pneumonia. She was then readmitted with a third episode of pneumonia and developed a *Candida glabrata* bloodstream infection while

receiving antibiotics through a central venous catheter. Treatment was instituted with micafungin. However, due to concerns of poor vascular access, her central line was initially retained following the start of treatment.

Unfortunately, she continued to have positive blood cultures for *Candida glabrata*, so her central line was ultimately removed, and after the central line was removed, the blood culture became negative. So this patient will need at least 14 days of echinocandin treatment, but difficulties in establishing and maintaining IV access limit the ability to treat daily with echinocandins.

The case illustrates the paradox that we face, where the treatment guidelines recommend both early removal of the catheter and continued IV treatment. Rezafungin would offer a treatment option that would preclude the need for daily IV micafungin dosing and for central venous access procedures.

So to conclude our presentation, rezafungin

is part of a class of drugs that is well characterized and well understood. Rezafungin approval would offer patients and physicians a meaningful option in difficult-to-treat infections. Efficacy and safety were consistently shown across two randomized clinical studies compared to another echinocandin. At minimum, comparability was demonstrated between the agents. Microbiology and pharmacokinetic data support possible advantages of rezafungin, including no identified drug-drug interactions and once-weekly administration that allows for flexible catheter management. The data demonstrate a favorable benefit-risk balance for patients with limited treatment options.

In summary, rezafungin offers healthcare providers a treatment option for candidemia and invasive candidiasis that can address the unique clinical, microbiologic, and/or pharmacologic needs of our patients. As highlighted by the cases I presented, I am confident that clinicians will know the patients and clinical scenarios in which rezafungin would be used.

Thank you. I'd now like to return the presentation to Dr. Sandison to take your questions.

Clarifying Questions

DR. BADEN: I would like to thank the applicant for a terrific presentation, concisely shared with us, despite this amount of data.

We will now take clarifying questions for Cidara Therapeutics. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak, and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of follow-up question with, "This is all for my questions," so we can move to the next panel member.

So I would like to invite my panel members

to raise their hands, and we will start the questions to the applicant. If we are unable to complete all the questions by 11:00, we will continue questions to the applicant after the open public session, after lunch; so we will get to all the questions.

Let me start with Dr. Bennett.

(No response.)

DR. BADEN: We do not hear you, Dr. Bennett.

(No response.)

DR. BADEN: While Dr. Bennett's mic is being corrected, I will ask Dr. Green to ask his question.

Dr. Bennett, please do fix your mic, and then we will get to your question.

DR. GREEN: Thank you, Dr. Baden. This is Dr. Green. My question I believe is probably best aimed at Dr. Flanagan.

During Dr. Clancy's clinical perspective presentation, he spoke to us about data about the role of rezafungin with *Candida auris*, but I did not see during your presentation any of the

in vitro or animal data of this new product against *C. auris*, and I wonder if you have that data on a slide that you can share with the committee. Thank you very much.

DR. SANDISON: This is Taylor Sandison from Cidara. I'm going to ask Dr. Flanagan to come and discuss this.

DR. FLANAGAN: Actually, in the briefing book, we do have a slide on target attainment for several different *candida* species, including *Candida auris*, and maybe we can start by showing that one. I'm sorry. I don't have the number from the briefing book.

(Pause.)

DR. FLANAGAN: But, actually, we have in vitro and in vivo data. BF-16 I believe is the briefing book slide. It may have several -- yes, that's it. And it's probably hard to focus down in here, but the *Candida auris* data is in the middle-right panel, and that's results from Dave Andes' lab with, I believe, four different isolates of *Candida auris*, Cleveland Clinic, I believe, as

well as from Houston as well, that showed comparable efficacy to other echinocandins or better efficacy in those studies.

Can I see NC-12, please?

Here's one such study where we looked at rezafungin again in a couple different doses relative to, in this case, amphotericin B versus vehicle, and saw significantly greater efficacy in this kidney model against *Candida auris*.

DR. BADEN: Dr. Green, if you have any follow-up, let me know; otherwise, you can take down down your hand.

Dr. Bennett, is your mic line working?

(No response.)

DR. BADEN: If not, Dr. Clark?

DR. CLARK: Thanks. This is Nina Clark, and this is also for Dr. Flanagan.

In the briefing booklet, it was describing synergistic activity with rezafungin and other agents, in the antimicrobial interaction studies, and I was just wondering if you could tell us which agents it was synergistic with and for which fungi,

if you have that. Thank you.

DR. SANDISON: This is Taylor Sandison. I'm going to ask Dr. Locke to come and answer that question, please.

DR. LOCKE: Hi. This is Jeff Locke, Cidara. Therapeutics. As part of our NDA package, we performed a very comprehensive in vitro synergy antagonism study with rezafungin in combination with representatives of all approved antifungal classes, as well as a variety of antibacterials against relevant fungi and bacteria, and no antagonism was observed in any of those combinations.

If you'd like to see specific examples where synergies was observed, we could get you a slide after the break.

DR. CLARK: Yes. Thank you.

DR. BADEN: Thank you.

DR. SANDISON: And that was our answer.

DR. BADEN: Excuse me?

DR. SANDISON: I just said that was our answer.

DR. BADEN: Okay. Yes. Thank you.

Dr. Murphy?

DR. MURPHY: Hi. This is a question about the noninferiority margin that was chosen. The noninferiority margin generally represents how much worse the experimental arm can be and still be considered similar, and you chose 20 percent for the phase 3 study.

Does this reflect a problem with accruing patients for this type of study or was it thought that this was the noninferiority margin that was most appropriate for this type of study? Thanks.

DR. SANDISON: I'm going to ask Dr. Das to answer that question.

DR. DAS: Anita Das, Cidara. Yes. We chose a 20 percent noninferiority margin based off of an extensive literature review that came down to 16 studies of no treatment or inadequate treatment, and for the control arm, we looked at the four previous clinical trials of echinocandins. But for the M2, which is what you're referring to, 20 percent was chosen for several reasons. One

would be the potential benefits of rezafungin and also the feasibility was an issue, but primarily we were using it based off of a limited use indication.

DR. BADEN: Dr. Murphy, do you need to follow up?

(No response.)

DR. BADEN: If not, then Dr. Swaminathan. And somebody is typing with the mic open. Please mute your line if you're not talking.

Dr. Swaminathan?

(No response.)

DR. BADEN: We cannot hear you, Dr. Swaminathan, if you're talking.

(No response.)

DR. BADEN: I will let you fix your line, Dr. Swaminathan. In the meantime, Dr. Patel.

DR. PATEL: Good morning. This is Nimish Patel from the University of California San Diego. I think it may be helpful [indiscernible].

DR. BADEN: Dr. Patel, can you talk closer to your mic? It's a little hard to hear you.

DR. PATEL: Okay. Is this any better?

DR. BADEN: Yes, it is. Thank you.

DR. PATEL: Okay. I think it may be helpful [indiscernible], if possible. But my question [indiscernible - audio muffled].

Were there any investigations between the exposure and outcome for the efficacy analyses? And for the 4 patients that experienced tremor, were these individuals of low or normal body size, and that could potentially explain a higher exposure in these individuals? I know that one of them, based on the briefing document [indiscernible]. I think that's another population that had high exposure. I was wondering if the sponsor could clarify that.

DR. SANDISON: This is Taylor Sandison, and we had a little difficulty hearing the question, but it sounded like you were asking about the relationship of body size to safety outcomes, or potential exposure to safety outcomes.

DR. PATEL: This is correct.

DR. SANDISON: Okay. I'm going to ask

Dr. Flanagan to answer that question.

DR. FLANAGAN: Thank you. Shawn Flanagan.

I'd first like to show the briefing book table so the rest of the members of the panel can see what you're referring to.

Can I have BF-13, please? This is now in patients from the population PK modeling of all of the phase 2 and 3 data, and as you pointed out, measures of body size -- be it body surface area, or weight, or BMI -- were all important determinants of the PK variability. But as you can see from the bottom of this plot, the overall distribution between subjects with either very large body size or very small body size is relatively small and over the entire patient population, which represented very diverse subjects and had no real physiological or clinical significant changes. These exposures are all within plus or minus 30 percent, so not a large change.

In terms of the question as to whether or not the PK exposures were predictive of either good

or bad effects with the drug, I know you were looking at the safety events. In terms of safety, we looked at serious adverse events versus measures of rezafungin exposure from the Bayesian output from the population PK model data of the phase 2 and phase 3 subjects, and we found that there was no correlation between key exposure parameters AUC and Cmax with safety, and I have a similar slide for efficacy I can show you if wanted to see that.

DR. SANDISON: This is Taylor Sandison from Cidara. I'd also like to add, in terms of the -- I think there was a question about the relationship potentially of exposure to tremor. We also had 81 subjects in our phase 2 study that were treated at 400 once weekly, the higher dose, and there were no events of tremor in that arm. If you were interested, we can get you the weights of the individual patients with tremor after the break.

DR. BADEN: Dr. Patel, any additional comments?

DR. PATEL: That will be all. Thank you.

DR. BADEN: Thank you.

Mr. Flatau?

MR. FLATAU: Hi. This is Arthur Flatau, and I had a question about the deep tissue penetration. Dr. Clancy presented one patient from the expanded access program, but I'm wondering if there was any other clinical evidence that there's clinically meaningful better treatment from rezafungin compared to the other drugs.

DR. SANDISON: We have some clinical data. Let me try to pull it up here in a second. EF-9, please.

I'm looking at some of the tissue distribution and invasive candidiasis data from the phase 2 and phase 3 study. You can see here what the numbers look like for rezafungin and for caspofungin in terms of overall success, which was the primary outcome for STRIVE, global cure for ReSTORE, and then all-cause mortality that was pooled.

I would, however, say that while we have seen, in addition to the expanded access, the patient that improved with this, there was a small

increase in improvement maybe for rezafungin here, but that these subjects aren't necessarily representative of the patients that might benefit from rezafungin in the community. So I'd like to ask Dr. Clancy to come up and respond in terms of how the drug might be used in the patients that might benefit.

DR. CLANCY: Yes. I think the best clinical data for getting to where the infection is and clearing the infection is the clearance of blood culture data, where it's clearly shorter time to clearance of blood culture. You never know with bloodstream infection, in most cases, who has end-organ involvement or not, but about half of patients do have some sort of end-organ involvement from the old autopsy literature, so that faster blood culture clearance includes patients who both would and would not have end-organ infection as part of their bloodstream infection.

I'll also point out that in the clinical trial, patients like I presented would actually be excluded from the clinical trial because of

exclusion criteria, and those types of patients in particular are ones who you might believe that rezafungin would offer greatest utility: complicated abdominal surgeries; prior antifungal exposure; high levels of immunosuppression; extremely sick and complicated patients, and those are people who don't get enrolled in clinical trials of this sort.

DR. BADEN: Thank you, Dr. Clancy.

MR. FLATAU: Can I follow up?

DR. BADEN: Yes.

MR. FLATAU: You mentioned the faster clearance a little bit from subject, but I think in the briefing literature it was about 4 hours faster.

Is that clinically meaningful?

DR. SANDISON: This is Taylor Sandison again. I'd like Dr. Clancy to discuss that, please.

DR. CLANCY: Well, to me as a clinician, it's clinically meaningful. It's shorter duration of disease and more rapid time to microbiologic

clearance. Whether in the end it'll translate to survival benefit in these patients who have multiple comorbidities and complicated underlying diseases is something that we don't know and have to track once the drug is out there. But I view it as a clinically relevant endpoint; that, after all, what we're striving for when we're treating these patients, first and foremost, is getting rid of the bug at the site of infection.

MR. FLATAU: Okay. Thank you. That's all.

DR. BADEN: Any additional follow-up, Mr. Flatau?

MR. FLATAU: No, that's it. Thank you.

DR. BADEN: I have a clarifying question to the Cidara team. Was the 24-hour microbiologic clearance a prespecified endpoint in the protocol and the analysis?

DR. SANDISON: Yes, it was.

DR. BADEN: At 24 hours.

DR. SANDISON: Yes, it was.

DR. BADEN: Okay. Thank you.

It is now 11:00. I am aware that there are

at least a half dozen more panel members who have questions. Please do not forget your questions. I am aware of your interest in asking them. We will return to asking questions of the applicant after the open public session.

We will now take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with other panel members during the break. We will resume at 11:10 Eastern time. Thank you. We are now on break.

(Whereupon, at 11:00 a.m., a recess was taken.)

DR. BADEN: Thank you all. We will now resume.

We'll now proceed with the FDA presentations, starting with Dr. Li.

Dr. Li, please?

FDA Presentation - Xianbin Li

DR. LI: Good morning. I will be presenting the efficacy assessment. I'm Xianbin Li, a statistical reviewer from the Division of

Biometrics IV in the Office of Biostatistics. In order to seek approval of rezafungin for the treatment of candidemia/invasive candidiasis in adult patients, the applicant submitted an NDA with efficacy data from two trials, one phase 2 exploratory dose-finding trial, STRIVE, and one phase 3 noninferiority trial, ReSTORE. Both trials were multicenter, randomized, double-blind, and active controlled.

In the presentation, I will first discuss the phase 2 trial. The primary objectives of the trial include assessing safety and tolerability of rezafungin in the safety population and the overall success of study treatment at day 14 in the microbiological ITT population or mITT for short.

The study had multiple parts. Initially, in part A, subjects were randomized 1 to 1 to 1 to high-dose rezafungin, low-dose rezafungin, or caspofungin. Prior to initiation of the phase 3 trial, in order to increase numbers for the overall safety database, part B was added via two protocol amendments using a 2 to 1 randomization ratio to

rezafungin, the high-dose group at first based on the interim analysis of part A, later changed to the low-dose group after the full analysis of part A or the caspofungin group.

Two unblinded efficacy reviews were conducted. One review was for selected efficacy and safety data for the first 70 subjects enrolled in part A to confirm it would be safe to continue to part B without interruption. The second was a review of all parameters for all 107 subjects enrolled in part A. Based on this review, it was determined that the dose regimen for the phase 3 trial would be the low-dose regimen. Therefore, the rezafungin group in part B was also changed to the low-dose regimen. Multiplicity was not considered or addressed for this trial with a descriptive interpretation.

The primary efficacy outcome was overall response at day 14. Overall response was defined as resolution of signs of the disease and mycological eradication. As mentioned before, analyses were descriptive. Only an exact 2-sided

95 percent confidence interval with an estimated overall success rate in each treatment group was planned. Mortality through day 30 and a follow-up visit was an additional efficacy endpoint, as well as several other secondary efficacy endpoints.

This table shows a summary of day 30 all-cause mortality for the overall study, including part A/B together. The highest and lowest mortality rates were observed in the high-dose and the low-dose rezafungin groups, respectively. The difference in mortality between the low-dose rezafungin group and the caspofungin group was minus 7 percent, with a 95 percent confidence interval of minus 21.2 percent to 7.3 percent.

Mycological eradication overall and by study part is shown in this table. At day 5 for the overall study, the low-dose rezafungin group showed a numerically higher rate than the high-dose rezafungin group although both groups had received a single 400-milligram dose at this time point, and no difference would be expected to be seen from a

clinical perspective. At day 14, the low-dose rezafungin group had numerically the highest rate among the three groups.

In conclusion, the phase 2 trial provided initial evidence, suggesting efficacy to allow for further study of rezafungin in a pivotal study. But given the lack of inferential testing, the multiple amendments and interim analyses with no multiplicity adjustment, and the differences observed between the two rezafungin groups at day 5 when both had received the same dose, caution is needed when interpreting the results from this exploratory study.

Now I'm going to discuss the phase 3 trial. This diagram shows the design of the trial. Rectangles show rezafungin treatment with solid ones for required treatment and slashed ones for optional extended treatment circles show study visits. There were four planned study visits after day 1.

Subjects were randomized in a 1 to 1 ratio to either rezafungin or caspofungin. The

rezafungin dose was the same as the low-dose rezafungin group in the phase 2 trial. Randomization was stratified by diagnosis and APACHE II score, and the absolute neutrophil count. The primary efficacy analysis population was mITT population, which included randomized subjects who received any amount of study drug and had a documented *candida* infection from a baseline specimen.

The primary efficacy endpoint for day 30 all-cause mortality was assessed using a 20 percent noninferiority margin. Secondary efficacy endpoints included global response, mycological response, clinical response, and a radiological response. Global response was based on the last three endpoints.

This trial was a noninferiority trial. A justification of the noninferiority margin for day 30 all-cause mortality was conducted by the applicant and the FDA. The FDA determined that the treatment effect of an echinocandin-based regimen, M1, was at least 31 percent. M1 was derived using

an estimate of the day 30 all-cause mortality rate for no treatment or inadequate treatment determined based on a literature search that identified clinical studies or other historical evidence on the effect of no treatment or inadequate treatment in patients with candidemia and/or invasive candidiasis and the estimate of the day 30 all-cause mortality rate for treatment with an echinocandin-based regimen determined, based on four contemporary clinical trials that were conducted in support of the approvals of caspofungin, anidulafungin, and micafungin.

Noting the importance of preserving the treatment effect for an endpoint of all-cause mortality from a clinical perspective, a 10 percent noninferiority margin was recommended for a pivotal phase 3 trial, however, a wider noninferiority margin of 20 percent could be considered to obtain a limited use indication. As previously mentioned, the applicant chose to design this trial based on a 20 percent margin.

Now I'm going to talk about subject

disposition. 199 subjects were enrolled, randomized, and included in the ITT population; 93 and 94 subjects were included in the mITT population for the two treatment groups. About 40 percent of the subjects discontinued from the study mainly due to death, and 34 percent and 28 percent of subjects discontinued treatment from the two treatment groups, respectively, mainly due to death and adverse events.

As shown in this table, the mean age was about 60 years old. About 62 percent of the subjects were male. About 70 percent of the subjects had candidemia only at baseline. Overall, the two treatment groups were comparable in baseline demographics, clinical characteristics, risk factors, treatment compliance, and concomitant medication use.

Now I'm going to discuss the analysis of the results of the primary efficacy endpoint, day 30 all-cause mortality. The mortality rate in the rezafungin group was numerically higher, with a difference of 2.4 percent and a 95 percent

confidence interval of minus 9.7 percent to 14.4 percent, meeting the 20 percent noninferiority margin as indicated by the upper limit of the confidence interval.

As seen in this table, the global response cure rate increased from day 5 to day 14, and then dropped slightly over time for both treatment groups. The cure rate between the two treatment groups was comparable with all confidence intervals including zero. For mycological response, the two treatment groups were comparable. A numerically mycological eradication was observed for rezafungin compared to caspofungin at day 5, although this difference decreased at later time points.

For clinical response, the two treatment groups were also comparable, interesting to note that for clinical response at day 5, rezafungin had a numerically lower clinical cure rate than caspofungin, which is the opposite trend from that seen for mycological response.

In conclusion, the phase 3 trial demonstrated noninferiority of rezafungin to

caspofungin with respect to day 30 all-cause mortality with a 20 percent noninferiority margin. It provided evidence for efficacy to support indication with a limited use statement.

Now that I have reviewed the two trials individually, I'm going to discuss pooling of the phase 2 and 3 trials. Prior to this meeting, the applicant did not propose a limited use indication. So while our concerns regarding pooled analysis may not be as much of an issue since the applicant has now proposed a limited use indication, I will still discuss them for completeness.

It is acknowledged that the results of the phase 2 and 3 studies pooled showed that the upper bound of the 95 percent confidence interval for the difference in day 30 all-cause mortality was 7.7 percent. However, due to the issues with the phase 2 trials mentioned before and to be expanded on in the next slide, we do not consider that the pooled results are sufficient for claiming a 10 percent noninferiority margin, the margin recommended by the FDA for approval of full

indication, was met.

We are concerned that there was the potential for inflating the estimate treatment effect with the pooling of the studies. The primary assessment was not prespecified to be based on the integrated results [inaudible - audio gap] -- for supportive [inaudible] --

DR. BADEN: We are not hearing our FDA colleague.

(Pause.)

DR. FRIMPONG: Good morning. We're currently having some technical difficulties. Please bear with us for a minute as we try to resolve the technical issues.

(Pause.)

DR. LI: Hello? Can you hear me?

MALE VOICE: Yes, we can hear you.

(Pause.)

MALE VOICE: Do you guys hear us in the room?

DR. BADEN: I just heard somebody ask if they could be heard; so yes, you can be heard.

MALE VOICE: Awesome. Thank you.

DR. LI: Can you hear me now? This is Dr. Li.

DR. BADEN: Yes, Dr. Li. Yes, we hear you.

DR. LI: Thank you.

We will start from slide 21. Is that ok?

DR. BADEN: Yes, please.

DR. LI: Okay.

We are concerned that there was a potential for inflating the estimated treatment effect with the pooling of the studies. The primary assessment was not prespecified to be based on the integrated results, and there's a need for supportive evidence given a single phase 3 trial.

There was also a potential for the phase 2 trial to overestimate the efficacy of low-dose rezafungin selected for further development because the observed differences between the rezafungin group were possibly due to chance. This may be supported by the observed differences specifically for mycological eradication between the rezafungin groups seen at day 5 when no difference would be

expected from the pharmacological and clinical perspective, which may have led to the lower day 30 all-cause mortality results for the low-dose rezafungin group by chance.

From the FDA's adaptive design guidance for trials intended to provide substantial evidence of effectiveness, statistical hypothesis testing methods should account for the adaptive selection of a best dose or doses from among multiple doses evaluated in the trial. Therefore, we do not agree with pooling the phase 2 and 3 trials for the primary assessment of efficacy in support of the indication claim, as we believe the pooled results potentially provide an overestimate rather than a more precise estimate of the treatment effect.

The primary assessment of efficacy of this NDA is based on the results of the phase 3 trial, with supportive evidence provided by the phase 2 trial. The phase 3 trial was designed with a 20 percent noninferiority margin, which was determined to be an acceptable margin from a clinical standpoint to support the limited use

indication. The study met the 20 percent noninferiority margin, but it did not meet a 10 percent noninferiority margin. Thank you very much for your attention.

FDA Presentation - Owen McMaster

DR. McMASTER: Good morning. My name is Owen McMaster. I'm a pharmacology/toxicology reviewer in the Division of Pharmacology-Toxicology for Infectious Diseases, and I'll be describing the tremors that have been observed in the nonclinical studies of rezafungin.

Rezafungin is an echinocandin synthesized from anidulafungin. Anidulafungin is known to be associated with tremors in pediatric patients. Another echinocandin, Cancidas, also lists tremors among the adverse reactions, and so it's not unexpected that rezafungin would be associated with tremors. Rezafungin is a cationic amphiphilic drug, a class of drugs known to be associated with phospholipidosis, which appears as concentrically lamellated accumulations of lipid-rich materials inside some cells. Phospholipidosis is considered

to be non-adverse.

Rezafungin is eliminated slowly from the plasma with an elimination half-life of 39 to 59 hours. When radiolabeled rezafungin was administered to monkeys, the highest accumulation was observed in the spinal nerve dorsal root ganglia. Elimination of radioactivity from tissues was very slow, and the elimination half-life of the spinal nerve was estimated to be 874 hours. Monkey studies up to 4 weeks duration did not provide clear evidence of rezafungin-related tremors, however, tremors were reported in several longer duration in monkey studies of rezafungin. I will discuss the findings of three studies of rezafungin in which tremors were observed.

NC-118 was a study of rezafungin in juvenile monkeys dosed every 3 days for 3 months, followed by a 4-week recovery period. NC-154 was a follow-up study which also dosed juvenile monkeys every 3 days for 3 months, but which only used female animals, had a longer reversibility period, and collected more detailed neurological data.

NC-190 was a longer 6-month study which used adult monkeys and evaluated the effects of weekly rezafungin as opposed to every 3 days in the previous studies, and had an even longer 52-week recovery period.

The term "tremor" is used to describe involuntary twitching or trembling of muscles, characterized by small contractions of localized areas of the body which may be continuous or intermittent. Intention tremors are simply tremors which are more pronounced when movements are initiated.

The applicant does not consider tremors to be adverse. Prior to today's meeting, the applicant proposed that the prescribing information should include the statement shown on this slide, indicating that no adverse finding occurred in the 13-week monkey study.

NC-118 used 2-to-4-year-old monkeys, which are clearly included in juveniles since sexual maturity is reached at 4 years of age for the female and 6 years of age for the male. Monkeys

were dosed once every 3 days at 0, 3, 10, 30, or 60 milligrams per kilogram for 3 months, and then followed by a 4-week recovery period. The highest, 60-milligram-per-kilogram dose, was about 16-fold the clinical dose based on AUC comparisons.

At 60 milligrams per kilogram, there was an increased incidence of neurobehavioral findings, so beginning on day 42, the high dose was reduced from 60 milligrams per kilogram to 45 milligrams per kilogram. Since tremors, hunched posture, labored respiration, vocalization, and thin body continued in the high-dose females, dosing was terminated early for the high-dose females on day 49.

Tremors were typically seen during or around the time of infusion and were rare at the two lower doses. At 3 milligrams per kilogram, a single female showed tremors on day 84 and a single male showed tremors on day 42. At 10 milligrams per kilogram, a single female showed tremors on day 70. There were far more tremors at 30 and 60 milligrams per kilogram. At 30 milligrams per kilogram, tremors began on day 48, and at 60 milligrams per

kilogram, they began on day 35. Only one recovery female showed tremor during the second and third week of the recovery period.

This slide illustrates the timing of the tremors, and I've highlighted the increasing numbers of animals showing tremors at the 60- and 30-milligram-per-kilogram doses. For example, at the top-right of this slide, we see that 4 out of 5 males and 5 out of 5 females showed intention tremors prior to infusion at the 60-milligram-per-kilogram dose.

Monkeys also showed axonal degeneration, increased cellularity, and demyelination at the two highest doses, with minimal to marked intracytoplasmic inclusions in the peripheral nerves at all doses. For example, severe axonal degeneration of multiple fascicles in the right sciatic nerve was observed in one male at 60/45 milligrams per kilogram at the terminal necropsy. After recovery, one 60/45 male had moderate axonal degeneration in the left sural nerve.

Demyelination of mild to moderate severity was also observed at doses above 30 milligrams per kilogram at the end of the dosing and in recovery animals. Electron microscopy confirmed thinning, loss, and splitting of the compact myelin sheath at the 30 and 60-milligram-per-kilogram doses, but with higher incidence at the higher dose.

Study 154 was a follow-up 13-week study in monkeys with a longer 13-week recovery period. It provided more detailed neurobehavioral assessments such as measurements of nerve conduction. The rezafungin dose used in this study was 30 milligrams per kilogram, which is equivalent to about 9 times a clinical exposure based on AUC. Only females were used in this study since females were the more sensitive species in the previous 13-week toxicity study. At least some juveniles were used in this study since ages of the monkeys ranged between 3 and 5 years old. Sexual maturity is reached at 4 years of age for female monkeys. Half the monkeys were assigned to terminal necropsy at the end of dosing, while the other half were

assigned to a 93-day recovery period.

This slide illustrates the tremors observed in female monkeys dosed at 30 milligrams per kilogram every 3 days in NC-154. The yellow bars show the periods of tremor. Tremors were observed frequently in most animals, beginning on day 22. I want to highlight the fact that tremors persisted for as much as 44 days after the end of dosing into the recovery period but were not observed beyond that point. As with the previous study, neuropathology findings were recorded in these animals, as is illustrated, with the example of animal number 2505, which showed Schwann cell proliferation; axonal degeneration and regeneration; vacuolated histiocytes; decreased myelin sheath; as well as Schwann cell inclusions.

To summarize, in NC-154 conducted in juvenile females, tremors began on day 22. Although tremors persisted up until 44 days after the end of dosing, they were not observed in the final 47 days of the reversibility period. Animal 2505 showed demyelination, axonal

degeneration, vacuolated histiocytes, axonal regeneration, and Schwann cell proliferation. There were also non-adverse findings such as Schwann cell inclusions, which constituted evidence of phospholipidosis. This non-adverse finding did not reverse during the 13-week recovery period.

The final study I'll discuss is NC 190, which is the study of once-weekly dosing of rezafungin at doses up to 30 milligrams per kilogram. The high dose is about 9 times the clinical exposure. Unlike the earlier studies in which animals were dosed for 13 weeks, animals in this study were dosed for 26 weeks and adult monkeys were used in this study.

Another unique feature of this study was that the clinical evaluations were conducted blind, so observers were not aware if they were observing controlled or treated animals. There were toxicokinetic evaluations, nerve-conducting evaluations, and the 52-week reversibility period.

The results of this study were unexpected since tremors were recorded in all experimental

groups, including controls. For example, the data highlighted on the top of this table shows that 5 out of 6 control males and 2 out of 6 control females showed tremors. The incidence of tremor in the 30 milligrams per kilogram animals was only marginally higher, 6 of 6 males and 4 of 6 females showing tremors. The specific reason behind the marked increase in detection of tremors, even in controlled animals in this study compared to previous studies, remains under review. However, when tremors are divided according to severity, the effect of rezafungin can be observed. Tremors were considered to be of minimal severity if they were barely perceptible, with no impact on the quality of life. Minimal tremors were observed in all study groups, including controls. Moderate and severe tremors were only observed in rezafungin-treated animals.

Moderate tremors were defined as being more easily perceptible but with no impact on the quality of life. Moderate tremors were observed at 5 and 15 milligrams per kilogram. The exposure at

5 milligram per kilogram was similar to the clinical exposure. Severe tremors were overtly perceptible and affected the quality of life; for example, impacting the ability to grasp or manipulate food, or impairing the ability to move normally or affecting posture. One 30-milligram-per-kilogram animal had tremors so severe that he missed his mouth on a couple of occasions with treats.

Although the number of animals affected is small, the increase in moderate and severe tremors is important because of the small number of monkeys in the study and because it is consistent with the increased incidence of rezafungin-related tremors observed in the two previous studies. In addition to this increase in moderate and severe tremors, the vast majority of whole-body tremors, hind-limb tremors, and locomotor associated tremors were in treated animals.

In addition to the increase in tremors in rezafungin-treated animals, minimal axonal degeneration was observed in

30-milligram-per-kilogram animals at the end of dosing and in 5 and 30 milligrams per kilogram animals at the end of recovery. Non-adverse phospholipidosis was observed in all groups and in some recovery animals.

NC-190 confirmed a drug-related increase in moderate and severe tremors after weekly rezafungin. Cidara does not consider these tremors to be adverse since tremors, quote, "did not interfere with daily activities." FDA takes the position that tremors are adverse at any treatment dose unless a known mode of action determines the observation irrelevant. In one monkey, tremors were so severe that he missed his mouth on several occasions. This clearly constitutes an instance of tremors interfering with daily activities.

In summary, rezafungin is an echinocandin synthesized from anidulafungin, which lists tremors among the potential adverse effects in its prescribing information. Tremors were increased in rezafungin-treated juvenile monkeys as early as day 22 following every 3-day dosing. In a 13-week

every 3-day dosing, tremors persisted up to 44 days after the end of dosing but were not detected in the rest of the recovery period.

In a blinded follow-up study of weekly rezafungin in adult monkeys, a drug-related increase in moderate and severe tremors was observed. Some rezafungin animals treated showed histopathological evidence of axonal degeneration, demyelination, and Schwann cell proliferation. Rezafungin administration has been consistently shown to be associated with dose-related neurotoxicity, including tremors in monkeys. Thank you.

FDA Presentation - Shrimant Mishra

DR. MISHRA: Hi. My name is Shrimant Mishra. I'm a clinical reviewer who's going to be discussing some of the broad safety findings from the clinical development program.

Just looking at our clinical safety database, there were 8 phase 1 studies. These were primarily PK and safety studies done in healthy volunteers. The dose ranged from 50 milligrams to

1400 milligrams. Dosing could have been a single dose or up to 4 weekly doses, and again, they were ranging from studies that were single ascending dose studies, multiply ascending dose studies, to QT studies, as well as studies in subjects with hepatic impairment.

Looking at the phase 2 and the phase 3 studies, those really formed the Integrated Summary of Safety that we're basing a lot of our findings on. There were 232 rezafungin-treated patients in both of these studies, however, only 151 of those patients received the proposed dose of a 400-milligram loading dose, followed by 200-milligram weekly doses.

There were an additional 81 patients that were studied, as already been discussed, in the phase 2 trial that received a 400-milligram loading dose, followed by 400-milligram weekly doses. Median duration of treatment was 14 days, so that would have been basically 2 weekly doses, and the maximum treatment was 28 days, so that would have been about 4 weekly doses.

There were 8 expanded access patients. These patients were patients who weren't eligible for the pivotal trials for a variety of reasons. This might have been patients with prosthetic joint infection, endocarditis, or unable to tolerate azoles; and these patients received a range of duration of rezafungin treatment and could be as short as 2 weeks or as long as greater than 100 weeks.

There are two ongoing studies. One is an extension of the invasive candidiasis/candidemia phase 3 studies being done in China. To our understanding, there's roughly around 7 rezafungin-treated patients currently in that study, and there's a prophylaxis study that's taking place both in the U.S. and overseas. In this study, patients receive rezafungin as a protection against invasive fungal disease. Again, the patient population is patients with hematologic malignancies, bone marrow transplantation, and they can receive up to 13 weeks of treatment of rezafungin. To our knowledge, currently there's

roughly around 110 patients who have received rezafungin in this study, and all we have from both of these studies is really just top-line blinded interim safety information.

Looking at the overview of adverse events from the Integrated Summary of Safety -- again, this has already been discussed -- there was a very high rate of adverse events in both arms, over 90 percent in the rezafungin arm and over 80 percent in the caspofungin arm. That's again not unexpected, given the amount of comorbidities and the general demographics of this patient population. Over half of the patient population had serious adverse events and roughly a quarter had serious adverse events with a fatal outcome.

Just looking a little bit more at deaths, the most common etiologies for deaths were septic shock, multiple organ dysfunction syndrome, sepsis; and we examined all the case narratives for all the deaths in the phase 2 and phase 3 studies, and no death could reasonably be attributed to rezafungin. Again, these patients had significant

comorbidities. Oftentimes they were co-infected with other pathogens, and in many situations, death occurred as a result of treatment decisions to transition to palliative care. Talking about serious adverse events, the etiologies are very similar to the deaths; again, septic shock, multiple organ dysfunction syndrome, sepsis, so again, not expected.

Looking at treatment emergent adverse events, the treatment emergent adverse events that occurred in the rezafungin arm at greater than or equal to 10 percent incidence was hypokalemia, pyrexia, and diarrhea. The pyrexia and vomiting occurred in the rezafungin arm at a rate that was at least 5 percent greater than in the caspofungin arm, and these adverse events are also seen in the anidulafungin label, so not totally unexpected.

As the sponsor noted, there were 3 adverse events of special interest that were followed. Phototoxicity was followed because of nonclinical findings in a rat study, as well as findings in a phase 1 study that suggested that there might be

some phototoxicity potential. Erythema with UV light light exposure is how it was defined.

In the phase 2 and phase 3 study, there was one patient in the phase 2 study which did have sunburn, and there was a question of phototoxicity. But this patient had a lot of confounders, including just a lot of exposure, like several hours of exposure in the sun without any sunscreen, so it's a little unclear whether rezafungin played any part of this or not.

There were infusion reactions that were followed. This is a known class reaction. These reactions for the most part, they could occur very quickly once the infusion started, and they could be associated with warmth, flushing, nausea, abdominal discomfort, chest tightness/dyspnea, and occasionally they required treatment discontinuations or discontinuation, then restarting at a lower rate; but oftentimes the symptoms went away on their own without any discontinuation. The final adverse event of special interest that was followed was

neurotoxicity, specifically tremors, peripheral neuropathy, and ataxia was also followed.

Looking at this neurotoxicity issue in the Integrated Summary of Safety dataset, the incidence of adverse events in the nervous system disorders was, basically, similar between the rezafungin arm and the caspofungin arm, however, there was an imbalance in the incidence of tremors that was noted, with a higher incidence in the rezafungin arm. There were 4 cases in the rezafungin arm versus zero cases in the caspofungin arm. As regards to the other types of neurotoxic events, peripheral neuropathy and ataxia, those occurred at similar rates in both treatment arms. In the 400/400 milligram arm of the phase 2 study -- so that was the higher dose arm -- there were no cases of tremor, ataxia, or peripheral neuropathy noted.

Looking at the tremor cases, tremors, as has already been noted, is listed as an adverse reaction in the caspofungin and anidulafungin labels. There are 4 cases noted in the rezafungin arm and, again, none in the caspofungin arm.

Generally, there were alternative plausible etiologies. Patients may have had electrolyte disturbances and any neurologic comorbidities that might have explained the findings, however, we should note that some of these same findings -- whether it's electrolyte disturbances, comorbidities, et cetera -- were found in the caspofungin arm, and we did not see tremor cases in that arm.

Just briefly discussing the four clinical cases of tremors, the first case was an 84-year-old female that developed mild rest and intention tremors in her upper extremities 3 days after her second weekly infusion. She continued onward with two more weekly infusions, and her tremors resolved about a month later without any specific therapy.

The second case was a 67-year-old male with Parkinson's disease and acute right-sided CVA, and also had right-sided cerebellar infarction. This patient developed mild tremors of both upper extremities, along with left eye deviation and left facial twitching 12 days after the last infusion,

which would have been the second rezafungin infusion, and these symptoms resolved the next day.

The third case involved a 77-year-old female that developed mild tremors of both hands 13 days after her last weekly infusion, which was also her second infusion. It was described as an intention tremor that occurred with application of eye makeup and resolved about a month later. The patient did have concomitant hypokalemia, and when the hypokalemia was treated with spironolactone, the tremors seemed to resolve at the same time.

The last patient was a 28-year-old female that had tremors of the hands and feet 4 days after her last infusion, which was also her second infusion. This resolved 2 days later without specific treatment. Again, it was noted that the patient had concomitant hypocalcemia and was given calcium gluconate on the day the tremors resolved.

Our clinical safety conclusions, again, while the size of the safety database is modest, the safety findings are consistent with the expectations for the echinocandin class in this

patient population. Our assessment of neurotoxicity potential is ongoing, and we should note that the current safety assessment really covers up to 4 weeks of drug exposure only. I think some of the concerns that we have with more prolonged exposure, we'll get some answers to that once the prophylaxis study is finished and we have those study results. Thank you.

FDA Presentation - Jalal Sheikh

DR. SHEIKH: Hello. It's almost good afternoon. I'm Jalal Sheikh, clinical microbiology reviewer of this NDA in the Division of Anti-Infectives, Office of Infectious Diseases, FDA. Before presenting the clinical microbiology assessment of rezafungin's antimicrobial activity, let me refresh our memory regarding some basics of echinocandins as an antifungal drug class.

Though it's a busy slide, I'll try to make it easier for you. On the left-hand side, the upper part of this picture explains the production of beta 1, 3 glucans in normal fungal cells, showing here as chains of green beads, which is an

essential component of the fungal cell wall produced by the beta 1,3-glucan synthase located in the fungal cell membrane.

On the bottom part of the picture, it explains the mechanism of action of echinocandins. As an antifungal drug class, all echinocandins uniquely target to inhibit the beta 1,3-glucan synthase, thereby disrupting the production of beta 1,3 glucan. We can clearly see that the depletion of beta 1,3 glucans collapses the cell wall, ultimately causing cell death.

Speaking of echinocandin resistance, the catalytic subunits of beta 1,3-glucan synthase are composed of three structural genes known as *fks*1, *fks*2, and *fsk*3; so therefore, in general, any mutations that happen in these genes are associated with echinocandin resistance. However, mutations usually happen in the highly conserved regions known as hotspot region 1 and 2 of *fks*1 and *fks*2 genes. These hotspot regions are only 8 to 9 amino acid long, and sometimes single mutations translated to a single amino acid substitution has

been shown to be a huge impact on echinocandin resistance, resulting in higher MICs.

Rezafungin is a second-generation echinocandin drug derived from anidulafungin, and therefore it is a structural analog of anidulafungin. The structural modification provides rezafungin improved chemical stability to host degradation pathways, and therefore increases its half-life that allows weekly dosing. Similar to other echinocandins, rezafungin demonstrates in vitro and in vivo activities against most *candida* species, including *Candida auris* and some filamentous fungal species.

The applicant submitted in vitro and in vivo activities data of rezafungin and comparative echinocandins, namely anidulafungin, caspofungin, and micafungin in this NDA for comparison. The MIC90 values which indicate the minimum drug concentration that inhibit the growth of 90 percent of tested isolates are submitted from several studies against different *candida* species.

In this table, MIC90 values of rezafungin,

anidulafungin, caspofungin, and micafungin against recent clinical isolates of predominant *candida* species are provided for comparison, and we can clearly see that, overall, rezafungin in vitro MIC90 values are comparable to other FDA-approved echinocandins against targeted *candida* species with little to no differences.

The applicant stated that rezafungin has better in vitro activity against echinocandin in resistant isolates with *fks* mutations. In vitro MIC data have been submitted from a small subset of 27 isolates from four different predominant *candida* species: *Candida albicans; Candida glabrata; Candida krusei;* and *Candida tropicalis.* This isolates harbored mutations in *fks* genes mostly in hotspot region 1 of *fks*1 and few in hotspot 1 region of *fks*2 genes. From our analysis, we found that rezafungin had similar in vitro activity against isolates with *fks* mutations compared to anidulafungin. Compared to caspofungin, rezafungin has better in vitro activity against these isolates. The applicant could not provide

micafungin MIC data against these isolates.

The applicant also submitted in vitro data from other clinical microbiology studies and compared with comparator echinocandin drugs. Notably among them, we found against azole-resistant isolates, rezafungin exhibited in vitro activities similar to other echinocandins. Against fluconazole non-susceptible isolates, rezafungin MIC90 barely was similar to anidulafungin and caspofungin, however, micafungin activity was higher than other echinocandins.

The spontaneous mutation frequencies, which is an indicator of resistance development over time for rezafungin against tested *candida* isolates, appear comparable to other echinocandins, and rezafungin demonstrated fungicidal activity at 4-fold or higher MICS at 24 hours for most tested isolates, and those results are comparable to other echinocandins.

In this slide, we captured and summarized the in vivo data obtained from several studies conducted to demonstrate the in vivo activity of

rezafungin. In vivo studies are conducted in disseminated candidiasis mouse model with *Candida albicans* isolates. Rezafungin administration was compared to either untreated control, anidulafungin, micafungin, fluconazole, or amphotericin B. As expected, rezafungin demonstrated better in vivo activity compared to untreated control and fluconazole.

Overall, similar in vivo activities were observed when rezafungin was compared to either anidulafungin or micafungin at comparable doses. Although rezafungin demonstrated better activity compared to micafungin in three in vivo studies, we found that rezafungin doses used in those studies were much higher compared to micafungin.

As my statistical and clinical colleagues provided the details of the rezafungin clinical program, I'd like to briefly cover some of the highlights pertinent to clinical microbiology discipline. For efficacy and safety analysis, individual and pooled data were presented from both phase 2 and phase 3 studies. The evaluation of

mycological eradication was conducted as clinical efficacy secondary endpoints in both studies at day 5, day 14, and day 30.

For clinical microbiology analysis, day 14 pooled data were primarily used for mycological response, mycological eradication by baseline MIC values of the clinical isolates, and for the breakpoint analysis with rezafungin breakpoints recommendation.

This table summarizes the baseline predominant *Candida* species isolated from the pooled microbiological ITT population in both treatment arms. We can see *Candida albicans* were isolated at the highest frequency at baseline, followed by *Candida glabrata, tropicalis,* and *parapsilosis* in both treatment arms. A total of 58 and 69 *Candida albicans;* 38 and 35 *Candida glabrata;* 27 and 22 *Candida tropicalis;* 14 and 27 *Candida parapsilosis; a*nd 5 and 3 *Candida krusei* isolates were obtained at baseline from rezafungin and caspofungin treatment arms, respectively.

This table summarizes the mycological

response at day 14 among the mITT population in both treatment arms by different *Candida* species identified at baseline. As shown in the table, based on the 14-day mycological response, mycological success was achieved in rezafungin treatment arm among 67 percent subjects with *Candida albicans;* 84 percent subjects with *Candida glabrata;* 74 percent subjects with *Candida tropicalis;* 79 percent subjects with *Candida parapsilosis;* and only 40 percent subjects with *Candida krusei.* On the right-hand column of this table, rezafungin MIC90 values against baseline clinical isolates were found to be almost similar to the MIC90 values that were obtained from different surveillance studies.

I'll end my presentation with this summary slide. Overall, rezafungin demonstrated similar in vitro activity against most *Candida* species compared to other echinocandin drugs. Limited in vitro data suggest that against *Candida* isolates with *fks* mutations, rezafungin appears to demonstrate slightly better activity compared to

caspofungin, but this activity is comparable to anidulafungin.

Similar in vivo activity was observed in murine animal models compared to other echinocandin comparators; for example, micafungin and anidulafungin. When compared to other echinocandins, rezafungin has similar activity against both azole-resistant and susceptible isolates, and similar mutation frequencies are observed compared to other echinocandins.

Thanks for your attention. Now, I am passing to my clin-pharm colleague, Dr. Bensman.

FDA Presentation - Timothy Bensman

DR. BENSMAN: Great. Thank you.

My name is Timothy Bensman. I'm the clinical pharmacology reviewer for this new drug application, and I'll be providing a brief and focused clinical pharmacology assessment of rezafungin from the FDA's perspective.

Several pharmacological advantages of rezafungin compared to FDA-approved antifungals have been postulated in this new drug application.

The first is probability of target attainment, or PTA, with nonclinical PK/PD data. Nonclinical PK/PD literature is referenced in the NDA submission to suggest an underdosing concern with FDA-approved echinocandins for *Candida* species, and it's hypothesized that rezafungin may be able to treat infections caused by *Candida* species that have higher MIC values compared to the FDA-approved echinocandins, as measured by these nonclinical PK PTA values.

For the FDA-approved echinocandins, there are FDA or CLSI current breakpoints that are informed by publicly reported clinical success rates against *C. albicans* and *C. glabrata,* and as shown in the table on this slide, the reference PTA analyses underpredicts the observed clinical success for the current FDA-approved echinocandins. Of note, the reported MICs are the highest MICs that had reasonable case counts.

For rezafungin, review of PTA findings is ongoing, but preliminarily there is potentially a substantial improvement in maximal MICs covered by

rezafungin, with 90 percent probability of target attainment compared to caspofungin. These are MICs of 0.5 milligrams per liter for *C. albicans* and up to 8 milligrams per liter for *C. glabrata.* However, as shown by the table below, the rezafungin clinical program does not afford a determination of concordance between PTA and clinical outcome at these MICs. Counts at the highest MIC are too few and show that the clinical trial does not cover isolates with MICs as high as what is postulated by the of probability target attainment.

Another pharmacological advantage of rezafungin compared to FDA-approved antifungals might be drug tissue penetration. It's stated that there is a substantially improved distribution of rezafungin to infected tissues in a nonclinical invasive candidiasis mouse model, increasing the likelihood of achieving the required PK/PD target at the site of infection compared to other echinocandins.

To evaluate the drug tissue penetration differences, we assessed the submitted data as well

as publicly available literature, and we noted the following observations. At the doses associated with approximate humanized systemic drug concentrations, rezafungin did not appear to show substantially better tissue penetration, as there was no difference in hepatic fungal burden when compared to micafungin. In publicly available literature, it suggests that anidulafungin has greater drug penetration in rat liver, kidney, and lung tissue as compared to micafungin or rezafungin.

Unfortunately, there's no drug tissue penetration information available for more exclusive sites such as the brain and prostate. And lastly, while there were some limitations, the available clinical data did not suggest better tissue penetration, given no substantial difference in day 30 all-cause mortality rates between rezafungin and caspofungin in a subgroup analysis of patients with invasive candidiasis.

One more pharmacological advantage of rezafungin compared to FDA-approved antifungals

might be around drug-drug interaction risks. It's suggested that rezafungin shows a low potential for interactions with other drugs, and the applicant notes that patients with candidemia and invasive candidiasis commonly have multiple comorbidities requiring polypharmacy.

In order to evaluate, we assessed the submitted data as well as some publicly available literature, and we made the following observations. Rezafungin drug-drug interaction studies suggest no or low DDI risks, and the azole antifungal drug products are frequently encountered and exhibit a wide range of DDIs and severity levels, with risk management recommendations ranging from dose adjustment to increased monitoring, as recommended in drug-specific USPIs. For the echinocandins, drug-drug interaction risk is generally no or low, with the exception for caspofungin. For caspofungin, there's a higher alternative dosing regimen recommended when administered concomitantly with other CYP inducers.

To summarize our preliminary conclusions,

for probability of target attainment with nonclinical PK/PD, the reference PTA values for the FDA-approved echinocandins underpredicted literature-reported clinical success rates at MICs at or near MIC 90s; and there's no relationship or correlation that could be identified between these PTA values and clinical outcomes.

Furthermore, the rezafungin clinical program did not establish a correlation between PTA values and clinical outcomes; therefore, the clinical significance of improvements in rezafungin PTA compared to FDA approved echinocandins is unknown. For drug tissue penetration, there is insufficient evidence to demonstrate that rezafungin achieves better tissue penetration or activity at the site of infection in than FDA-approved echinocandins. Then lastly, for drug-drug interaction risks, rezafungin has a low DDI risk potential that is more favorable than currently FDA-approved azoles and caspofungin. Thanks.

FDA Presentation - Heidi Smith

DR. SMITH: This is Heidi Smith. I'm a

clinical team leader in the Division of Anti-Infectives. I'm going to bring you through a brief summary of the assessments you just heard from the FDA team.

For the efficacy assessment, a 10 percent noninferiority margin for day 30 all-cause mortality endpoint was recommended to support candidemia/invasive candidiasis treatment indication without a limited use statement. This preserves approximately two-thirds of the estimated echinocandin treatment effect on a mortality endpoint in patients with candidemia and invasive candidiasis.

Efficacy data from a single rezafungin phase 3 noninferiority trial showed that the primary endpoint of day 30 all-cause mortality was within a 20 percent NI margin but did not meet a 10 percent NI margin, and a phase 2 exploratory dose-ranging study provides supportive evidence of effectiveness.

For the safety assessment, nonclinical studies of rezafungin in non-human primates

identified drug-related neurotoxicity. The findings in subchronic dosing studies included tremors, typically developing after day 35, and histopathologic changes included axonal degeneration and demyelination.

The clinical safety database included 151 patients with candidemia and invasive candidiasis receiving the proposed rezafungin and clinical dose and an additional 81 patients who received a higher dose for up to 28 days. A higher incidence of tremors was observed in the rezafungin arm, but all were mild and reversible. Otherwise, the safety findings were consistent overall with the FDA-approved echinocandins.

From a clinical microbiology and clinical pharmacology perspective, rezafungin is primarily distinguished from the FDA-approved echinocandins by an extended half-life supporting once-weekly dosing. The microbiological activity against *Candida* species in vitro is comparable, and in vivo activity in murine models of candidemia and invasive candidiasis is similar.

The clinical significance of the postulated improvement in rezafungin probability of target attainment compared to FDA-approved echinocandins is not known. There is insufficient evidence to demonstrate that rezafungin achieves better tissue penetration or activity at the site of infection than FDA-approved echinocandins. And finally, rezafungin has a low drug-drug interaction risk potential.

The points that we'd like the committee to consider, the applicant is seeking approval of rezafungin for the treatment of candidemia and invasive candidiasis based on a single phase 3 adequate and well-controlled noninferiority study, meeting the prespecified 20 percent noninferiority margin. For the day 30 all-cause mortality endpoint, the treatment difference, rezafungin minus caspofungin, was 2.4 percent and the 95 percent confidence interval ranged from minus 9.7 percent to 14.4 percent.

Supportive evidence was provided by a phase 2 dose-ranging study, and the integrated

safety dataset from phase 2 and phase 3 studies consisted of 151 subjects with candidemia and invasive candidiasis receiving the proposed rezafungin clinical dosing, plus an additional 81 subjects receiving a higher dose for up to 28 days.

That concludes the FDA presentation. Thank you.

Clarifying Questions

DR. BADEN: Thank you.

I would like to thank our FDA colleagues for presenting a tremendous amount of data very concisely. Thank you.

We will now take clarifying questions for FDA. Please use your raise-hand icon -- and I'll ask that my panel members take down your hands, and then re-up them, as it's unclear who was hold over.

Please your raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon after you have asked your question. When acknowledged, please remember to state your name for the record before

you speak, and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I see several panel members have raised their hand. We will start with Dr. Siberry.

DR. SIBERRY: Thanks very much, Chair. This is George Siberry, and my question is for Dr. McMaster about the tremors, studies of tremors in the animal studies.

First, there seems to be a lot of association with potassium and other electrolyte disturbances related to the echinocandins when discussing the human studies, and I wanted to know if electrolyte disturbances were evaluated and ruled out in the animal studies. And separately, my understanding from what you presented was, even

in those animals who had a longer duration of tremors, it did seem that in all cases, the tremors resolved. I just wanted to confirm that I understood that correctly. Thank you very much.

DR. McMASTER: Thank you. So I'll take the second question first. Yes, in all cases, I think most clearly in Study 154, where they were followed for 47 days after the end of dosing, we saw no subsequent tremors after the end of that incidence in the follow-up period.

To the first question, we have no definitive association between the electrolytes and the tremors. Thank you.

DR. BADEN: Thank you.

Dr. Hilton?

DR. HILTON: I see Dr. Hilton taking your hand down.

Dr. Bennett?

DR. HILTON: Is it down now?

DR. BENNETT: This is Dr. Bennett, and I have a question for Dr. Li.

DR. BADEN: Please, Dr. Bennett.

DR. BENNETT: This is Dr. Bennett, and I have a question for Dr. Li, if I may.

My question is, is this the correct way to restate the use of confidence intervals in your analysis of efficacy? That is, if you look at the end of the confidence limits, is it possible that the result could have been a 14-day global assessment, which was 60 percent, as high as 75 percent, which is wonderful, or as low as 45 percent, which is obviously much less wonderful.

Similarly, with the all-cause mortality, it could have been as high as 38 percent, and that would compare with the registration trial of anidulafungin, which showed 23 percent, obviously much lower than 38 percent. But I don't know if I'm using confidence intervals correctly.

Would you comment on that, Dr. Li? That's the end of my questions. Thank you.

DR. LI: Thank you. We calculated the confidence interval based on the incidence rate between the two groups. We can see the difference in the confidence interval. For the primary

efficacy endpoint, we looked at the upper limits of the confidence interval. We used the common method for the confidence interval calculation, so it shows it's less than 14.4 percent. It's less than the 20 percent margin.

I'm not sure if I have answered your question. It could be 14 percent; that's worse than the active control, but it's an acceptable margin from the FDA's point of view.

DR. BENNETT: Thank you. That answers my question. That's a satisfactory response. Thank you.

DR. BADEN: Thank you.

Dr. Hilton, we'll try again.

DR. HILTON: Can you hear me?

DR. BADEN: Yes. Yes.

DR. HILTON: Great.

I wanted to ask the FDA statisticians and investigators about the choice of the 20 percent noninferiority margin. They talked about a database evidence for that selection, but they didn't talk about the variation in the types of

outcome variables in relation to choice of a noninferiority margin. In my opinion, serious outcomes such as mortality should not have a generous lenient noninferiority margin. Nobody would, at face value, consider 20 percent additional deaths to be acceptable. That's my comment.

DR. LI: This is Xianbin Li. When we were deriving the noninferiority margin, we did consider the variability in the data from clinical trials or trials with treatment or inadequate treatment. We derived the margin 31 percent with the consideration of the variability from the trials.

It's true that 20 percent is a higher margin, but we are seeking the input from the committee about the benefits and risks about the application of this drug. This is why, really, we seek the input from the committee. Thank you.

DR. HILTON: Thank you.

DR. BADEN: Follow-up, Dr. Hilton?

DR. HILTON: In my opinion, that's not acceptable, sufficient logic. I think the clinical

basis has to be considered in addition to the statistical basis, and for such a severe outcome, where you have no chance of doing anything further to help the patient, it's just too high.

DR. BADEN: Thank you.

If no other comment from our FDA colleagues, then I will go to Dr. Hardy.

DR. KIM: Hi, Dr. Baden. This is Peter Kim.

DR. BADEN: Yes?

DR. KIM: We'd like to respond to Dr. Hilton's second comment.

DR. BADEN: Please.

DR. MISHRA: Hi. This is a Shrimant Mishra, the clinical reviewer. We actually have discussed that point clinically about whether it was acceptable in terms of this 20 percent margin. But again, I think sort of the crux of the AC meeting is trying to find whether there is a population that might benefit, depending on the need that's met. So again, I think that's really what we're trying to figure out here. Thank you.

DR. BADEN: Thank you.

Dr. Hardy?

DR. HARDY: Thank you. This is Dr. Hardy from Los Angeles. I just had a clarification question for Heidi Smith or someone else there at CDER's leadership.

Can you explain for us the type of approval that Cidara is looking for, meaning limited use indication? How does that differ from other sorts of FDA approvals for investigational agents like this? Could you clarify that, please? Thank you.

DR. KIM: Hi, Dr. Hardy. This is Peter Kim. As opposed to a full indication, I think we and the applicant are potentially proposing what we would consider a limited use indication in patients who may have unmet needs; patients who have limited or no alternative treatment options. This takes into account the fact that we may not have all of the efficacy and safety data that we would necessarily consider important for a full indication.

So part of our charge to the committee would be to ask the committee what population or populations may have the unmet need for which this

drug, rezafungin, may provide a potential treatment option.

Does that help?

DR. HARDY: Yes, it helps very much. Thank you very much.

I just have one quick follow-up, and that is, how does the FDA manage a limited use indication in terms of drug sales and distribution versus a regular or unrestricted use indication?

DR. KIM: Dr. Hardy, we would specifically have additional labeling considerations in the situation with a limited use indication, specifically delineating the limitations of the data to support approval; trying to identify the population with the unmet need for which the benefits outweigh the risks; and certainly the indication would be of a type similar to what we provided as an example, such as drug X is indicated for the treatment of infection Y in patients who have limited or no alternative treatment options. Approval of this indication is based on limited clinical safety and efficacy data.

Does that help?

DR. HARDY: It does? How does that differ from compassionate use, compassionate use as managed by the FDA? Almost exactly what you said, it reminds me of what was formerly or still currently considered to be compassionate use of an investigational drug in certain situations, in certain patients.

DR. KIM: Hi, Dr. Hardy. This is Peter Kim again. Thank you for the question. The distinction would be compassionate use programs would be for unapproved drugs, whereas if we labeled this drug for a limited use indication, it would certainly be on the market and approved.

DR. HARDY: Got you.

DR. KIM: Does that help?

DR. HARDY: Thank you very much. Yes, thank you.

DR. BADEN: Dr. Kim, are there other limited use drugs on the market currently?

DR. KIM: Hi, Dr. Baden. Yes, and in the briefing document, we note we have references

specifically to two. One is Recarbrio, which has limited use indications for complicated urinary tract infection and complicated intra-abdominal infection, as well as plazomicin, which has a limited use indication for complicated urinary tract infections. Additionally of note, Avycaz in the original approval, the initial approval, had a limited use indication as well. Thank you.

DR. BADEN: Yes. Thanks. I remember those discussions.

Thank you very much. I would like to ask a question to Dr. Mishra or other agency colleagues.

The safety data set for the proposed dosing is 151 individuals. How do you look at the adequacy of that safety database given the complexity of this population? Is it an adequate safety database.

DR. MISHRA: Hi. This is Dr. Mishra. I think we would say that the database, it is modest compared to our usual clinical programs, however, given the seriousness of the indication, potentially some difficulty enrollment, and again,

considering that we're also looking at a limited use population, it's acceptable. But yes, it is certainly smaller, and there is a greater degree of uncertainty when we're interpreting all of the information that we've received.

DR. KIM: Hi, Dr. Baden, and thanks Dr. Mishra.

Dr. Baden, this is Peter Kim again. As you noted, it would be 151 patients at the proposed dose and duration, plus an additional 81 at a higher dose than that proposed, with a similar duration. But it is on the thinner side, but once again, that circles us back to our question for the advisory committee on whether the benefits outweigh the risks, or potential risks, associated with this drug. Thank you.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you. This is Mike Green. This is a question for either Dr. McMaster or Dr. Mishra. I know that in conversation, it was stated that both for anidulafungin and for, I

think, caspofungin, that tremors are noted as a potential side effect. Even though it wasn't seen in this study, can you give us some sense of the frequency or the prevalence of tremors with use of either of those echinocandins so we can put that into the context of what we're seeing in this study with the rezafungin? Thank you.

DR. MISHRA: I don't know if we have actual number. We'd have to look into that a little further. When I've looked through the literature, there's not really any clear-cut discussion in terms of -- there's not any clear-cut findings of neurotoxicity when you look through the published literature with echinocandins. So in terms of specific numbers of tremors or peripheral neuropathy, I have to get back to you with that.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Thank you, Chair. This is a quick follow-up for Dr. Kim.

In terms of the limited use indication, compared to a standard licensure indication, are

there any additional restrictions on practitioners using this drug off label once it's licensed with that limited use indication? And second, is there a pathway or an expectation that the sponsor would come back with additional data later for a full indication and a revision?

DR. KIM: Hi. This is Peter Kim. I'll answer the second part of your question first. Yes, we would hope that additional data would be provided, additional evidence of efficacy and safety, to move to a full indication. That's always optimal. Certainly, we are aware of the fact that the applicant is studying rezafungin in a longer term and large prophylaxis study.

Then regarding your first question, mainly it's in the way we would label the drug, and certainly we'd be interested in the committee's input if there are particular populations where this drug may be of particular importance, who may have particular unmet needs. Then, basically we deal from the labeling perspective as to how the drug would be used.

Is that helpful?

DR. SIBERRY: I just want to confirm that even though it's got this special limited use indication, once licensed that way, practitioners could still use that license drug using their own best judgment as they would want, including off label. Is that correct?

DR. KIM: So it would depend on the actual wording of the labeling, depending on how the labeling was set. And then certainly how payers may interpret that labeling, that may also affect how healthcare providers may use the drug.

Regarding your question of restrictions, it depends on how the wording of the labeling ultimately ends up, and that's part of our question to the committee; if there are particular populations that this drug should be specifically labeled for, or if a broader limited use indication, such as what is in the Recarbrio label or the plazomicin label, would be more appropriate to allow for more discretion among healthcare providers as to how they use the drug. Thank you.

DR. SIBERRY: Thank you very much.

DR. BADEN: Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. Hi. Can you hear me ok this time?

DR. BADEN: Yes.

DR. SWAMINATHAN: Oh, good. Good.

I'm not sure who can best answer this question, but I guess it's a question about the interpretation of the statistics. In the all-cause mortality analysis of the phase 3 study, there's a very high mortality. There's over 20 percent mortality in this population in 30 days, so this is a very sick group, presumably, with a lot of comorbidities. The confidence intervals here are minus 9.7 to plus 14.4, and the real difference between the two groups is 2 deaths.

I'm having a hard time knowing what exactly I can conclude from this, one way or the other, in terms of efficacy. Can you help me with that?

DR. LI: This is Dr. Li. Thank you for your question. For the results from the phase 3 trial,

the treatment could be 9.7 percent better than the active control or 14.4 percent worse than the active control. So this is the possible range for the estimated results.

Again, all-cause mortality is an objective and a highly meaningful endpoint, so whether or not this upper limit is acceptable for the clinicians, this is a topic that we would like to seek input from the committee about whether or not this result is acceptable, is favorable for the approval. Thank you.

DR. SWAMINATHAN: It just seems to me that the numbers here don't have the power to really conclude much in terms of relative efficacy.

Is that fair?

DR. LI: Yes. This is Dr. Li again. This trial is designed as a noninferiority study, so the sample size is relatively small. We could not have any test for superiority. Thank you.

DR. SWAMINATHAN: Thank you.

DR. LI: Yes. This is Xianbin Li. I'm a statistician. The confidence interval is

determined by two parts. One is the effect size. In this case they are very similar. The other part is an inherent variability, so that is related to Dr. Li's sample size. When the sample size is small, then we have more uncertainty, higher variability; that's what you see. The small sample size is a key factor there.

This was related to what Dr. Hilton talked about, the 20 percent margin. I totally agree with you. For the serious disease, it's not ethical to lose too much efficacy, but again, the small sample size could be a factor. We look for a 10 percent margin for unlimited use, but based on the discussion, we allowed 20 percent for limited use. Thank you.

Do you have any follow-up about that?

DR. SWAMINATHAN: No. Thank you.

DR. BADEN: Thank you.

Dr. Rose?

DR. ROSE: Yes. Thank you. This is Stacey Rose. My question is about follow-up to Dr. Kim regarding the labeling, and maybe to provide some

guidance to the committee members, specifically regarding whether the labeling can indicate a restriction for a certain group.

For example, in the phase 3 studies because of the signal for the neurotoxicity, the exclusion criteria, patients with risk factors for neurologic toxicity were actually excluded. So I guess, to me, that makes me wonder whether we can reliably interpret the safety data for the neurotoxicity signals since there was a group of patients who may have been at higher risk of that adverse effect that were excluded from participation.

So can you maybe give us some guidance as to whether that's something we should consider as part of the labeling, like restricting the use for certain groups?

DR. KIM: Hi, Dr. Rose. This is Peter Kim. Thank you for the question. One potential labeling tool would be to include a limitation of use on the indication, and certainly we would be interested in the panel members' thoughts on such language if members deemed that so appropriate Thank you.

DR. ROSE: Thank you. That's the end of my questions.

DR. BADEN: Thank you.

Dr. Patel?

DR. PATEL: Thank you. Are you able to hear me this time around?

DR. BADEN: Yes, much better.

DR. PATEL: Okay, great.

My question is for Dr. Li, and I was wondering if he could provide some context about how rigid the committee should be evaluating the 20 percent and 10 percent noninferiority threshold. And I think this piggybacks on Dr. Swaminathan's concern [indiscernible], that because we're dealing with proportions in a small population, it seems that movement of one person in the other direction changes the proportion dramatically. In preparation for the meeting, I had worked out the math and had, I think, in the originals numbers 22 out of 93 rezafungin recipients had died. But had there only been 18 deaths, it would have hit that 10 percent noninferiority threshold.

Knowing that the noninferiority threshold was derived from the literature and preserving two-thirds of the treatment effect, and that there's no inherent meaning of that preservation value, I guess how stringently should we be evaluating that threshold?

DR. LI: Given the sample size of the trial, one or two more deaths in the treatment group will make the confidence interval less favorable. Because the confidence interval was so sensitive to the deaths in the two groups, I think it's not so easy to feel so comfortable about the 20 percent margin. If the sample size was much larger, then we would have a narrower confidence interval; for example, minus 3 to 10, and we would feel much better.

Thus, uncertainty about the treatment effect is one reason we are seeking input from the committee about the benefit-risk assessment. The 20 percent margin is an FDA determined acceptable margin; however, we welcome any input from the committee regarding this sample size in this

phase 3 study. I hope I have answered your question.

DR. PATEL: I think so, and I think what it does is it reinforces -- in coming to this meeting, I was prepared to defend that we're making a decision about this limited use statement on 4 deaths. Had those 4 deaths not occurred or the enrollment had 16 extra survivors, the 10 percent threshold would have been met, and we wouldn't be having this limited use conversation. Four deaths just seems pretty extreme to add on that statement that may handicap the use of a drug that has the potential to help a lot of people.

DR. BADEN: Is that a question?

DR. PATEL: I'm sorry. That was just me pontificating, and that's all for. Thank you.

DR. BADEN: There will be time for reflections later.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. Thank you. I also am concerned about the 20 percent noninferiority margin because say in cancer, they look for

benefit smaller than that, and that's the same type of population where everybody will die if they don't get treatment.

So it is concerning, but then I was looking at table 9 in the FDA briefing, and nobody talked about the subgroup analyses, but if you look at, say, age less than 65 or greater than 65, the 65 year old and above seems to have the benefit where the less than 65 doesn't. So I'm wondering if we just think that's spurious or if we're trying to think of populations where we could use this; if that is somewhere that we might look or what people think about these subgroups.

DR. LI: Thank you for the question. This is Dr. Li. Regarding the subgroup analysis, we do see better results in subjects 65 years old or older; however, due to the small sample size and the multiple comparison in subgroup analyses, we were cautious about a solid conclusion about the subgroup analysis. It may be confirmed in a future study or research.

DR. NIE: This is Lei Nie again. I'm the

statistician for the FDA. That's a great question.

In the sponsor's presentation, they talk about the subgroup analysis, and it appears the results suggest rezafungin could be better than caspofungin in the older population, in females; in patients with moderate and severe renal impairment.

As acknowledged by the applicant, some of the results do not have any clinical rationale. We agree that the interpretation of the subgroup may need to be very cautious. It could be that heterogeneity may arise due to chance or could be a signal if they are really signal or maybe further support the limited use.

What do you think, Dr. Hunsberger?

DR. HUNSBERGER: Yes. I agree that just the randomness could be the problem because if you look at the phase 2 study, where basically you had the 2 doses that were exactly the same for the first 14 days, but yet you saw kind of a dramatic difference even though they were exactly the same. So it could easily be that we're just seeing randomness, but if we're trying to look for areas

that suggest where we would limit the scope, this could be a place.

One thing I was wondering is that the sex and the age probably are highly correlated. I'm wondering if anybody broke out most of the older people, female or male. That could be intertwined, too, so that was another question. But it does seem like it's just a problem the sample size is way too small. And it seemed like there was suggestion that the reason this study was so small was because COVID came, and you couldn't recruit. And I'm wondering if we did another study, maybe we could recruit or are there other reasons other than COVID that we couldn't recruit.

DR. BADEN: I wonder if that's a question for the applicant on the other side of lunch.

DR. HUNSBERGER: Yes. Sorry. I did go on too much, so I apologize.

DR. BADEN: No, no, no. I appreciate all the comments and discussion, and there's more that needs to be had. However, it is now 12:49, and we need to break for lunch. Since we are ending five

minutes later, we will start five minutes later.

So we will reconvene at 1:35. Panel members, please remember that there should be no chatting or discussion of the meeting topic with other panel members during the lunch break. Additionally, you should rejoin prior to the appointed time to start. We will have time after the OPH for the applicant to be able to clarify many of the questions that did not go unanswered, so we will spend some time making sure all committee members are satisfied with the data presented from the applicant.

We will adjourn for lunch and resume at 1:35. Thank you.

(Whereupon, at 12:50 p.m., a lunch recess was taken.)

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

(1:35 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:35, and we shall resume the AMDAC meeting. We will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, the financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the

meeting.

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

I'd just ask that you all put your phones on mute if you're not talking.

Please confirm that you can hear me.

MR. THARP: I can hear you.

DR. BADEN: Okay. Thank you.

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

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way,

where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Again, I will ask all to put yourselves on mute if you are not talking.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization that you're representing for the record. Thank you.

MR. THARP: Hi. My name is Rich Tharp. I'm 51 years old and live in Spencer, Massachusetts with my wife Missy and my son Jacob. I have no financial disclosures.

In July of 2000, I underwent surgery for a torn aorta and a splenectomy with both of my legs and pelvis broke after a drunk driver hit me while I was crossing the street and then ran me over. The recovery from the accident still hasn't reached 100 percent, and I am still on social security disability.

In 2017, I was rushed to the hospital with fever and chills. Tests revealed that I had an infection from an aorta graft placed in my heart 17 years earlier. I had part of my upper-left lung that was clinging to the infected area removed, and had a replacement graft done. Cultures taken from my old graft required 6 weeks of some pretty strong antibiotics: IV piperacillin, IV vancomycin, and IV micafungin. I also received daily doses of oral fluconazole. I thought this was the end of it, but I was not out of the woods yet.

Two years later in 2019, I was back with recurring fever and chest pains. Coils from my new graft had protruded into my esophagus, making me eligible for caspofungin. I underwent numerous types of IV treatments once again. It's a good my thing my wife keeps [indiscernible] of these because I would never be able to remember all the names.

In going through all this, it's all a blur of IVs being stuck into you, and you're praying that one of them is going to work before they tell

you there's no longer any options. I was given IV micafungin, posaconazole [indiscernible], and finally 6 weeks of oral fluconazole [indiscernible]. Then in February 2020, just as COVID was overtaking the country, I underwent a two-stage procedure to replace my second graft. I was given IV micafungin again. I had developed a resistance to it.

This is a horrible thing to learn as a patient, that something that worked once for you is no longer an option. I was given two antifungal therapies, but both had stopped working to rid all of the toxicity. I was at a place where me and my family had feared, a place with no options. I was so tired, and we were all really worried about what would happen next. Thankfully I had doctors that didn't give up.

In April 2020, they were able to get me expanded access for the new investigational treatment, rezafungin, the one you were talking about today. I started out as an outpatient in IV therapy in May of 2020. I have continued taking

maintenance doses each week since. Chest CT scans have shown the fungal infection is gone, and I have my life back after years of living in and out of the hospital.

Some people will call my story a miracle. I am here today because I had doctors that fought for me. They searched for an option that worked and found one. Since I have been taking rezafungin, my family and I have had so much relief from the fear of the outcome that would have been if they hadn't treated me with the rezafungin.

My story is unique to me, but it is common experience for many other patients and the doctors who are fighting to save them. They deserve the same chance I was given, a chance to live. Please think of me and them as you make a decision today, and give them this treatment as a choice. Thank you.

DR. BADEN: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any

organization you're representing for the record. Thank you.

DR. MORALES: Good afternoon. My name is Dr. Megan Morales. I'm the medical director of Transplant Infectious Diseases at Virginia Commonwealth University. I have no financial disclosures.

Our transplant infectious diseases team here at Virginia Commonwealth University supports the more than 500 solid-organ transplants that take place yearly at VCU, in addition to an active bone marrow transplant and CAR T program as well. I therefore treat exclusively immunocompromised patients, and as committee members in similar roles know, these patients are especially vulnerable to severe infections, as well as opportunistic pathogens. However, the most common fungal infection in solid-organ transplant recipients is due to *candida.* This is true for all organ types, with the exception of lung transplant, where *candida* is the second most common fungal pathogen.

Both the American Society of Transplant and

the American Society of Transplantations and Cellular Therapy have invasive candidiasis guidelines, the ASTCT having published their updated guidelines earlier this month. They both highlight the shifting epidemiology of *candida* infections in these immunocompromised populations. These groups, in accordance with the IDSA, recommend echinocandins as first-line therapy for treatment of candidemia or invasive candidiasis.

Despite, and at times, insidious onset of *candida* infections, *candida* has the potential to cause significant morbidity and mortality in immunocompromised patients. Particularly in abdominal organ transplants, it's difficult to eradicate and often necessitates reoperation and washout of long antifungal courses, and is one of the few pathogens to necessitate removal of catheters and hardware due to its sticky nature, forming impossible to eliminate biofilms.

At the same time, the existing armamentarium of antifungals is actually quite limited. There's been a shift in the epidemiology of *candida*

infections toward more non-albicans infections, and with that, we have seen increased resistance as well, both acquired and inherent. Polyenes are an antifungal of last resort due to toxicity. Echinocandins are some of the best tolerated antimicrobials that we use, and unlike azoles, have no significant drug-drug interactions, which is important in the transplant world.

Other currently available echinocandins, however, need daily infusion, which require PICC or central line placement, or sometimes placement in a skilled nursing facility for patients who need to complete long courses for abscesses or endovascular infections after they're discharged from the hospital.

Rezafungin is unique among the echinocandins class in its prolonged half-life, which allows for weekly infusion that could be administered in the transplant or infusion center and allow patients to recover at home. While the convenience to patients is important by front-loading the dose, there may be a diminished risk of developing resistance. It

achieves better intraperitoneal penetration, and levels are detectable more rapidly in intra-abdominal abscesses, both points that are critical for effective drug delivery and treatment of intra-abdominal infections.

In 2020, I applied for and received approval to use rezafungin under an emergency IND protocol. I was taking care of a lovely patient who had azole-resistant *candida* peritonitis thought to be related to a peritoneal catheter from another hospital before being transferred and undergoing liver transplant at our institution. She subsequently developed intra-abdominal abscesses, which repeatedly cultured azole-resistant *candida*. We treated her with standard-of-care therapy, including micafungin and surgical washout, however, the invasive candidiasis in her abdomen continued to worsen.

We decided to try rezafungin due to superior data in murine models showing higher penetration into the peritoneal space. A scan after 4 weeks showed improvement, and there was near complete

resolution by 10 weeks. She ultimately completed 12 weeks of weekly IV rezafungin infusions with complete cure of infection, which at the time of treatment was the longest course a patient had received. She's done wonderfully in her recovery from that point, and we've detailed this experience in the Journal of Antimicrobial Chemotherapy in the June 2022 issue.

In closing, rezafungin may offer us a once-weekly option for the treatment of candidemia and candidiasis, with a favorable PK/PD and side effect profile. This would fill an important need for transplant recipients and other immunocompromised patients. Thank you very much for your time today.

DR. BADEN: Thank you.

Speaker number 3, your audio is now connected. Speaker number 3, begin and introduce yourself. Please state your name and any organization you're representing for the record. Thank you.

DR. THOMPSON: Hello. Good afternoon. I'm

Dr. George Thompson, professor of medicine at the University of California Davis here in Sacramento, California. I do have a relevant disclosure. I've served as a consultant for Cidara in assisting the design of this clinical trial, and I've been in infectious disease practice for the last 16 years, and approximately half of my clinical time has been taking care of patients with a number of invasive fungal infections.

The patients I see with invasive *candida* infections here in the hospital continue to suffer, though, from the associated morbidity and mortality of this disease. And despite the availability of a number of antifungals, which have already been mentioned, we continue to see patients fail currently available agents.

We see patients with refractory candidiasis, and we continue to see patients with the sequelae of uncontrolled, ongoing infection with *candida* species, and it's no surprise that additional agents are urgently needed in clinical practice, and we thus chose to participate as a clinical site

in this study that completed the rezafungin versus caspofungin trial to help with this unmet need.

Our experience with rezafungin here was extremely positive, and our patients were very glad to participate and help advance our understanding of the disease and the treatment options. Patients with invasive candidiasis in some cases need several weeks of therapy, and once-weekly intravenous options substantially decrease the healthcare demands that our patients have to navigate.

I'm also very excited about the favorable pharmacokinetics of this agent and the potential to clear patients' infections more rapidly, hopefully decreasing their time in the ICU or admitted to the hospital, and we're very eager for this agent to potentially be available for our patients and added to the antifungal armamentarium. Thanks so much for your time.

DR. BADEN: Thank you.

Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce

yourself? Please state your name and any organization you're representing for the record. Thank you.

DR. SIKKA: Hello. My name is Monica Sikka. I'm an ID physician and associate professor of medicine at Oregon Health and Sciences University in the VA Portland Health Care system. I have no financial disclosures.

I've been practicing general ID for the last 13 years. In regards to invasive candidiasis infections, I've had a handful of patients with both native and prosthetic valve endocarditis. These patients are very challenging because the guidelines recommend liposomal amphotericin or high-dose echinocandins and flucytosine for 6 weeks, followed by suppression.

Amphotericin is difficult to administer outside of the hospital setting, but when it is, it can last almost the whole day. Echinocandins are daily infusions but can also be quite difficult for patients, and with prosthetic material, echinocandins work better on biofilm than azoles.

I'm here today to share my experience with using rezafungin through expanded access use in the hopes that it will help you understand the potential role this therapy could play in the treatment of patients like mine who needed options.

My patient is a 50-year-old male who underwent a sigmoid colectomy for a complicated perforated diverticulitis in August of 2018. His post-surgical course was complicated by short-gut syndrome and a high-output fistula that required TPN through a PICC. A year later, in August of 2019, he presented with a 3-week history of fevers, chills, sweats, and bone pain. His blood cultures grew *Candida parapsilosis*, and an echocardiogram was consistent with endocarditis of the aortic valve with a large vegetation. His infection was thought to be due to his requirement for the TPN, and he underwent a valve replacement later that year in September and was initially treated with micafungin but transitioned to oral fluconazole with a plan to continue it until the fistula was repaired in early 2020.

Unfortunately, because of lack of funds, the patient was off of the fluconazole for 1 to 2 weeks in December of 2019. In February of 2020, he was admitted for his planned takedown of the fistula, and he'd been feeling well prior to that admission and was given fluconazole before the surgery, but developed hypotension, fevers and ileus post-op. His blood cultures again grew *Candida parapsilosis*. The isolate was resistant to fluconazole, and an echocardiogram was consistent with endocarditis of the prosthetic aortic valve.

After 2 months of being in the hospital and about 21 days on liposomal amphotericin and flucytosine, my patient understandably requested to go home. To cure his infection, surgery was thought to be necessary, but to tolerate the procedure, he needed to be stronger and nutritionally optimized after having just completed the surgery. He was discharged home on itraconazole for suppression.

In November of 2020, he reported a week history of flu-like symptoms with cough, chest

burning, shortness of breath, and fevers up to 102 degrees Fahrenheit. He thought it was from the flu shot he had received recently, but blood cultures were obtained and again grew *Candida parapsilosis*.

The echocardiogram showed a large vegetation on his prosthetic aortic valve, and he remained fungemic for 24 days. He initially received liposome amphotericin, micafungin, and flucytosine, which continued as outpatient infusions. He then developed acute kidney injury, so we had to stop the amphotericin after about 3 weeks. He was transitioned to higher dose micafungin daily and flucytosine, which continued for about 5 months via a PICC, and during that time he had to have the PICC line changed because it was dislodged.

The daily infusions over this long period of time were understandably becoming a burden for my patient, and he requested something oral, but we didn't feel comfortable in an oral azole given his relapse. This is why we requested expanded access use of rezafungin weekly and started his treatment

in April of 2021.

I can report that he tolerated the treatment extremely well without any side effects. A year after his relapsed infection, he was back at work, had gained weight, and said he felt strong enough for surgery. He was evaluated by CV surgery and deemed high risk for recurrence. He remained on suppression for his infection with rezafungin for about 20 months, and in early December of 2022, after a second opinion by cardiovascular surgery, cardiology, and infectious diseases, he underwent replacement of the aortic valve, followed by 6 weeks of rezafungin and flucytosine. He completed that 6-week course of treatment last Thursday and will be monitored off of antifungals since his valve has been replaced.

Like my patient, patients with these severe infections can require long-term therapy or suppression. Daily infusions can be burdensome to patients and can make it hard for them to work or travel. The rezafungin once-weekly infusion allowed my patient to have his valve replaced, get

back to work, and have some semblance of normal life. He and I have been so grateful for access to this treatment option. Thank you for your time.

DR. BADEN: Thank you.

Speaker number 5, your audio is now connected. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. PAXTON: Hello. My name is Sue Paxton. I'm 71 years old and live in Manakin Sabot, Virginia, which is the small town on the western outskirts of Richmond Virginia. I have no financial disclosures regarding this matter.

I am speaking today to share my experience with rezafungin in the hopes that it helps you understand why a treatment like this is so desperately needed by other patients out there like me. In 2020, I successfully received a liver transplant for end-stage liver disease. In the days leading up to my transplant, I had been in shock and required a ventilator. Also, I experienced recurrent peritonitis, which my doctor

thought was due to my catheter. After being given a few IV antibiotics without success, I was transferred to another hospital for testing, and the doctors determined that I had a *Candida krusei* infection.

After 2 weeks of some pretty intense ID treatments, I was cleared to receive a transplant. I thought to myself, "Okay. You've been through this all, and now you're going to recover and get back to living." However, the *candida* infection was not done with me yet. It was sitting in my body just biding its time. Two days after surgery, I was still in the hospital with severe abdominal pain. Words cannot describe the pain that I was going through and the disappointment going through my mind and my family's. I had to fight through this for my family and understand the root cause in such pain.

The doctors performed a CT scan of my abdomen. They had to drain two liters of body fluid out of my body. They also found abscesses in my abdomen and pelvis. I was a mess. Cultures

showed that it was the same *candida* fungal infection, which now is resistant to the treatment that I had been given before. The cycle of building up fluids and draining fluids from my body continued. I thought this had to be the end of me physically and mentally and not keep this up.

Thankfully I had doctors that didn't give up on me, for me, and for my family. We invested in the investigational treatment for the *candida* infection and made the decision to try this investigation treatment. This is one that you are reviewing today, rezafungin. My advocates, my doctors, reached out to see if they could get me expanded access to it.

While my application was being considered, I kept going, but the pain was intense, and the fluid in my abdomen kept coming back despite treatments that just weren't working. Due to this worsening state of my health, with the available treatment of rezafungin, rezafungin was made available to me.

I received infusions in an outpatient center for a total of 12 weeks. After the first

4 treatments, I began to feel much better. By week 7 I was able to eat, and I was actually hungry and was able to put weight back on, which I badly needed, as my body was like a skeleton from all I had been through. My energy was back and I felt alive. Each time I went back, I got closer and closer to becoming whole again. By week 12, my infection was gone. Since 2020, I haven't had any fluid accumulation or issues sinse.

Since the hellacious [indiscernible] year of 2020, and not mentioning the pandemic, I have been recovering as a whole. I have energy, determination, and love to share all around. I have been able to spend time with my friends, my family, my two daughters, four grandchildren, and four granddoggies. I'm an active part in their lives and able to watch my grandchildren play sports and excel in school. I get to laugh and joke with my friends, and love reading novels, cooking, and working with brain game books.

My story is my own personal experience, but I hope you understand how fierce this *candida*

fungal infection is, and how it affects individuals similar to myself. Patients like me who are fighting it, and the doctors who are fighting to save them, need rezafungin. Without this, I would not be here. Please give them this treatment as an option. Sincerely, Susan Paxton. Thank you very much.

DR. BADEN: Thank you.

Speaker number 6, your audio is now connected. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you're representing for the record. Thank you.

(No response.)

DR. BADEN: We cannot hear you, speaker number 6, if you're talking.

(No response.)

DR. BADEN: Is speaker number 6 not available?

(No response.)

DR. BADEN: We are connecting sound to speaker number 6.

(Pause.)

DR. FRIMPONG: Okay, speaker number 6 -- last name that begins with a "T" – if you could please speak into your microphone. We're unable to hear you.

(Pause.)

DR. BADEN: We are still unable to hear speaker number 6.

(Pause.)

DR. FRIMPONG: OPH Speaker number 6, it looks like on your end, you're muted. If you could unmute and speak into the microphone. We're unable to hear you.

(No response.)

DR. FRIMPONG: Good afternoon. We're going to take a two-minute break to reconnect speaker number 6 for the OPH session, so please bear with us.

(Pause.)

DR. BADEN: Speaker number 6, your audio is now connected. Will speaker number 6 begin and introduce yourself? Please state your name and any

organization you're representing for the record. Thank you.

(No response.)

DR. BADEN: Go ahead, speaker number 6, please. You're on mute.

(No response.)

DR. BADEN: We cannot hear speaker number 6.

MS. TRIGG: Hello?

DR. BADEN: Yes. We can hear you. Please go ahead.

MS. TRIGG: Okay. My name is Kate Trigg, and I'm the infectious disease research manager at UC Davis Health. I do not have any financial disclosures; apologies for the connection issues as well.

I have been working at UC Davis Health for almost seven years as a clinical researcher with George Thompson, who spoke previously as a PI for clinical research studies. I worked on the phase 2 study directly as the clinical coordinator, enrolling participants, and moved into a management role during the phase 3 study. We treated nearly

50 participants between the two and have conducted other candidemia and candidiasis studies with novel therapeutics.

I've seen challenges with patient populations as a boots-on-the-ground researcher related to difficult to treat and follow patients. Many with candidemia are homeless or IV drug users, and those with invasive candidiasis often have a source control issue, leading to the deterioration and complicated hospital sources that we see on the ID consult service.

I work for a patient, and I'd like to share her success story with you. A woman with a complicated course was emergently transported to us from a small regional hospital 4 hours away, and was found to have candidemia just before her transfer. Upon arrival, she was intubated, and we enrolled her. After just 2 days, she was extubated and was eager to return home. Her recovery was swift and without any major complications once the appropriate treatment and care was provided.

From my perspective, rezafungin was well

received by participants in our clinical trials, and they often recovered very quickly. The once-weekly option, while not present in our clinical trial, was something that each patient expressed interest in, and as many recovered quickly, it was marked by a discharge from the hospital and also motivated many.

Participants who enrolled into these studies were quite sick, some incapacitated due to their infection and complicated course, and it was wonderful to see their course improve and infection cured in many cases. Thank you, and I appreciate your time today, and apologies again for the technological issues.

Clarifying Questions (continued)

DR. BADEN: Thank you, and I'd like to thank all of the open public hearing speakers for sharing their thoughts for the committee to carefully consider.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. We will now go

back -- there is an echo. Can somebody please mute themselves?

We will now resume clarifying questions for all the presenters thus far. I ask my fellow panel members to raise their hand icon to indicate that you have a question.

Please mute yourselves if you are not talking.

Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up questions with, "That is all for my question," so we can move to the next panel member.

DR. KIM: Dr. Baden?

DR. BADEN: Yes?

DR. KIM: This is Peter Kim. We wanted to circle back on one question for FDA regarding the

incidence of tremors in the caspofungin and anidulafungin labels. Our understanding on the --

(Crosstalk.

DR. BADEN: -- [indiscernible] provide that information?

DR. KIM: Our understanding on the read of the labels is the incidence was less than 5 percent, and I'll let Dr. Mishra provide any additional detail.

DR. MISHRA: Yes. That was from the clinical trials. Those were more on postmarketing adverse events. Again, it was from the clinical trials. I think in the anidulafungin label, what it says is there were 68 pediatric patients, and the incidence was less than 5 percent. I don't have a number, the number of trial patients for the caspofungin label, but again, it was listed as less than 5 percent incidence.

DR. BADEN: Thank you for providing that statement.

DR. SANDISON: Dr. Baden, this is Taylor Sandison with Cidara. We also have answers to

questions that we had deferred till after the break. Is this a good time to respond?

DR. BADEN: Yes. So what I was going to move to was to ask my colleagues on the panel to raise their hands if they have questions, and then to go to the applicant, Cidara, to provide any clarifications. And then I think there are many more questions from the committee that we would like you to help us clarify and understand.

So please, go ahead and provide the additional information.

DR. SANDISON: Okay. We're going to bring up AA-2. And while we're waiting for that, I just want to say that we're interested in the conversation that was held earlier. So just as a reminder, we are seeking a limited indication even though we did do the study in a general population, because that was, as we agree with the FDA, the best way to get the drug tested in as many patients as we possibly could.

So here we go with AA-2. Yes, it's up. Dr. Locke is going to answer this question.

DR. LOCKE: Hi. This is Jeff Locke, Cidara Therapeutics. This slide shows data that were requested earlier by Dr. Clark. This table shows the in vitro synergy antagonism data that were generated in a standard checkerboard assay format in the 96 well plate, following CLSI M27 guidelines.

We evaluated rezafungin in combination with amphotericin B, fluconazole, posaconazole, and 5-flucytosine against 6 strains of representative *candida* species, using two different MIC endpoints. As you can see by the color coding, there was no antagonistic interactions in any of the combinations of rezafungin with these drugs against the strains tested. Essentially, any value of 2 shows that there is no impact on either MIC value when tested in combination, and any value lower suggested there's some benefit in activity.

For each strain, there is at least one drug combination with rezafungin that resulted in additive, even very highly additive activity. In looking at the three right-hand columns, where a

more stringent MIC endpoint of 100 percent was used, there were some instances of true synergism represented by FICI values less than 0.5. And overall, the most consistent trend in highly additive or synergistic activity was seen when rezafungin was combined with azoles against *Candida auris.*

DR. SANDISON*:* Okay. Moving on to, I believe it was Dr. Patel had a question about the weights of individual patients that had tremor. We're bringing up the slide now. We have actually BMI here that's represented for each of the tremor patients, as well as the percentile of that BMI. So actually, they weren't clustered at the bottom of the BMI. It was actually fairly well distributed between 27.1 and 90.4 percentile.

Dr. Hunsberger I believe had asked questions about whether there was a combination of greater than or equal to 65 years; and gender, whether there was pooling of females in that group in terms of all-cause mortality. So we looked that up, and the numbers that we had here, you can see actually

there were more males in the 65 and older group, and you see the mortality broken down here. Again, this is the pooled analysis for both studies at the top and the ReSTORE alone at the bottom.

Finally, there was a question about whether COVID impacted the choice of the noninferiority margin and sample size. I'm going to ask Dr. Das to answer that question.

DR. DAS: Anita Das for Cidara. The study was designed and started prior to the start of the COVID pandemic. The first patient was enrolled in October 2018, and enrollment took over three years. The sample size was a fixed sample size. It was fixed at the time of design and was not changed while the study was ongoing.

DR. SANDISON: That concludes our after-the-break responses.

DR. BADEN: Thank you.

I think there are going to be several more questions from the committee to the applicant, and perhaps to the agency. I will start with one follow-up question to the applicant while my panel

members raise their hands.

An important issue that has been raised has been the noninferiority margin and reasons why that degree of margin was considered.

Can the applicant please help us understand the challenges with enrollment? You enrolled 199, I think; and if you had enrolled 299, we'd have much better data to make our assessment. Can you give us a sense of the challenges with enrolling this study to help us understand feasibility by time?

DR. SANDISON: Yes, absolutely. We started the study back in 2018, and we went to every site in the world that we felt could run this study with reasonable rigor to be able to present it to a regulatory authority for approval. We went to over 130 sites in Europe, Asia, South America, North America, and just throughout the world, and it took us just over three years between three and three-and-a-half years to enroll 199 patients. We stopped at that point because that was what our sample size was determined to be, based on the

20 percent NI margin and a 90 percent power. So that was how we got to that that number and stopped at that number.

DR. BADEN: Thank you. And obviously with time, there's always risk with change in standard of care. Thank you for sharing that challenge of being able to enroll this study in three years.

I'd like to invite Dr. Bennett to ask his question, and please specify if it's to the agency or the applicant.

DR. BENNETT: This is Dr. Bennett, and I have a question for the company as to a continuing study in China. I want to know if you're using the same protocol that you had previously in China. And I don't know what you could do with the data. I don't know if the FDA will allow you to add these two studies together or whether it's a separate study.

So tell me more about the ongoing study in China and what you're going to do with some data, because one obvious thing is, wouldn't it be nice to have larger numbers? Yes. But is China going

to allow you to do that? So could you go back and talk about what you're going to do with the data from China?

DR. SANDISON: Yes, sure. The ongoing ReSTORE China study is actually very similar, almost the same as what we did globally. In fact, we just continued the ReSTORE study ongoing in China. The purpose of that is because the Chinese Center for Drug Evaluation requires a certain number of patients to be of Chinese origin, so to fulfill that requirement, we needed to continue the study. And after the study is completed, those additional patients will be added to the current global study for presentation to the Chinese authorities. Of course, if the agency is interested, we will be able to share those data with the agency.

I will note, though, that the numbers that we will get from that study are incremental to what we have already enrolled, so we do expect an additional 47 or so patients in a 1-to-1 ratio of rezafungin to caspofungin to be enrolled.

DR. BENNETT: That answers my question completely. Thank you.

DR. BADEN: Thank you.

Dr. Rubin from the agency wanted to clarify a point from this morning.

Dr. Rubin, please clarify.

DR. RUBIN: Hello. This is Dan Rubin. I'm a statistical team leader at FDA. I wanted to make a few responses to some of the discussion this morning about noninferiority designs and about confidence intervals.

According to the usual logic of a noninferiority design, a drug could have a favorable benefit-risk profile if it meets a margin because there would be a willingness to trade some degree of loss of efficacy for some other advantage such as safety or convenience. Now as pointed out by Dr. Hilton, it's very hard to apply this logic with a mortality endpoint because a drug that decreases survival would be hard-pressed to have a favorable benefit-risk profile.

So the practical challenge that we run into

is one could say, "Well, let's decrease the margin to a very small value," and as pointed out by the applicant, as you decrease the margin, the sample size needed for a feasible study really increases. So even planning a study for a 10 percent margin rather than a 20 percent margin would mean a quadrupling of the sample size.

Now once that study has been done and it's not powered to rule out a narrow margin, as we've seen, there can be quite a bit of uncertainty about the treatment effect on mortality. We've seen from the 95 percent confidence interval that we can say with statistical confidence that rezafungin may be 9.7 better than caspofungin, but it might also be 14.4 percent worse.

Now in terms of where we think it is in that range, of course there's reason to hope that we're not at the most unfavorable value, given the point estimate was fairly similar between the two drugs and the fact that this is another echinocandin, but that is kind of what we can say, strictly speaking, from the confidence interval. But as was pointed

out by my colleagues, I think given this uncertainty, that's one major reason that we're seeking input from the committee.

Then I'd also invite my clinical colleague, Dr. Smith, to make any comments from a clinical standpoint about the 20 percent margin. Thank you.

DR. SMITH: Yes. Thank you. This is Dr. Smith, and just to point out that this was developed under a flexible development program, which allows us to consider uncertainty in the data at the time of NDA submission when we're trying to address an unmet need for a serious disease such as candidemia and invasive candidiasis.

As Dr. Rubin pointed out, there are trade-offs. To design a trial with a smaller NI margin, you need to have a larger enrollment, takes longer to enroll, which is longer until we get the data to review for possible approval. So again, our ask of the committee is to provide assistance with the risk-benefit assessment of whether there is a population of patients that have an unmet need for this serious infection for whom the benefits of

a drug would address an unmet need and potentially outweigh the risks related to the uncertainty from a smaller development. Thank you.

DR. BADEN: Any further clarification? That was very helpful.

DR. SANDISON: Dr. Baden, this is Taylor Sandison from Cidara. If possible, we have some clinical experts here who would like to also clarify the importance of these considerations of benefit-risk.

DR. BADEN: I mean, if it's related to the margin, to how we think about the noninferiority margin, that would be helpful.

DR. SANDISON: Okay. Then I would like to introduce Dr. Clancy.

DR. CLANCY: Yes. I'll just quickly say, as a clinician and thinking about the margin and trade-offs, the trade-off is you wouldn't have the drug available to treat people who gave testimony this afternoon. Those are the very cases that are not in the clinical trial where we envision this drug being used.

DR. BADEN: Understood.

DR. SANDISON: That completes our response.

DR. BADEN: Thank you.

I would like to go back to my panel members for further clarifying questions.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. Hi. I was going to ask Dr. Clancy; you're one of the leading experts in *fks* mutations and how they lead to resistance. Correct me if I'm wrong, but from what I have learned is that the in vitro data as far as the MICs and the activity of rezafungin against these organisms of higher MICs and so on is not that different from at least some of the other echinocandins.

One of the suggestions has been the PK characteristics in the front-loading would lead to a greater activity efficacy in vivo, and I think you gave one example of that. But even if it's observational, how much clinical data is there that the PK really provides an advantage in terms of treating resistant or less susceptible organisms?

DR. CLANCY: Dr. Swaminathan, you're right. The point isn't that the MICs between the echinocandins show difference, but because you're able to get peak concentration and you get the AUCs that you get with the front-loading of this drug, you're able to exceed MIC to such great extent that the AUC-to-MIC ratio becomes quite favorable, and that's the advantage over the existing agents. So to compare them on in vitro MIC measurements is really sort of the wrong measurement here.

There's anecdotal evidence at this point from case reports on rezafungin and utility such as the case I presented, where you might derive benefit from the loading. Certainly in the preclinical models, the work of David Andes, and Paul Ambrose, and people like this, I think within the field have established that these PK/PD parameters actually do have value, and they should be how we dose drugs.

As you know, in the antibacterial space, beta-lactams, and even going back in the day with aminoglycosides, these increasingly have been

brought into antimicrobial treatment practice in other spaces, and they work, and they've been shown to work, for example, with beta-lactams, maximizing time above MIC.

So I think it's just a matter of time of accumulating the data once the drug is out there and being used, but I'm fully confident that as in the animal models, the human data is going to validate these parameters, and in the future, this is how we'll be dosing all our drugs.

DR. SWAMINATHAN: Thank you.

DR. SANDISON: This is Taylor Sandison. Just to add one quick thing to that, because of the comparator, caspofungin, we weren't able to enroll *fks* mutants into our study at baseline. We did have one that ended up being an *fks* mutant on rezafungin that did improve and had successful outcomes, and we have experience with two in our expanded access that also had successful outcomes, as you can see listed here on this slide. And that concludes our response. Thank you.

DR. BADEN: Thank you.

Dr. Hilton?

DR. HILTON: Hi. Joan Hilton speaking. I put a quick question in the chatbox for Cidara. Does efficacy vary by either prior history of echinocandin use or to the ability to take azoles? What I'm trying to get at is unmet need.

DR. SANDISON: Yes. This is Taylor Sandison from Cidara. We do have some data on that. I'll just remind the panel that there is exclusion criteria for use of other drugs to a great extent, so I'm going to bring up what we have for prior echinocandin use and for no prior echinocandin use.

I will say that what we found in our phase 2 especially, there's going to be some bias that's inherent here because people who are started on empiric therapy tend to be those who are the most sick, but this is the data that we have for that.

DR. BADEN: Thank you.

DR. HILTON: Thank you. There may be other baseline risk factors that are more relevant than the ones that I named. I just wanted to get at what trade-offs you were considering when you

allowed a noninferiority margin. Maybe that could be summarized.

DR. SANDISON: Is that addressed to us or addressed to the agency?

DR. HILTON: I'm thinking it would be addressed by the company, but either is ok with me.

DR. SANDISON: Okay. Yes. This has to do with the M2, which 24 percent was chosen, given the potential efficacy, and safety, and benefits of rezafungin over the available echinocandins, in addition to the azoles where you have drug-drug interactions, et cetera. We know that rezafungin can have activity against multidrug-resistant *glabrata* -- this may be the only treatment option there -- and it has a large safety margin compared to other echinocandins. So when we were going through this process with the agency, there were a number of places where we felt that there were potential benefits to be had, and that went into the determination of the M2.

DR. HILTON: Thank you.

DR. BADEN: Thank you.

Dr. Clark?

DR. CLARK: Thanks. Nina Clark. I had two pharmacokinetic questions for the applicant. One was, given the differences in PK for rezafungin based on patient albumin levels, did you look at albumin as a subgroup, or albumin levels as a subgroup, for clinical outcomes in the pooled data?

Then my second question was, there were some extremely high creatinine clearances noted, at least in the FDA briefing, and I know that the drug's not normally cleared, to a big extent, renally; but do you know if markedly high renal clearances could have any effect on outcomes? Thank you.

DR. SANDISON: I will ask Dr. Flanagan to answer that question.

DR. FLANAGAN: Hi. Shawn Flanagan. Going back to the slide that we showed earlier on the covariate effects, when we were talking about BMI before, we also have albumin on this as well, and there are effects.

When we talk about PK, we're speaking about

the total concentrations. The echinocandins are heavily protein bound, and rezafungin is similar to the echinocandins there. So there is an effect of albumin, and it's statistically significant in the PK. The overall magnitude of change is not great.

We're looking on this slide between quartiles or quintiles, and they're going from really no change from the average to roughly 40 percent greater, and what we see in patients relative to healthy subjects is that these are subjects that have low albumin levels. They're going to have less protein binding and lower plasma levels. Their free concentrations that are important for efficacy are either unchanged or greater than in healthy subjects.

Creatinine clearance, it's not on this, but it was in the model, and it did not come out as significant. We've done studies just looking at creatinine clearance ranging from severe renally impaired subjects on dialysis or not on dialysis, all the way up to subjects who have altered and augmented renal clearance, with creatinine

clearance in the few to several hundred range, and there's no difference in the PK of rezafungin. There's no meaningful renal elimination of this compound, so you wouldn't expect to see changes with creatinine clearance.

DR. CLARK: Thanks very much.

DR. BADEN: Thank you. A follow-up question on the PK and dosing; you chose to go forward with the 400/200, not the 400/400, did that have any safety concerns, or do you think there was no augmented efficacy or PK with the 400/400?

If it is concentration-dependent killing, as you sort of suggest, wouldn't higher concentrations be better? Help me understand your dosing choice for 200.

DR. SANDISON: This is Taylor Sandison. There are two things to consider here, I think. One is the PK evaluation, so I'll just show from the start here the weekly-free drug AUC-to-MIC ratio.

As we know, most of the hard work is done in that first week of dosing at the 400-milligram

dose, which is the same in both groups, so as it happens, we expected that there wouldn't really be much difference between the two. Ultimately, an additional 200 milligrams in weeks 2, 3, and onward would maybe get you an additional dilution in terms of MIC when trying to capture specific pathogens. This felt like after that first week, it was probably not worth the additional dose, but that didn't really have to do with toxicity and necessarily reduced efficacy. As we saw in STRIVE, we felt like those numbers actually were fairly similar. I'm going to bring up the safety data from that.

We didn't see any evidence of toxicity in the higher dose group there. The adverse events -- severe adverse events, serious adverse events -- were all lower in the 400 once-weekly compared to the 400/200. So based on our evaluation here, the difference between the two is likely, again, to do with the smaller sample size in that phase 2.

DR. BADEN: Thank you.

Dr. Rose?

DR. ROSE: Thank you. This is Stacey Rose. I hope I'll be able to frame this question in a way that is helpful for the committee and is answerable by the sponsor, the company. I'll try and frame this.

When I try and look at the outcome, the mortality outcome, I also want to make sure that the way that it was constructed would have given a fair shot to the comparator. I understand that it is totally within IDSA guidelines to have given a minimum time for the caspofungin arm of 3 days before someone would do an oral step-down therapy; but on the other hand, I am trying to determine whether it was really apples to apples because for the rezafungin arm, those folks at a minimum got 2 doses, which means their exposure was really a 14-day exposure to the echinocandin, whereas in the caspofungin arm, a good percentage of them got a much more limited exposure to the actual echinocandin.

So can you maybe help me understand, from

your perspective, how it is that it is still appropriate to compare these two arms, recognizing that the drug exposure, when you're thinking about the echinocandin piece at least, would have potentially favored rezafungin in terms of the outcome?

Did I frame that in a way that's comprehensible?

DR. SANDISON: This is Taylor Sandison. Yes, for me it is, and this was a major concern of ours as well in that you have to have a study that is feasible in terms of patients. They're not going to want to take once-daily IV drugs. They're leaving the hospital. That's not what's done in real life. So to maintain patients on the study, you have to have some sort of reasonable way to still test them.

What we did to address this is that we had very strict criteria for stepping down. For caspofungin patients who did step down, they had to have been on the drug for a certain amount of time. They had to have blood cultures that were negative

for at least 48 hours. They had to be free of all signs and symptoms of candidemia and invasive candidiasis at the time that they stepped down. They had to be able to tolerate oral medication. They had to be ready for discharge, and they had to have a pathogen that was susceptible to fluconazole with proven microbiology data.

So given all of those things, we made every effort to make sure that those were equal. Then for those patients who did step down in comparison to those in rezafungin who stepped down to placebo, there was no difference in mortality between those groups.

DR. ROSE: Thank you.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Yes. I guess this would be directed to the agency.

This limited use of indication, first, would that preclude all of the types of patients who were excluded from the trials? Also, this drug might well be used like other echinocandins because of a lack of drug-drug interactions, as can be seen with

azoles, for example. But here we have the potential exclusion of patients who are at risk for neurologic dysfunction, and would the labeling be able to, then, contraindicate concurrent use of certain drugs because they're inherently potentially neurotoxic?

DR. KIM: Hi. This is Peter Kim. Thank you for the question, Dr. Swaminathan.

So certainly, the indication is yet to be written, constructed, in collaboration with the sponsor, if we head towards an approval. So once again, we're redirecting this question back to you and the committee as to if certain patient groups should be precluded from the indication or not. And certainly, we have mechanisms to certainly recommend against use in certain patients or patient groups, as well, in the labeling, but this is part of of our charge to the committee, one, to understand from you all whether or not there are clinical scenarios in which rezafungin fills an unmet need; and then, two, if not, what additional information would be needed to allow for a more

favorable benefit-risk assessment; and completely agree, this is a tough question, and this is why we're coming to you, to get your opinion on this as well. I hope that helps. Thank you.

DR. BADEN: Great.

Dr. Green?

DR. GREEN: Yes. This is Mike Green. My question is for Dr. Clancy.

Given what we've learned, and not learned, from the data that's been presented today and that we reviewed in advance of this meeting, if you were in our shoes, what patient cohorts would you include in a limited use approval?

Thank you, Dr. Clancy.

DR. CLANCY: Well, I'll tell you, Dr. Green, where I envisioned the drug having its greatest use and the greatest need, and there will be some constellation of people who lack IV access, can't get IV access, or have medical complications related to IV access in whom you wouldn't want a PICC or port.

I see a need in complicated, deep-seated

candidiasis cases, particularly within the intra-abdominal cavity following transplantation and complex abdominal surgeries, where abscesses, peritonitis, and widely distributed infections within the abdominal cavity are there, and the PK and drug distribution made a difference.

Prior azole exposure with resistance and, as was alluded to earlier, the inability to use azoles because of drug-drug interactions and prolonged QTc intervals, I think those are the two major reasons that we can't use them in the population that we would want to use these agents, and transplant recipients in particular, as you well know. That's potentially, in some of the *fks* mutants that are associated with lower level echinocandin resistance in particular, where you'd be able to make use of the PK/AUC issue and get well above the MICs, even against a putatively resistant bug to other echinocandins.

So I think those are the settings where it's going to have its greatest value.

(Crosstalk.)

DR. CLANCY: A fairly routine candidemia, you've got the choices that you've got, including other echinocandins, so there's not really use there unless people can't tolerate the other drugs.

DR. GREEN: So a follow-up question to that, again, I phrase my question deliberately based on the data that's available to us, so I think that your initial cohort, those that would not tolerate a line, or maybe would need a line for a very, very long period of time, avoiding that line seems like a plus and a logical jump, and the data that we have probably is supportive of that.

Again, do you think that the data that we were presented from the clinical trials, the phase 2 and phase 3 clinical trial, validates that there is efficacy as opposed to a belief that there will be efficacy in those other populations, the deep-seated infections where the higher exposure and preloading may be a benefit? But we haven't really seen studies that confirm that, and anecdotes, of course, may be favorable, but then the next three anecdotes may counteract that.

So would you agree with me that the data at this time is most established for those that would need to have lines for long times and that shouldn't have lines at all or for a very long period of time? Thank you.

DR. CLANCY: I think that I may reframe it to say that we have excellent preclinical data, including animal model data, in particular with abscesses in the intra-abdominal model, that we actually did with Dr. Perlin. I'll agree with you that the clinical trial data aren't there necessarily to support those conclusions, however, the clinical trials were incapable of addressing those patient populations because they were excluded. I think the cases that you heard today were people with no other treatment options and aren't getting treated or getting treated suboptimally.

So to me, that's the cost benefit. We can now offer something that at least has the preclinical data to support some possibility of improved efficacy as opposed to being unable to

give them anything, or to continue to give them already failing regimens.

DR. BADEN: Thank you for those thoughts.

I would like to now move to Dr. Siberry and your question.

DR. SIBERRY: Great. Thank you very much, Dr. Baden. This question is for the manufacturer. In light of this discussion about how we might envision a narrow use for those without other options, I'd like to get your opinion on two populations, first, adolescents, and second, pregnant people.

So on the first, rather than 18 years old, an artificial legal construct rather than a biologic one, is there a way to understand from the data you have what lower weight limit seems to be represented enough in your studies to make that the basis for potential inclusion?

Second, for pregnancy, I note and read that the REPROTOX studies were reassuring. This is different from caspofungin, where the preclinical studies actually suggested potential embryo-fetal

toxicity. In light of that, in situations where a pregnant person has no other feasible antifungal options and has candidemia, do you see a reason to have language, of course shared decision-making, that would include treatment of pregnant people within this narrow plan? Thanks so much.

DR. SANDISON: This is Taylor Sandison. I'll take the second part first, and then defer to Dr. Flanagan for the first.

We have not had a discussion about the treatment of pregnant people. Obviously, they're a very vulnerable population, and I think we would have to be certain, first, that no harm would be done. So I think we would require discussions and possibly further studies before we would embark on that. It is interesting to hear, though, that you see a potential difference between what caspofungin might do to a pregnant person versus the nonclinical results we had for rezafungin.

I'll ask Dr. Flanagan to come up to respond to the PK versus weight for adolescents.

DR. FLANAGAN: Hello. Shawn Flanagan. As

we showed earlier -- and we can probably bring up the slide again, though, on the population PK data -- there's a weight component, but it is not that significant in which it would call for different dosing in very small subjects. In terms of the the PK differences, they would not be enough to change dose, and the adult dose would be suitable for adolescents. As is suggested in some guidance, it's available now.

DR. SIBERRY: If I could quickly follow up, did your weight go down to 35 kilos? I'm just trying to get a sense of what weight was represented enough to help [indiscernible].

(Crosstalk.)

DR. FLANAGAN: Yes, 34 kilos was the lower bound. The lower quartile was approximately 54 and less.

DR. SIBERRY: Super. Thank you so much.

DR. FLANAGAN: You're welcome.

DR. BADEN: Thank you.

Any other questions from committee members for clarification from the agency or the applicant?

(No response.)

DR. BADEN: Seeing no further hands raised, I would like to proceed with the charge to the committee from Dr. Kim.

Charge to the Committee – Peter Kim

DR. KIM: Hi, everyone, and thank you, Dr. Baden.

Can we bring up the slide with the question?

Okay. Thank you very much for the discussion and the questions. This has been very helpful, and we look forward to further discussion around this voting question. We have one question for the committee, and this is a vote question.

Is the overall benefit-risk assessment favorable for the use of rezafungin for the treatment of candidemia/invasive candidiasis in adults with limited or no alternative treatment options?

If yes, it would help us to understand the context of use for rezafungin; that is the clinical scenario, or scenarios, in which rezafungin fulfills an unmet need. If no, please comment on

the additional information that would be needed for the benefit-risk assessment to be favorable for the use of rezafungin in this or these populations. Thank you.

Back to you, Dr. Baden.

Questions to the Committee and Discussion

DR. BADEN: Thank you.

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

We will proceed with the questions of 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 proceed with our question, which is a voting question. Before we get to voting, I want to open it up for discussion amongst the panel about the question and some of the issues raised.

My question, to stimulate and share in our

think collective thinking, a big discussion point that we've been discussing over the last several hours has been the noninferiority margin of 20 percent or 10 percent, and then an acknowledgement that a three-year effort led to a 200-person study.

I'd be interested in some of my colleagues' thoughts, particularly our statistical colleagues, on how we weigh the imprecision that we have from a three-year study and a 200-person enrollment with the mortality outcome versus wanting a tighter margin, but the time to achieve that would likely be several more years. How do you think about that balance, particularly the statistical colleagues? But I open that to all of the committee members.

Feel free to chime in or raise your hand, and I will invite you in to help think through this balance, which is at the heart of, I think, what both the applicant and the agency have been struggling with since the inception of this program.

Dr. Hilton, thank you for engaging.

DR. HILTON: Sure. Thanks.

This is very challenging. I do think that critical studies in science are and should be permitted to take as long as they need to take, so I don't think -- well, I do recognize that FDA did agree to the 20 percent margin when the study was designed, so I'm just kind of raising that going forward, hoping that more studies won't be designed with such a wide margin.

Regarding this study again, we do have a closed phase 3 trial that did meet the margin that was specified in advance, but do we have adequate data collectively across all studies to approve this? I'm extremely uncomfortable with the idea --

(Crosstalk.)

DR. BADEN: I would stay away from indicating how you may vote.

DR. HILTON: Okay.

DR. BADEN: But in terms of the context that we're all weighing [indiscernible - feedback].

Thank you, Dr. Hilton. I didn't mean to cut

you off. Voting needs to occur before we [indiscernible].

DR. HILTON: Okay. Excuse me. Maybe I should just cut it there just to avoid stepping on my toes.

DR. BADEN: No, but thank you, but the conceptual issues are so important.

Dr. Hunsberger, I look forward to your comments on this challenge.

DR. HUNSBERGER: Yes. This is Sally Hunsberger, biostatistician. I do think this is a very difficult situation because of the wide confidence intervals. What we can see when we get into these small numbers, again, the phase 2 study showed the exact problem when you had two groups that were artificially split because they received the same treatment; yet one looked very promising and the other didn't, or was quite different. So it's just a matter of these small numbers and the randomness.

I feel the truth is that we don't know -- it could be 14 percent worse, and I think that's on

the table; do we feel comfortable giving a treatment that could be 14 percent less? I think trying to limit who would receive this is an interesting situation because it isn't who you treated.

If I understand the eligibility criteria, it wasn't people who had failed other treatments that were entered into this study, and that would be where we need the data to know if this is a good use of this treatment for people who failed other treatments. Again, I go back to cancer, and that's the way they would design studies there, and they wouldn't design it for this huge noninferiority margin for mortality as the endpoint.

So it's challenging to say that you should use it for a group of people that you really don't have data on. And then we go back to this --

DR. BADEN: [Indiscernible].

DR. HUNSBERGER: Sorry.

DR. BADEN: Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. I agree with all

that. I think that getting the kind of data that one would like to have is, as you pointed out, going to take a very long time.

One thing I wanted to ask Dr. Hunsberger, for example, is when we talk about that 95 percent confidence interval -- and it could be as bad as 14 percent worse -- if you look at the distribution of those likelihoods, isn't it much more likely that the difference is in the middle of that; that there's a sort of bell-shaped likelihood of it being -- that the likelihood that it's really much better or much worse is less than that mean that we have for the effect?

Does that make sense?

DR. HUNSBERGER: It's true. If you did a 90 percent confidence interval, which would be saying that we're 90 percent confident that the truth [indiscernible - feedback], the confidence interval would be much smaller.

Sorry. I'm getting an echo. But it might go from 15 percent -- or I'm sorry. It might go from 10 percent to minus 5 percent. So yes, if you

were comfortable with a 90 percent confidence interval, you might be able to rule out 10 percent. So you're right. The probability is that it's closer to the reduction of 2 percent rather than the 14 percent, but the smallness of the groups is reflected in this wide confidence interval, and I go back to that phase 2 study, where you can actually see how variable these small groups are with the estimates of the mortality.

DR. SWAMINATHAN: Lindsey, I'm not sure what I'm allowed to comment on, but you can censor me if it's not appropriate before the vote.

DR. BADEN: No, no. Please don't state or directly indicate how you're going to vote, but raising issues that reassure you, concern you, is appropriate and helpful.

DR. SWAMINATHAN: Okay.

It would help us to understand the context of use. I think in the real world, we often have a great deal of difficulty treating patients once they leave the hospital even with the same drug, and it often boils down to insurance coverage and

just almost silly things, like patients don't have insurance to get IV setups at home, and it makes it very, very difficult to give once-daily echinocandins.

I think even if there's a possibility that this is similar -- for which I agree there isn't conclusive proof based on these numbers, but there's preclinical data, it's a class, it's not a new drug -- that practically it would afford treatment, potentially for people who would not otherwise be able to get this treatment.

Some of these other things were brought up that we use drugs like this even if we don't know that they're better, but because we think that they're better based on nonclinical data as salvage therapy. So when we have patients who are failing antifungal therapy, we have to go get compassionate use approval and do an individual IND for each patient, and it often precludes patients getting these drugs in time or they have to only get it in an academic medical center where you have the bandwidth to do that.

So there's, I think, a lot of logistical reasons while this drug, even if it's not necessarily going to be used in every candidemic patient, gives one the opportunity to treat people. So there's a benefit that's not necessarily a direct proven medical superiority, for example.

DR. BADEN: Understood. Thank you.

Mr. Flatau?

MR. FLATAU: Yes. This is Arthur Flatau again. I think that given that this is a rare disease, and it seems to have, I would say, modest benefit of being once weekly as opposed to daily, that would be useful and put another tool in the doctor's toolbox for treating this. But I would hate to see this be put off because we don't have perfect data in a rare disease setting.

Certainly, I think we need more study of this drug; particularly, the data is pretty limited in terms of it doesn't penetrate tissues better than the existing drugs and things like that. But I would hate to not see this being used. It seems to be about as safe as the other drugs in this

category and doesn't seem to be hugely better, but it does have that modest benefit of being once weekly. I think that's the benefit I see, that we can conclude with some confidence at this time. That's my thoughts on it.

DR. BADEN: Thank you.

Dr. Bennett?

DR. BENNETT: I'd like to hear what my colleagues think about starting therapy of candidemia or deeply invasive candidiasis with rezafungin. I don't think we would -- and I'll justify that in a minute -- but if that is what my colleagues think, then I can see defining the unmet need as limited to patients who need prolonged therapy but for whom an azole oral is not indicated.

So why would we not start right away? I'd like to look at the reasons that I would not start right away. I don't see an advantage over the existing echinocandins, and I'm not convinced that they're a primary therapy with resistant organisms. I've been unimpressed with the correlation between

MICs and outcome in candidiasis, so I don't think if I saw it was resistant species, that I would pick rezafungin.

What about Neil Clancy's thought about abdominal infections? These are very complicated because often they are bacterial as well as fungal and need good drainage. It's often hard to get good drainage over the vulnerable spots, so I don't think there's any reason to try to pick out abdominal or deep infections as a need to start with rezafungin. And then the need for prolonged therapy, well that is a separate question.

What about the other, conversion of blood cultures? I don't find that helpful. Aminoglycosides, gentamicin increased there the rapidity of clearing of *Staph aureus* infection from [indiscernible], but it didn't actually improve outcome; and the [indiscernible], the earlier treated response with fluoroquinolones didn't translate an overall effect. So early clearance is not where it's at; it's the final result.

What about the patients who do want to get

rid of an IV? Let's remember these are all very complicated patients who came in the house with something else, comorbidities, and we will need the IV in place for a while to treat the comorbidities. So the time when you want to get rid of the IV is later, not initially.

So at any rate, I would have said that there is an unmet need, and it's for prolonged therapy in patients for whom an oral azole is not indicated; and that's the end of my comments, Dr. Baden.

DR. BADEN: Thank you, Dr. Bennett.

Dr. Hardy?

DR. HARDY: Hello. This is Dr. Hardy from Los Angeles. When I look at the question, I guess the thing that comes up in my mind most is what limited or alternative treatment options were even studied in the two trials that we're asked to look at here, in that all these patients had candidemia or invasive candidiasis, and they were randomized equally to a proven licensed drug or an unproven drug comparator. There wasn't a criterion for resistance or failure of previous therapy

necessarily as part of the entry criteria for the trials that we've been asked to look at.

So what it really boils down to here, I think, is the ability to give a drug once a week with a temporary infusion source unique enough to say that that is an unmet treatment option. In many ways, I think we can probably say that it is because there are patients who can go home from the hospital and be intermittently treated, which is the practicality of what this drug really offers some patients and, again, is that enough to be able to distinguish a drug for even limited approval?

If anything, I think what we would need to really do is think hard about what else we would want this company to do in order to be able to continue to do research with this drug as part of their post-approval commitments to really show that there is, in fact, some efficacy, but reserve this drug for those persons who have limited intravenous access problems, or who need to be out of the hospital for other reasons, and be able to receive this medication on an infusion basis of once a

week. But even that oftentimes is not compelling enough to say that should be the basis for approval of a new drug, even on a limited basis.

So I think the question somewhat is even not clearly defined as to what we're supposed to vote on, but I guess we're going to have to find some ways to come up with that before this meeting is over.

DR. BADEN: Thank you. We will come back to the formal process to vote on the question shortly.

Dr. Siberry?

DR. SIBERRY: Thanks very much, Dr. Baden, and I'm following your instructions to think about what has me concerned and what has me relatively reassured.

From an efficacy standpoint, I was also concerned about predicating this on a single trial with a 20 percent noninferiority interval, but I'm reassured that the actual results have a point estimate that is relatively close. If the point estimate had been much more unfavorable and the confidence interval just barely missing 20, I think

that would make me more concerned, but the actual point estimate and seeing kind of the side-by-side comparisons overall, I find reassuring.

In terms of safety, same thing. I was concerned about this potential for tremors being something that hadn't been adequately studied, but when I heard more about the animal studies and more about the details of the tremors observed, and knowing that they are enrolling several hundred in a 13-week prophylaxis trial that uses the same dose, 400 followed by 200 weekly, I anticipate that that will be the opportunity to continue to get more information, so that reassures me. Thanks.

DR. BADEN: Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: I can't help but think of, when people bring up what additionally this brings to the table and how good the data, the approval of isavuconazole. It was almost anecdotal, the data that was used to obtain that approval, but yet it has proven to be very useful in a variety of contexts. The same sort of issues with is there

additional benefit and primarily the long latency and less frequent infusion, could be said of all the vancomycin type drugs that have an extended half-life, but yet they do have their place.

I can think of several occasions in the past six months where we've had patients in either the leukemia service, stem-cell transplant, or solid-organ transplant, where I would have been calling up Neil Clancy and saying, "What can I get for this guy? Because he's still candidemic." And he would have probably told me that I'd have to go through the paperwork and get the compassionate use approval from this company. I think that even though it's not a large number of patients, these are some of the most needy patients, and it would be great to be able to just prescribe it.

I agree with Dr. Bennett. I don't think it should be, nor do I think it will be, approved for just garden variety candidemia upfront because you can start them on caspofungin, get the sensitivities, put them on fluconazole, so I don't see this as being your run of the mill, and I

suspect it'll be highly restricted on every hospital formulary.

DR. BADEN: Thank you, Dr. Swaminathan.

I see no further hands, although, Dr. Swaminathan, good thing that we're not the committee a little over 20 years ago that reviewed caspofungin for its initial approval as first in class, as I think the data were logarithmically thinner.

The agency and our committee, as we are facing today, has to make very difficult decisions on imperfect data, given the needs of our patients and the data that are available. So that is why I think our colleagues at the agency have brought us together, so thank you for helping to further highlight the challenge.

I see Dr. Perez has raised his hand.

Dr. Perez?

DR. PEREZ: Thank you, Dr. Baden. Yes, following on what you just said, I think, to me, it is very reassuring that rezafungin is indeed -- the molecule looks a lot like anidulafungin, and the

modification has a tremendous impact on its PK and on all of that, but at the end of the day, it's a new version of a drug that has a great track record, such as is anidulafungin, within a class of echinocandins that are very well known by us as well.

DR. BADEN: Thank you.

Seeing no further hands or hearing no further commentary, although I welcome them if anyone has further comment, I will proceed to the voting question.

Dr. Frimpong -- wait. Sorry.

Dr. Green, I see you raised your hand. Please go ahead and comment.

DR. GREEN: Yes. Hi. This is Mike Green. Thanks, Dr. Baden.

I guess I would not be doing my job as one of the two pediatric infectious disease specialists on the committee if I didn't follow up on Dr. Siberry's earlier exploration of going into the adolescent age group, even on the data that is already available, and of course raising the

concern on the issues that have been raised and the potential benefit, particularly needing the home therapy with daily infusions that apply to children as well as to adults.

I would just add to our comments about the challenges with home therapy, that I don't know about the rest of you, but we have had a number of patients go home that we're trying to do home IV and other drug infusions, and we cannot get home care companies for them because like other aspects of health care, they are suffering from shortages.

So I just hope whatever decisions we make, if we do defer or if we support a limited use, that the agency and the company build a plan together to look at this in younger age groups, including adolescents but also pediatrics, and eventually pediatrics down to a young age group, hoping that the tremor signal does not show worse in young people like it did perhaps in the animal model. Thank you.

DR. BADEN: Thank you.

We will now proceed with our question, which is a voting question. Dr. Frimpong will provide the instructions for the voting.

Dr. Frimpong?

DR. FRIMPONG: Our question is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you'll be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button. That is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you only need to select

the radio button that corresponds to vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to; however, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. BADEN: I do not see any questions. I don't think there are any questions about the process, so I will now read the question.

Is the overall benefit-risk assessment favorable for the use of rezafungin for the

treatment of candidemia/invasive candidiasis in adults with limited or no alternative treatment options?

If yes, it would help us to understand the context of use for rezafungin; that is the clinical scenarios in which rezafungin fulfills an unmet need. If no, please comment on the additional information that would be needed for the benefit-risk assessment to be favorable for the use of rezafungin in these populations.

Are there any questions about the wording of the question?

(No response.)

DR. BADEN: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 1.

DR. FRIMPONG: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. FRIMPONG: The voting has closed and is

now complete. Once the vote results display, I'll read the vote results into the record.

(Pause.)

DR. FRIMPONG: The vote results are displayed. I'll read the vote totals into the record. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however, you should also address any subparts of the voting question, if any.

There are 14 yeses, 1 no, and no abstentions.

DR. BADEN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish to. I will start with the order on the screen.

Mr. Flatau?

MR. FLATAU: Hi. Yes. This is Arthur Flatau. I voted yes. I think the modest benefit

of weekly dosing is helpful. I think we all hope that rezafungin is useful for deeper tissue penetration, but there's not much data, so I urge further study on that. Thank you.

DR. BADEN: Dr. Perez?

DR. PEREZ: Hi. This is Federico Perez. I voted yes because the data presented substantiate that the benefit is likely to exceed any risk, and this would be an option for patients who have no other alternatives. Thank you.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: This is George Siberry. I voted yes. While I don't think there are enough data here to recommend this for routine use, I do think there are enough efficacy and safety data to justify the use in patients with these life-threatening illnesses who have no alternative treatments essentially available to them.

I will add that I think that this should include adolescents perhaps with a lower weight range, again, for the same reasons. If they have no alternative, then this may be an incredibly

important option. And finally, for pregnant people with candidemia, we don't protect them by excluding them from a drug like this if this is the only viable option, so I would also ask for language that is permissive or shared decision making for pregnancy. Thank you.

DR. BADEN: Dr. Hilton?

DR. HILTON: I don't think that the full body of the evidence meets the clinical trials approval criteria set out in the FDA documents, so in particular, I do not think that a pooled analysis makes sense when you don't specify that the analyses will be pooled until after you know what the results are. I think that the company is well on its way to approval, especially based on this drug. Their evidence is growing and it's looking great in their favor, but I think it's really important that standards be maintained.

DR. BADEN: Thank you.

Dr. Bennett?

DR. BENNETT: This is John Bennett, and I voted yes. I'd like to congratulate the company on

a very well-designed study and adequate data collection. I don't agree with all of their conclusions, but I think they did a fine job of running the study. I think that rezafungin is indicated for patients who need further therapy and for whom an oral azole is not indicated.

That's the end of my comments, Dr. Baden.

DR. BADEN: Thank you.

Dr. Baden. Lindsey Baden. I voted yes. I think the data demonstrate comparable activity with the comparator, however, I share everyone's concerns that the data are quite limited and that additional data are needed to better understand safety and efficacy. However, given the available data and the increased convenience and accessibility of this class of agent, it warrants being available to those patients who have no other alternatives for treating their fungal infection. Be it a toxicity side effect or logistic issue, there is value in the ability to treat our patients with this class of agents who would otherwise not have access to it, so I voted yes.

Dr. Green?

DR. GREEN: Yes. Hi. This is Michael Green, and I voted yes. This was a challenging decision due to the small sample size of the single phase 3 study and, consequently, its limited power; and because of this, an observed difference in the primary endpoint of 30-day all-cause mortality of 2.4 percent was associated with an upper limit of 14.4 percent when confidence intervals were determined.

While the observed result is quite acceptable and reassuring, the upper limit of 30-day mortality is certainly concerning. In my mind, we definitely need more data before allowing full approval. The question, though, is whether there is an appropriate population and acute need of a limited use of approval and who that population is.

The potential antifungal superiority achieved by higher drug exposure or better in vitro activity, to my mind, is unproven at this time. Accordingly, while those who've failed treatment

with available drugs might be a candidate for inclusion in this limited use approval, we don't actually know that these patients would benefit. However, a population that would seem appropriate would be inclusion of those who are going to need more prolonged treatment perhaps greater than 2 or 4 weeks of therapy. This would seem a cohort would definitely benefit from weekly infusions, with the ability to be at home, and potentially without a central line by use of infusion centers.

This would be even more relevant for those who require chronic or suppressive therapy like we heard about during the public comment and some of the examples that Dr. Clancy gave. I also would include those being treated for *candida* infections related to IV drug use in whom you would not want to send home with a central line.

For this reason, I voted yes for the limited use with the target population as noted above. I hope that the sponsor will accrue additional data either from the ongoing phase 3 study in China, though that sounds like that's limited numbers, or

implementation of additional study. With more numbers, we'll have a narrow confidence interval.

Finally, I'd like to see data accrued in kids and pediatrics because we use echinocandins all the way down even to the premature population and would like to see the potential benefits of this really available for the entire spectrum of age. Thank you very much.

DR. BADEN: Dr. Patel?

DR. PATEL: Hi. This is Nimish Patel, and I voted yes. For me, the safety and efficacy presented today by both the company and the FDA was reasonable. Where I think the unmet need is, it's not necessarily an individual one but an unmet need from a societal perspective. It is well known that the inpatient burden of invasive candidiasis is quite high. I think this offers a very exciting approach to treating patients and facilitating earlier discharge from inpatient settings, and I think there is a really elegant economic story that will likely emerge from the potential approval of this agent.

DR. BADEN: Thank you.

Dr. Clark?

DR. CLARK: Yes, Nina Clark. My yes vote was based on the need to expand the availability of a limited pool of antifungal agents that we currently have in the setting of more resistance and difficulties using the available agents and even widespread drug shortages. I thought that the safety and efficacy data were acceptable, particularly for a known class of drug, and met the FDA guidance for a limited use indication and should be labeled as such. I guess I might add cautions for those who have underlying neurologic disease and those with localized infections that were excluded from the trials. Thank you.

DR. BADEN: Dr. Murphy?

DR. MURPHY: This is Richard Murphy. I voted yes. I think the totality of the human and animal data suggests that it's probable that rezafungin is as efficacious and as safe as caspofungin. The groups in my practice in whom I would find this drug useful would be patients in

whom ongoing venous catheter use is contraindicated or undesirable, patients who use injection drugs, and patients with failure of initial therapy for candidemia and invasive candidiasis.

DR. BADEN: Thank you.

Dr. Walker?

DR. WALKER: Hi. Dr. Roblena Walker. I voted yes. Although the data is limited, I voted yes specifically for the patients who wouldn't have any other available treatment options. However, it may be useful to assess benefits, or risks, amongst other populations, specifically among other ethnic groups such as Latinos, African Americans, as well as among children and pregnant women. Thank you.

DR. BADEN: Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sally Hunsberger. I voted yes. I do think this study was a missed opportunity to go longer, knowing that it would take maybe four or four-and-a-half years, but we would actually have quite a bit of data that could really have helped us out a lot, so I do think it was a missed opportunity.

I agree totally with all of the things Dr. Green said. I think you have to limit it to people with no treatment options. I don't think you can just say across the board, although the problem is that's not the population we have any data in, so I do think they need to pursue another study, a randomized study. Now that it would be considered noninferior, there should be equipoise, and then doing another study should be possible. So I think this needs to be followed up with another study, but at this time I voted yes with limited indications. Thank you.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Yes. Sankar Swaminathan. I voted yes. I agree that the efficacy data are not as statistically compelling as one would like, but this is a drug with a known mechanism of action and plenty of animal data that I feel fairly comfortable that it is, in fact, efficacious.

There are limited drugs in our armamentarium against those difficult and refractory cases, which occur particularly in immunocompromised patients,

and I think that having this available, and also, as others have said, having the ability logistically to send people home with a drug that would otherwise take daily IV therapy that's often for a variety of financial, insurance, and other logistical reasons not possible, there's a lot of benefits in specific patients with this drug. Thank you.

DR. BADEN: Dr. Rose?

DR. ROSE: Yes. Stacey Rose, and I voted yes. I think others have articulated the reasons quite well, so I won't necessarily rearticulate, although I will mention, I do like the idea considering the practicalities of this drug as part of what we articulate in the limited use statement, something along the lines of when once-weekly IV dosing is preferred, because I do think that those practical implications of the dosing are important here.

In terms of other populations that I think we need more data for a risk-benefit assessment, I think we've all articulated a need for how this

drug performs in patients with deep-seated infections. I think there's also some claims from the sponsor regarding the efficacy as part of treatment for resistant strains of *candida*, and I think we should investigate or get more data, perhaps even from real-world data, once the drug is approved. But I think we need to see more information there before we can perhaps add resistant infections to our list of indications for this drug, and then as others have stated, the importance of looking for the efficacy in populations such as kids, adolescents, and pregnant populations.

Then I just wanted to restate what someone else had mentioned earlier and which came up in discussion, which is I think we should consider whether we need to articulate that the studies were conducted with the exclusion of folks who perhaps were at a higher risk for neurologic complications, and that that may be something that clinicians need to consider when they're considering using rezafungin. Thank you.

DR. BADEN: Dr. Hardy?

(No response.)

DR. BADEN: You're on mute, Dr. Hardy.

(No response.)

DR. BADEN: We still do not hear you.

To the technical support crew, is there any issue with Dr. Hardy's connection?

(No response.)

DR. BADEN: It looks like you're on mute, Dr. Hardy.

DR. HARDY: Hello? Can you hear me now?

DR. BADEN: Yes, can hear you now.

DR. HARDY: Great.

Hi. This is Dr. David Hardy. Being the last, I also voted yes because of many of the very good points made by others, particularly Dr. Green and Dr. Clark.

I just want to emphasize that I think the unmet need here is certainly the ability to use this therapy as an outpatient. While it is an intermittent weekly intravenous infusion that is something that can be practically accomplished more

easily than other available therapies, it has met, I think, just the bare minimum standards for safety and efficacy, which are so important for FDA approvals, and those need to be further explored and investigated before any further approval beyond a limited indication is ever granted, and will become part of what I would say would be the post-approval requirements that the FDA would require of the company. That's it.

DR. BADEN: Thank you.

In summary, the 14 yeses and 1 no, the no was concerned that the strength of the evidence was inadequate given the severity of the outcome, and the pooled analysis approach does not make sense in this setting. The yes had several supportive comments and comments to take care with if this agent were to move forward.

It is part of a class we know well; that's very reassuring. It has weekly dosing, which has incredible advantages in the clinical arena. There was a concern that the comments around better tissue penetration, better activity against

resistant organisms, and better intra-abdominal treatment were not substantiated by the data, but these were not compelling considerations from the overall tenor of the discussion.

In those patients who have no alternatives or limited alternatives, or have incipient complications from lines or drug interactions with the azoles or inactivity of the azoles, this has a favorable set of attributes. The concern about safety, the data are limited, and the issues raised on the neurology front need to be borne in mind and considered carefully if this agent were to be used, and the need to have data in other important complications; more diverse complications, younger individuals, pregnant individuals also need data to help guide potential use.

So overall, the yeses were in favor of a limited use indication. The paradox in that comment is that the population that would be recommended in the limited use were largely unstudied. Ergo, follow-up data in this population would be very important, however it is moved

forward, to have reassurance that this agent behaves the way we think it will in this population who could benefit the most.

I think that captures the comments. I'm open to any of the committee members to correct any of my statements.

(No response.)

DR. BADEN: Excellent.

Hearing no corrections, I will take that as a compliment, and before we adjourn, are there any last comments from the FDA?

(No response.)

DR. BADEN: You're on mute or we have --

DR. FARLEY: Sorry. We think we fixed it now, Dr. Baden. Can you hear me?

DR. BADEN: Yes, we can hear you now.

DR. FARLEY: Sorry. It is this platform.

John Farley for the agency, and on behalf of the agency, we want to thank a number of parties. We want to thank the sponsor for their preparation for today in their presentations, as well as their responsiveness to our questions throughout the

review cycle. I want to thank the open public hearing speakers today for their very valuable perspectives, and insights, and lived experiences. I want to thank the FDA review team for excellent preparation today.

Lastly, we are very grateful to the committee for their valuable advice and recommendations today. We thank you for your service today and in the future as we anticipate a busy spring ahead. So thank you very much, and good evening.

Adjournment

DR. BADEN: Thank you, and I echo Dr. Farley's comments. The comments from the agency, from the applicant, were tremendous. The committee engagement was a terrific discussion, and I'm certain will be very helpful to the agency in its deliberations; and to our handlers for making this platform work despite it thwarting us, we thank you for pulling it off and allowing us to have a very successful discussion; and to all who have joined and listened, we hope this has been

helpful in understanding how the approval process works and how we weigh very challenging issues to bring better medications to our patients.

So we will now adjourn the meeting. Thank you all.

(Whereupon, at 3:56 p.m., the meeting was adjourned.}