FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Virtual Meeting

Monday, April 17, 2023

9:00 a.m. to 2:52 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Takyiah Stevenson, 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)

Laura C. Block, PharmD

(Patient Representative)

Founder/Partner

Usagi Medical Group

Cary, North Carolina

Joan F. Hilton, ScD, MPH

Professor, Biostatistics

Department of Epidemiology & Biostatistics

University of California

San Francisco, California

FDA PARTICIPANTS (Non-Voting)

John Farley, MD, MPH

Director

Office of Infectious Diseases (OID)

Office of New Drugs (OND), CDER, FDA

Adam Sherwat, MD

Deputy Director

OID, OND, CDER, FDA

Peter Kim, MD, MS

Director

Division of Anti-Infectives (DAI)

OID, OND, CDER, FDA

Dmitri Iarikov, MD, PhD

Deputy Director

DAI, OID, OND, CDER, FDA

Mayurika Ghosh, MD

Clinical Reviewer

DAI, OID, OND, CDER, FDA

Karen Qi, PhD

Statistical Reviewer

Division of Biometrics IV

Office of Biostatistics, CDER, FDA

Simone Shurland, PhD

Clinical Microbiology Reviewer

DAI, OID, OND, CDER, FDA

Xiaohui (Tracey) Wei, PhD

Clinical Pharmacology Reviewer

Division of Infectious Disease Pharmacology

Office of Clinical Pharmacology, 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

(9:00 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 are not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email is currently displayed.

My name is Dr. Lindsey Baden, and I will be chairing this meeting. I will now call the April 17, 2023 Antimicrobial Drugs Advisory Committee, AMDAC, to order. Dr. Stevenson is the acting designated federal officer for this meeting and will begin with introductions. We'll first start with the standing members of AMDAC.

Introduction of Committee

DR. STEVENSON: Good morning. My name is Takyiah Stevenson, and I am 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: Dr. Lindsey Baden. I'm an infectious diseases physician investigator at Brigham and Women's Hospital, Dana-Farber Cancer Center, and Harvard Medical School in Boston.

DR. STEVENSON: Dr. Green?

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

DR. STEVENSON: Dr. Hardy?

DR. HARDY: Good morning. My name is Dr. David Hardy. I'm an infectious disease specialist and serve as an adjunct clinical professor at the Keck School of Medicine at the University of Southern California in Los Angeles.

DR. STEVENSON: Dr. Hunsberger?

DR. HUNSBERGER: Hi. I'm Sally Hunsberger. I'm a biostatistician at NIAID at NIH. Thank you.

DR. STEVENSON: Dr. Murphy?

DR. MURPHY: Hi. Richard Murphy. I'm an infectious disease physician at White River

Junction VA Medical Center, and I am affiliated with Geisel School of Medicine at Dartmouth.

DR. STEVENSON: Dr. Patel?

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

DR. STEVENSON: Dr. Perez?

DR. PEREZ: Good morning. My name is Federico Perez. I'm an infectious disease physician at the Cleveland VA Medical Center and Case Western Reserve University in Cleveland, Ohio.

DR. STEVENSON: Dr. Siberry?

DR. SIBERRY: Good morning. I'm George Siberry, pediatric infectious disease physician and medical officer at the U.S. Agency for International Development, Office of HIV/AIDS. Thank you.

DR. STEVENSON: Dr. Swaminathan?

DR. SWAMINATHAN: Hello. I'm an infectious disease physician and researcher at University of Utah Health, and I'm the chief of the Division of

Infectious Diseases.

DR. STEVENSON: I'm sorry. Dr. Swaminathan, could you say your full name and affiliation, please?

DR. SWAMINATHAN: Yes. Sorry. Sankar Swaminathan, University of Utah School of Medicine.

DR. STEVENSON: Thank you so much.

Dr. Walker?

DR. WALKER: Good morning. I'm Dr. Roblena Walker, CEO and research scientist of EMAGAHA, INC. in Atlanta, Georgia. Thank you.

DR. STEVENSON: Dr. Richa Chandra?

DR. CHANDRA: Hello. I am Richa Chandra. I am representing the pharma industry on this advisory committee as a non-voting member today, and I work as the clinical development head for infectious diseases at Novartis Pharmaceuticals. Thank you.

DR. STEVENSON: Now I will introduce the temporary voting members.

Dr. Block?

DR. BLOCK: Hi. I'm Laura Block, and I'm

acting as a patient advocate today with direct experience with sepsis and pneumonia in the ICU, but I am a retired hospital pharmacist. I work as an event medic with Usagi Medical Group.

DR. STEVENSON: Dr. Hilton?

DR. HILTON: I'm Joan Hilton. I'm professor of biostatistics at UCSF School of Medicine.

DR. STEVENSON: Thank you.

I will now introduce the FDA participants.

Dr. Farley?

DR. FARLEY: Good morning. I'm John Farley, director of the Office of Infectious Diseases within the Office of New Drugs at CDER, FDA.

DR. STEVENSON: Dr. Sherwat?

DR. SHERWAT: Good morning. My name is Adam Sherwat. I'm the deputy office director from the Office of Infectious Diseases.

DR. STEVENSON: Dr. Kim?

DR. KIM: Good morning. My name is Peter Kim. I'm the director of the Division of Anti-Infectives in the Office of Infectious Diseases. Thank you.

DR. STEVENSON: Dr. Iarikov?

DR. IARIKOV: Good morning. My name is Dmitri Iarikov. I'm the deputy director in the Division of Anti-Infectives, CDER, FDA.

DR. STEVENSON: Dr. Ghosh?

DR. GHOSH: Good morning. This is Mayurika Ghosh, clinical reviewer, Division of Anti-Infectives, CDER, FDA.

DR. STEVENSON: Dr. Qi?

DR. QI: Good morning. My name is Karen Qi. I'm the statistical reviewer from FDA, CDER, Office of Biostatistics.

DR. STEVENSON: Dr. Shurland?

DR. SHURLAND: Good morning. My name is Simone Shurland, and I'm the clinical microbiology reviewer of CDER, Division of Anti-Infectives.

DR. STEVENSON: Dr. Wei?

DR. WEI: Good morning. My name is Xiaohui Tracey Wei. I'm the clinical pharmacology reviewer in the Division of Infectious Disease Pharmacology from the FDA.

DR. STEVENSON: Thank you, everyone. I will

hand it back to the chairperson.

DR. BADEN: Thank you, Dr. Stevenson.

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 be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

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

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

media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during break or lunch. Thank you.

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

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug Administration, FDA, is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, 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 their 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 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 the discussion of new drug application, NDA, 216974, for sulbactam-durlobactam for injection, submitted by Entasis Therapeutics, Inc. The applicant's proposed indication is the treatment of hospital-acquired bacterial, HABP, and ventilator-associated bacterial pneumonia, VABP, caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex, or ABC, in adults. This is a particular matters meeting during which specific matters related to Entasis Therapeutics' NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public

statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. 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 Pharmaceutical Corporation.

We would like to remind members and temporary voting members that if the discussions involve any other product or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you, and now I will hand it back to the chairperson.

DR. BADEN: We will now proceed with FDA introductory remarks from Dr. Sherwat.

Dr. Sherwat?

FDA Opening Remarks - Adam Sherwat

DR. SHERWAT: Good morning. My name is Adam Sherwat, and I'm the deputy director of the Office of Infectious Diseases in the Center for Drug Evaluation and Research. I would like to welcome the advisory committee members and the applicant, Entasis Therapeutics, to today's meeting to discuss the new drug application for sulbactam-durlobactam. The purpose of today's advisory committee meeting is to discuss whether the data contained in the new drug application for sulbactam-durlobactam, abbreviated as SUL-DUR, for injection support a favorable benefit-risk assessment for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, which will be abbreviated as HABP and VABP, due to susceptible strains of *Acinetobacter* species, including carbapenem-resistant *Acinetobacter baumannii-*

calcoaceticus complex, which will be referred to as CRABC organisms.

CRABC infections represent an unmet medical need in the U.S. due to the emergence and spread of *Acinetobacter* resistance and limited treatment options. Nosocomial pneumonia is the most common disease caused by *Acinetobacter* species, with approximately 50 percent of *Acinetobacter* healthcare-associated infections in the United States caused by CRABC. Patients with CRABC infections appear to have a higher risk of mortality than patients with carbapenem-susceptible *Acinetobacter baumannii* infections, with overall mortality rates in HABP/VABP caused by CRABC ranging from approximately 45-to-60 percent.

The sulbactam-durlobactam development program is an example of a streamlined program for targeted therapy for a high unmet need pathogen, namely CRABC. For antibacterial drugs with the potential to treat serious infections in patients who have few or no available treatments, FDA may consider a more flexible program to facilitate

development, provided there are adequate data to demonstrate that the drug is safe and effective and the statutory standards for approval are met.

The efficacy data to support the proposed indication was from one phase 3 trial conducted in two parallel parts, Part A and Part B. Part A was a randomized, investigator-unblinded, assessor-blinded, non-inferiority assessment that compared sulbactam-durlobactam versus colistin for the treatment of HABP, VABP, ventilator pneumonia, or bacteremia caused by *Acinetobacter baumannii-calcoaceticus* complex organisms, which will be abbreviated as ABC.

Part B had a single arm to evaluate sulbactam and durlobactam for the treatment of ABC-infected subjects who were resistant to colistin or who were ineligible for Part A due to other factors. Because Part B was a single-arm design, the efficacy assessment of sulbactam and durlobactam was based on Part A.

In Part A, subjects were randomized in a 1-to-1 ratio to receive either sulbactam and

durlobactam or colistin. Randomization was stratified by infection type, baseline disease severity, and geographical region. Subjects in both groups received imipenem and cilastatin as the background therapy. The study duration was 7-to-14 days of treatment and 14 days of follow-up after treatment. The primary endpoint was 28-day all-cause mortality, assessed using a 20 percent non-inferiority margin. The FDA subsequent presentations will provide additional details on these design elements.

In summary, Part A in the phase 3 study demonstrated that sulbactam and durlobactam was non-inferior to colistin for the primary efficacy endpoint of 28-day all-cause mortality, as the upper limit of the 95 confidence interval for the treatment difference in mortality was 3.5 percent, meeting the prespecified 20 percent non-inferiority margin.

The primary efficacy analysis population was the CRABC microbiologically modified intent-to-treat population. This included patients

infected with *Acinetobacter baumannii-calcoaceticus* complex organisms, causing HABP, VABP, ventilator pneumonia, or bacteremia, where the baseline *Acinetobacter baumannii-calcoaceticus* complex organism was found to be resistant to carbapenem but not resistant to sulbactam, durlobactam, or colistin. Of note, approximately 96 percent of subjects in the CRABC microbiologically modified intent-to-treat population had HABP or VABP, and only 3 subjects had bacteremia.

The safety profile of sulbactam-durlobactam was generally consistent with other beta-lactam and beta-lactamase inhibitor drugs; however, the safety database was limited in size with less than 200 patients receiving sulbactam-durlobactam at the proposed dose and duration for the treatment of HABP and VABP. Given the limited size of the safety database, if sulbactam-durlobactam is approved, postmarketing safety monitoring will be important in further assessing the safety profile of this product.

Our question for the advisory committee is

whether the overall benefit-risk assessment is favorable for the use of sulbactam-durlobactam for the treatment of patients with hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex organisms; and if yes, to provide your rationale, and if no, to provide your rationale and describe what additional studies or trials are needed.

The following are my references for this introductory presentation. I would again like to thank the advisory committee for their participation in today's meeting, and thank you for your attention, and I will turn the meeting back over to Dr. Baden.

DR. BADEN: Thank you, Dr. Sherwat.

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

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

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

We will now proceed with the applicant's, Entasis Therapeutics, presentation.

Applicant Presentation - Shruta Rege

DR. REGE: Good morning. I'm Shruta Rege, senior vice president and head of Regulatory Affairs and Development Operations at Entasis Therapeutics. I would like to thank the FDA, the

chair, and members of the committee for giving us the opportunity to present our data supporting the safety and efficacy of sulbactam-durlobactam for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus*, including carbapenem resistant to *Acinetobacter.* Let me provide you with some background information for today's meeting.

Acinetobacter baumannii is a major global public health concern. This is a gram-negative opportunistic bacterial pathogen and is a predominant member of the *Acinetobacter baumannii-calcoaceticus* complex. For the rest of today's presentation, we will refer to this complex as *Acinetobacter.*

Acinetobacter is often associated with infections of the lungs, bloodstream, urinary tract, skin, and other soft tissues. These infections are associated with high morbidity and mortality, ranging anywhere from 30-to-70 percent globally in hospital acquired- and ventilator-

associated pneumonia.

These infections have become increasingly difficult to treat as multidrug-resistant strains have emerged. Carbapenem-resistant *Acinetobacter*, or you might also hear this referred to as CRABC, is considered an urgent public health threat by the U.S. Centers for Disease Control and Prevention and is also categorized as priority 1 critical by the World Health Organization. In fact, *Acinetobacter* is the fifth leading cause of death associated with resistance globally.

Recent guidance from the March 2022 Infectious Diseases Society of America states that there is no clear standard-of-care antibiotic regimen for infections caused by carbapenem-resistant *Acinetobacter*. This leaves physicians and patients with a significant need for a safe and effective treatment option that provides a clinically meaningful benefit over existing therapies.

Sulbactam-durlobactam, or SUL-DUR, as we will refer to it on the slides, is a targeted

therapy that was developed for the treatment of infections caused by this high unmet need pathogen, carbapenem-resistant *Acinetobacter.* Sulbactam, while commonly known as a beta-lactamase inhibitor, is also a well-understood beta-lactam with intrinsic antibacterial activity against a limited number of bacterial species, including *Acinetobacter.* Sulbactam works by inhibiting penicillin- binding proteins, which are required for bacterial cell wall synthesis, thereby resulting in cell death. However, increases in beta-lactamase mediated resistance have rendered sulbactam generally ineffective. Durlobactam, which is a beta-lactamase inhibitor, has potent activity against class A, C, and D beta-lactamases. When used in combination with sulbactam, durlobactam restores sulbactam's activity against resistant *Acinetobacter.*

Let me briefly review the relevant development and regulatory history. Durlobactam was discovered in 2012, and we started our first clinical study in 2016. Our clinical program

consists of eight total studies, including six phase 1 studies; one phase 2 trial in patients with complicated urinary tract infections and acute pyelonephritis, evaluating the safety and pharmacokinetics of sulbactam-durlobactam; and one pivotal phase 3 trial in patients with infections caused by resistant *Acinetobacter.*

In addition to the clinical program, Entasis also has an ongoing expanded access program for patients who were ineligible for participation in the clinical trials and who had serious and life-threatening infections caused by drug-resistant *Acinetobacter*. Entasis has worked closely with the FDA to design and develop a unique pathogen focused clinical program that followed FDA's unmet need guidance and also allowed for flexibility in the development of sulbactam-durlobactam.

FDA recognized the high unmet need and the potential for sulbactam-durlobactam to address this unmet need. In 2017, FDA designated sulbactam-durlobactam as a QIDP, or qualified

infectious diseases product, and also granted fast-track designation. In March of 2022, we had a pre-IND meeting where the FDA agreed that the phase 3 data, along with the microbiology, pharmacology, and toxicology data in the nonclinical package, were adequate for the FDA's review of the sulbactam-durlobactam new drug application. The new drug application for sulbactam-durlobactam was submitted in September last year and accepted for priority review in November of 2022.

In our presentation today, you will hear that patients with infections caused by carbapenem-resistant *Acinetobacter* have a significant unmet need that represents a major public health concern. Limited treatment options for these infections has led to increases rates of morbidity and mortality . We conducted microbiology and nonclinical pharmacology assessments that provide confirmatory evidence of sulbactam-durlobactam's activity against *Acinetobacter.* Phase 1, 2, and 3 data were utilized

for robust population PK modeling and PK/PD target attainment analyses were conducted to support our proposed dosing regiments.

In the phase 3 trial, sulbactam-durlobactam met the prespecified primary non-inferiority endpoint of 28-day all-cause mortality when compared to colistin. All prespecified secondary endpoints were also met, including clinical and microbiological responses, thereby supporting the clear benefit. Importantly, sulbactam-durlobactam was well tolerated across the clinical program with a favorable safety profile. The phase 3 trial also met the primary safety objective with a statistically significant lower incidence of nephrotoxicity when compared to colistin.

The totality of evidence supports a favorable benefit-risk profile for sulbactam-durlobactam, and this addresses the urgent unmet need for a safe and effective treatment option for patients with infections caused by *Acinetobacter,* including carbapenem-resistant strains. Based on the

totality of evidence, we're requesting that sulbactam-durlobactam be indicated in adults 18 years and older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex.

This indication reflects the population that was studied in our phase 3 trial and is also consistent with guidance from the FDA on labeling for antibacterial products. The proposed dose is 1 gram of sulbactam and 1 gram of durlobactam given every 6 hours and administered as a 3-hour intravenous infusion. Dose adjustments are recommended based on renal function.

With that background, here is the agenda for the remainder of today's presentation. Professor David Paterson will discuss the urgent unmet need for new treatments for infections caused by *Acinetobacter*; Dr. Alita Miller will then review the microbiology and pharmacology data; and Dr. David Altarac and Dr. Drew Lewis will discuss the

efficacy and safety data for sulbactam-durlobactam. Dr. Patrik Hornak will share his clinical experience with sulbactam-durlobactam, and I will then summarize with concluding remarks.

We also have additional experts with us today to answer your questions. All external experts have been compensated for their participation in today's meeting. Thank you. I will now turn it over to Professor Paterson.

Applicant Presentation - David Paterson

DR. PATERSON: Hello. My name is David Paterson, and I'm a professor at the Saw Swee Hock School of Public Health at the National University of Singapore. There I direct a clinical research network comprising 40 hospitals across Asia, and I remain clinically active. I previously spent 10 years working for the University of Pittsburgh Medical Center and have dedicated my career to researching and caring for patients with difficult-to-treat infections.

In my time as an infectious diseases physician, I've observed the rise of multidrug

resistance, and specifically infections due to carbapenem-resistant *Acinetobacter*, and for me, this is the number one unmet need for new antibiotics. So today I'll be discussing this urgent public health issue and why patients and physicians need a safe and effective treatment option for these devastating and life-threatening infections.

Infections due to multidrug-resistant *Acinetobacter* are a growing and global threat. The WHO has identified carbapenem-resistant *Acinetobacter* as a priority pathogen for the development of new antibiotics due to increasing resistance to existing therapies, and carbapenem-resistant *Acinetobacter* was associated with approximately 326,000 deaths worldwide in 2019.

Speaking specifically to the United States, the CDC has deemed carbapenem-resistant *Acinetobacter* an urgent public health threat, and in 2020, there was a significant increase in the number of multidrug-resistant, gram-negative infections in U.S. hospitals, of course, coinciding

with the COVID pandemic. Of these, the increase in carbapenem-resistant *Acinetobacter* cases was by far the greatest, with rates that were 78 percent higher than in 2019. So let me just take a step back to explain why *Acinetobacter* is such a problem.

Acinetobacter is a challenging threat to hospitalized patients, and this is because critically ill patients are susceptible to infections, and furthermore, the organism can survive a long time on a variety of surfaces. It's therefore quite easy to spread, making it a notable cause of outbreaks in the hospital and nursing home settings.

While pneumonia and bacteremia are the most common infections caused by *Acinetobacter*, these organisms have also been a notorious cause of skin and soft tissue infections, wound infection, and osteomyelitis in wounded U.S. military personnel. They can also cause urinary tract infections and post-neurosurgical meningitis.

Infections caused by *Acinetobacter* can be difficult to treat due in large part to the rising

rates of antimicrobial resistance. *Acinetobacter* is intrinsically resistant to penicillins and has also acquired resistance genes for almost all antibiotics used to treat gram-negative bacteria, including fluoroquinolones, aminoglycosides, cephalosporins, and carbapenems. Between 1997 and 2016, the SENTRY Antimicrobial Surveillance Program has reported decreasing susceptibility rates among *Acinetobacter* isolates for all observed antimicrobial agents, including carbapenems and in all geographic regions, and this creates a serious problem because once *Acinetobacter* exhibits carbapenem resistance, it generally has acquired resistance to most other antibiotics, leaving few, if any, remaining therapeutic options.

We see high morbidity and mortality in patients with infections due to *Acinetobacter, a*nd furthermore, these are associated with longer hospitalizations and increased healthcare costs. The incidence and prevalence of these infections are increasing in patients with long hospitalization and immunocompromised patients like

our transplant recipients, burns patients, or patients receiving treatments for cancer, and also patients in long-term care facilities.

These cases can become incredibly complex and sometimes life-threatening partly due to delayed or inappropriate antimicrobial therapy. This leads to mortality rates in the United States due to hospital-acquired or ventilator-associated pneumonia due to *Acinetobacter* at almost 30 percent. In addition, a recent analysis of U.S. healthcare costs showed that infections due to carbapenem-resistant *Acinetobacter* had the highest attributable costs among hospital-onset invasive infections, ranging from $20[000] to $128,000 per patient.

So let's discuss how we currently treat these patients. Guidance from the IDSA states there is no clear standard of care antibiotic regimen for infections due to *Acinetobacter.* They've identified developing clinical practice guidelines as a top initiative in their strategic plan. Beta-lactam, fluoroquinolone, and a minor

glycoside resistance to *Acinetobacter* has limited the effectiveness of these classes, and then resulted in reliance on carbapenems for treating these infections. However, carbapenem resistance has emerged as an urgent threat worldwide; in part because carbapenem use has increased for infections caused by multidrug-resistant gram negatives. In fact, in recent years, up to 69 percent of carbapenem-resistant *Acinetobacter* infections in the United States have been treated with our last resort antibiotics, colistin or polymyxin B, and this is an important point.

We do not have sufficient data available to make evidence-based treatment recommendations for this infection. Randomized-controlled comparative effectiveness trials between the commonly used agents are limited, so physicians often rely on combination therapy since no antibiotic regimen has shown clear efficacy. The ISDA guidelines also point out that data to help us prioritize specific agents with activity against carbapenem-resistant, or to understand the additive benefit of commonly

used combination regimens, are incomplete, highlighting the urgent and unmet medical need for this patient population. Without these ideal data, being available, physicians are simply left to try different agents or combinations based purely on their clinical judgment.

In summary, infections due to resistant, *Acinetobacter* species are a major public health concern both in the United States and also globally. They're associated with increased morbidity and, very importantly, increased mortality due to our limited therapeutic options. These infections are serious, they're life threatening, and they've become much more difficult to treat as resistance rates rise. As a result, carbapenem resistance has emerged as an urgent health threat worldwide, in part due to the increased use of carbapenems to treat multidrug-resistant gram negatives, including *Acinetobacter*.

As an infectious diseases physician who has seen too many patients run out of effective options, I need a new, safe effective therapy for

my patients with these serious infections, and I am encouraged by the clinical data you'll see today that sulbactam-durlobactam can fill this important unmet need.

Thank you. I'll now turn the presentation to Dr. Miller.

Applicant Presentation - Alita Miller

DR. MILLER: Thank you, Dr. Paterson.

I'm Dr. Alita Miller, senior vice president and head of research at Entasis Therapeutics. I will now review the microbiology and pharmacology of sulbactam-durlobactam.

As Dr. Rege mentioned earlier, sulbactam has a unique spectrum of antibacterial activity that's limited primarily to *Acinetobacter* species; however, sulbactam resistance in *Acinetobacter* is now common due to the acquisition of beta-lactamase gene. In fact, most clinical isolates of *Acinetobacter* encode multiple types of beta-lactamase, as shown on this slide.

The Venn diagram on the right shows the results of whole genome sequencing analysis that

was performed on 84 multidrug-resistant *Acinetobacter* clinical isolates. Each Ambler class of beta-lactamases is represented by a different color. As a reminder, class A, C, and D are serine beta-lactamases, while class B enzymes are metallo beta-lactamase. As you can see, all 84 of these isolates encoded a class D beta-lactamase. What was striking was that most isolates also encoded an additional class A or extended-spectrum class C gene. In fact, 45 percent of isolates that were analyzed encoded genes for class A, C, and D enzymes. In contrast, only one encoded for a class B beta-lactamase. Therefore, the only kind of a beta-lactamase inhibitor that can restore sulbactam activity in *Acinetobacter* is one with activity against all the serine beta-lactamase classes, which is exactly the spectrum of activity of durlobactam.

As shown earlier, durlobactam is a member of the DBO class of beta-lactamase inhibitors whose predecessors include marketed agents such as avibactam. The table on the bottom of this slide

compares the biochemical activity of durlobactam to avibactam against representative, purified beta-lactamases. Avibactam inhibits class A and C beta-lactamases, but has limited to no activity against class D enzymes, as shown on the first row of this table.

Durlobactam was designed to expand a spectrum of inhibition to include class D enzymes, which are key drivers of beta-lactam resistance in *Acinetobacter* species, as I showed on the previous slide. It is important to note that none of the DBO beta-lactamase inhibitors has activity against class B metallo beta-lactamases.

The expanded spectrum of durlobactam, as compared to avibactam against beta-lactamase, is shown on the second row of the table. Durlobactam not only has a broader spectrum of inhibition than avibactam against representative class A, C, and D beta-lactamases, it's also significantly more potent than avibactam against all the enzymes tested, as summarized in the third row of this table.

Historically, sulbactam has demonstrated clinical efficacy against infections caused by *Acinetobacter*. Unfortunately, this activity has been eroded in recent years due to the acquisition of beta-lactamases in this pathogen, as I mentioned before. This slide shows the MIC distribution of sulbactam alone, compared to sulbactam-durlobactam, in a global surveillance study conducted between 2016 and 2020 against 4,252 clinical isolates of *Acinetobacter*. To put this in perspective, over 50 percent of these isolates were carbapenem resistant.

The data for sulbactam alone, shown in light blue, the MIC_{90} corresponds to the MIC value at which the growth of 90 percent of isolates is inhibited. The MIC_{90} of sulbactam alone against this collection was 64 micrograms per mL, which is significantly higher than the susceptibility breakpoint of 4 microgram per mL, which is indicated by the dashed line on the left; however, addition of durlobactam restored the activity of sulbactam, as shown in dark blue. The combination

of sulbactam-durlobactam had an MIC_{90} of 2 microgram per mL, and 98 percent of isolates tested had sulbactam-durlobactam MIC values less than or equal to 4 microgram per mL.

Multiple studies were conducted in the laboratory to assess the potential for development of resistance to sulbactam-durlobactam in *Acinetobacter,* which was found to be quite low. The frequency of spontaneous resistance using both laboratory and contemporary clinical isolates was found to be in the 10^{-10} range at 4 times the MIC. Resistance emergence was also low in static time kill experiments, where sulbactam-durlobactam was bactericidal against multiple clinical isolates.

In large global surveillance studies, fewer than 2 percent of isolates had sulbactam-durlobactam MIC values greater than the preliminary breakpoints of 4 microgram per mL. In the phase 3 trial, 8 of 175, or 4.6 percent, of baseline *Acinetobacter* isolates had sulbactam-durlobactam MIC values greater than 4 microgram per mL. Five of these had an MIC of 8 microgram per mL, which is

the preliminary breakpoint for intermediate susceptibility, and the other three had sulbactam-durlobactam MIC values of 16 microgram per mL.

This graph shows the antibiotic susceptibility of 175 baseline *Acinetobacter* isolates from patients in phase 3. These were tested at the central laboratory against sulbactam-durlobactam and approved comparator agents. The Y-axis shows the percent cumulative inhibition of all strengths tested for each comparator agent at each MIC, as shown on the X-axis. The MIC_{90} is shown by the dashed horizontal line.

On this type of graph, the curves farthest to the left correspond to the most active antibiotics in vitro, whereas the curves that are right-shifted or hover near the bottom respond to antibiotics with poor or no activity in vitro. The antibiotics that were administered to patients in the phase 3 trial are labeled on this graph. Sulbactam-durlobactam is in blue, colistin is in

orange, and imipenem is in green. Note that imipenem was used as background therapy in the study and will be discussed further, later in the presentation.

You can see from this graph that the phase 3 baseline *Acinetobacter* isolates were highly antibiotic resistant. In fact, nearly all were carbapenem resistant, as shown by the green imipenem line on this graph. Overall they were 96 percent multidrug-resistant, 85 percent extensively drug resistant, and 15 percent percent pan drug resistant. In contrast, 4.6 percent of strains were considered non-susceptible to sulbactam-durlobactam based on the preliminary breakpoint of 4 microgram per mL.

The susceptibility to individual antibiotics is shown in the legend on the right. Again, sulbactam-durlobactam was by far the most active, with over 95 percent susceptibility observed. The next most active antibiotic in vitro was colistin with 83 percent susceptibility. However, that means that 17 percent were resistant to colistin,

which is notably higher than what we observed in surveillance studies, which was 4 percent colistin resistance.

Moving to non-clinical safety, we found that durlobactam was well tolerated in rat and dog toxicology studies out to 28 days of consecutive administration. Safety margins based on human dose equivalency ranged from 1.4 to 24.8-fold in rats and 8.3 to 16.6-fold in dogs. Durlobactam was devoid of any genotoxicity and no adverse findings were observed in a full battery of reproductive toxicology and safety pharmacology studies.

The pharmacokinetics of sulbactam and durlobactam are similar to other beta-lactams. Both sulbactam and durlobactam had linear, dose proportional pharmacokinetics, low protein binding, and low volume of distribution, exceeding plasma volume, indicating distribution to extravascular space. In a phase 1 study, sulbactam-durlobactam demonstrated good distribution into the lungs.

Both sulbactam and durlobactam are primarily renally eliminated as unchanged drug and have a low

potential for drug-drug interaction. Population PK analyses were used throughout the clinical development of sulbactam-durlobactam, and the final population PK model incorporated clinical data from Phase 1, 2, and 3 trials. The model showed that dose adjustments are needed based on renal function. No dose adjustments are warranted based on other covariates, including age, sex, race, weight, and site of infection. The population PK models were considered robust for the probability of target attainment analyses.

Sulbactam-durlobactam was found to be efficacious in murine neutropenic thigh and lung models of *Acinetobacter* infection. These models have an established track record of their clinical translatability in antibiotic drug development. In vitro and in vivo studies support that the PK/PD driver of efficacy for sulbactam is time above MIC or the percentage of time unbound concentrations remain above the MIC. A magnitude of 50 percent is required for a 1 log reduction in bacterial colony-forming units, or CFU, over 24 hours. For

durlobactam, the PK/PD driver of efficacy is AUC over MIC or the ratio of the area under the curve from time zero to 24 hours to the MIC. A magnitude of 10 is required for a 1-log reduction CFU when sulbactam also reaches its PK/PD target.

Using these PK/PD targets and population PK modeling, probability of target attainment analyses, or PTA, were conducted for the purposes for the proposed doses. The results for these analyses are summarized on this slide. The graph on the left shows the PTA in plasma and the graph on the right shows it in epithelial lining fluid or ELF.

An important component of these analyses is the overall sulbactam-durlobactam susceptibility of isolates from multiple global surveillance studies. The sulbactam-durlobactam MIC distribution for 7,026 global *Acinetobacter* isolates is shown in gray bars. The Y-axis on the right of both graphs corresponds to the frequency each MIC was observed for this collection of strains. Overall, 99 percent of isolates had an MIC of less than or

equal to 4 microgram per mL. The Y-axis on the left of both graphs corresponds to the PTA for sulbactam-durlobactam, with each renal function category shown in different colors.

These graphs show that the PTA across renal function categories exceeds 90 percent in both plasma and ELF, as indicated by the horizontal dashed line at MICs of less than or equal to 4 microgram per mL, as indicated by the vertical dashed line. Ninety percent is a well known and accepted PTA cutoff value that correlates with clinical efficacy.

In summary, this robust, nonclinical, microbiology, toxicology, and pharmacology package supports the sulbactam-durlobactam clinical development program, including the proposed indication and dosing regimen. Thank you. I'll turn the presentation to Dr. Altarac.

Applicant Presentation - David Altarac

DR. ALTARAC: Thank you, Dr. Miller.

I'm David Altarac, and I'm the chief medical officer at Entasis. Today I'll review the outcomes

and efficacy analyses from our pivotal phase 3 trial that demonstrate the clinically meaningful impact that treatment with sulbactam-durlobactam provides for patients with hospital-acquired and ventilator-associated pneumonia infections caused by *Acinetobacter*. The global, pivotal phase 3 trial enrolled patients with infections caused by *Acinetobacter*, including resistant *Acinetobacter.*

The trial was conducted in two parts. Part A was a randomized, assessor-blind, active-controlled portion designed to enroll patients with *Acinetobacter* hospital-acquired or ventilator-associated bacterial pneumonia, ventilated pneumonia, or bacteremia. In Part A, patients were randomized 1 to 1 to receive sulbactam, durlobactam, or colistin infusions, with both groups receiving imipenem-cilastatin as background therapy. Background therapy was necessary to ensure coverage for other bacterial pathogens, as polymicrobial infections are not uncommon. Patients received study treatment from 7-to-14 days as clinically indicated. Part B was

the open-label portion of the trial that included patients who are intolerant of colistin or had infections with *Acinetobacter* resistant to colistin. This also permitted enrollment of patients with infections in other sites.

At the time of the phase 3 trial, colistin was selected as the comparator, as there were no newly approved treatment options, and colistin was one of the few available options for treating serious resistant *Acinetobacter* infections. Despite the known toxicities, colistin still remains an often prescribed antibiotic, either alone or in combination to treat these serious, life-threatening infection.

Patients were assessed at end of treatment, test of cure, and late follow-up. Test of cure visit was to be completed 7 days after the last dose plus or minus 2 days, and survival was assessed at day 28. Adult patients were eligible for the trial if they had a known infection caused by *Acinetobacter* as either a single pathogen or member of a polymicrobial infection based on a

culture.

The rapid diagnostic test allowed for early detection and enrollment, but had to be confirmed by a positive culture. To be eligible, patients needed to have either no more than 48 hours of potentially effective antimicrobial therapy before their first dose or the clinically failing prior treatment. Clinical failure was defined as either clinical deterioration or failure to improve after at least 48 hours of antibiotic treatment. In addition, patients needed to have an APACHE 2 score between 10 and 30 or a SOFA score between 1 and 11.

For Part A, patients were excluded if they had an infection known to be resistant to colistin or polymyxin B. For both Part A and B, patients were excluded if they had a hypersensitivity or allergic reaction to any beta-lactam or any contraindication to the use of imipenem or cilastatin. Patients with pulmonary diseases that would preclude evaluation of a therapeutic response in patients with deep-seated infections were excluded.

I'd like to now discuss the endpoints for the trial. The primary efficacy endpoint was 28-day all-cause mortality in Part A evaluated in the carbapenem-resistant, *Acinetobacter,* microbiologic modified intent-to-treat population, which I will refer to as the primary efficacy analysis population.

The primary analysis was a non-inferiority assessment of 28-day all-cause mortality rates between sulbactam, durlobactam, and colistin. Non-inferiority was concluded if the upper limit of the two-sided 95 percent confidence interval was less than 20 percent. The sample size and 20 percent non-inferiority margin were selected based on several discussions and in agreement with the FDA. Calculation of the sample size assumed a 41 percent mortality rate in the colistin arm, a 36 percent mortality rate in the sulbactam-durlobactam arm, a 1-to-1 randomization, and an 80 percent power with a two-sided significance level of 0.05.

Based on the unmet need of this population

and through comprehensive literature review of hospital-acquired and ventilator-associated pneumonia trials in patients with serious *Acinetobacter* infections treated with colistin or delayed or no therapy, both FDA and Entasis independently determined a 20 percent non-inferiority margin for the study. We also assessed several prespecified, all-cause mortality endpoints at 14 days and 28 days in the intent-to-treat and microbiologic intent-to-treat populations. In addition, clinical cure and microbiologic favorable assessments were evaluated. I will come back to describe some of these endpoints in more detail.

Moving next to patient disposition, 181 patients were randomized and included in the intent-to-treat population. Ninety-eight percent of these patients received any amount of study drug, defined as the safety population for the study. Most patients in the intent-to-treat population had a confirmed infection caused by *Acinetobacter* at baseline and were included in the

microbiologic modified intent-to-treat population for efficacy analyses. More than 80 percent of this population was confirmed to have an infection caused by *Acinetobacter* that was carbapenem resistant, which, as defined earlier, was the primary efficacy analysis population.

Demographics and baseline characteristics were generally comparable between treatment groups across Parts A and B. These were critically ill patients, and this is consistent with the previous hospital-acquired and ventilator-associated pneumonia trials and, importantly, consistent with the likely populations seen with resistant *Acinetobacter* infections.

Age and gender distributions were similar. Nearly all patients were enrolled outside of the United States and predominantly from Eastern Europe or Asia Pacific. This is consistent with enrollment in some similar types of trials in hospital-acquired and ventilator-associated pneumonia. APACHE scores were slightly higher in the colistin arm, whereas more patients with

ventilator-associated pneumonias were randomized to the sulbactam-durlobactam arm. In Part B, patients were younger and more likely to have a bloodstream infection. A higher percentage of patients had a monomicrobial infection versus a polymicrobial infection in both treatment groups.

Now looking at the baseline isolates, as Dr. Miller previously described, most isolates were carbapenem and multidrug-resistant. Eighty-five percent of isolates were extensively drug resistant, meaning they were non-susceptible to all but two antibiotic classes used to treat *Acinetobacter*, and 15 percent were pan drug resistant or non-susceptible to all tested antibiotic classes approved for use to treat *Acinetobacter*. Over 90 percent of the *Acinetobacter* isolates were susceptible to less than or equal to 4 micrograms per mL of sulbactam-durlobactam even in the colistin-resistant, extensively drug resistant, and pan drug resistant subset.

Now let's look at the results. Sulbactam-durlobactam met the primary efficacy

endpoint of non-inferiority in 28-day all-cause mortality compared to colistin in the primary efficacy analysis population. The mortality rate in the sulbactam-durlobactam group was 19 percent compared to 32 percent in the colistin group. The treatment difference was minus 13 percent and the upper limit of the 95 percent confidence interval was 3.5. This result was well within the 20 percent non-inferiority margin and would have met a narrower non-inferiority margin of 10 percent.

To further assess mortality rates, we looked at all-cause mortality in several ways, and it was consistently lower with sulbactam-durlobactam than colistin across prespecified trial populations and endpoints. This forest plot shows the primary endpoint in the top row and the secondary endpoints that captured all-cause mortality, including 28- and 14-day all-cause mortality and across various analysis populations. All of these assessments favored sulbactam-durlobactam.

Shown here are data from some clinically

relevant subgroups. These data were consistent with the primary efficacy analysis, demonstrating a lower 28-day all-cause mortality in the sulbactam-durlobactam compared to colistin. Now, looking at mortality rates in age and gender, there were numerically higher mortality rates in the SUL-DUR arm in patients 65 to 75 and female; however, the sample sizes in these subgroups were small and did not suggest that the study conclusions were driven by any random imbalances in the baseline characteristics.

Clinical cure was defined as complete resolution or significant improvement of baseline signs and symptoms and no new symptoms such that no additional gram-negative antimicrobial therapy was warranted. At the test-of-cure visit, the clinical cure rate for the sulbactam-durlobactam group was 62 percent compared to 40 percent for the colistin group. The treatment difference was 21.6 in favor of sulbactam-durlobactam.

Moving to microbiologic response, sulbactam-durlobactam also demonstrated a

significant difference in microbiologic outcome compared to colistin, and microbiologic favorable assessment included eradication and presumed eradications. In the primary efficacy analysis population, microbiologic favorable rates were 68 percent for sulbactam-durlobactam and 42 percent for the colistin group. The treatment difference was 26 percent. Overall, the consistent results across endpoints and analyses populations demonstrated the robustness of the sulbactam-durlobactam efficacy data.

Turning to Part B, results in Part B patients who are intolerant to colistin or had *Acinetobacter* infections that were resistant to colistin were similar to patients in Part A treated with sulbactam-durlobactam. The consistency of these data further support sulbactam-durlobactam efficacy in resistant *Acinetobacter*.

In summary, sulbactam-durlobactam demonstrated efficacy in patients with serious lung infections caused by resistant *Acinetobacter.* Sulbactam-durlobactam achieved the primary efficacy

endpoint of non-inferiority for 28-day all-cause mortality in the primary efficacy analysis population. Prespecified secondary endpoints of clinical cure and microbiologic favorable assessments in the sulbactam-durlobactam arms were consistently greater than colistin at all time points and in all analysis populations. Overall, in the pivotal phase 3 trial, sulbactam-durlobactam demonstrated clinically meaningful efficacy.

Thank you, and I will now turn the presentation over to Dr. Lewis to review the safety data.

Applicant Presentation - Drew Lewis

DR. LEWIS: Thank you, Dr. Altarac.

Good morning. I'm Drew Lewis, vice president of clinical development at Entasis Therapeutics. Here, we'll discuss the safety data that support the benefit-risk assessment of sulbactam-durlobactam to address this critical unmet need. These data demonstrate that across the clinical development program, sulbactam-durlobactam was generally well tolerated and demonstrated a

safety profile similar to the established class of beta-lactam/beta-lactamase inhibitor combinations.

The clinical safety profile for sulbactam-durlobactam has been characterized in eight clinical studies with 380 patients exposed to durlobactam either alone or in combination with sulbactam. 181 individuals have received sulbactam-durlobactam at the proposed dose of 1-gram sulbactam/1 gram durlobactam every 6 hours, adjusted for renal function, and 158 individuals have received sulbactam-durlobactam at the proposed dose for at least 7 days.

The clinical program includes six phase 1 studies contributing to the understanding of the clinical pharmacokinetics of durlobactam, allowing for the dose selection in the phase 2 and phase 3 trials. The phase 2 safety and tolerability trial further characterized the safety profile in patients with complicated urinary tract infections, leading the way to the pivotal phase 3 trial. Phase 3 trial provides safety data in critically ill patients where sulbactam-durlobactam achieved

the primary safety objective of a lower incidence of nephrotoxicity and showed an overall favorable safety profile.

I'll first review the overall adverse event profile in the phase 3 trial. In the phase 3 trial, most patients were reported to have experienced an adverse event consistent with the degree of illness in the enrolled patients. Compared to the colistin-treated patients, patients treated with sulbactam-durlobactam had a lower overall incidence of adverse events, adverse events assessed as treatment related, serious adverse events, and adverse events leading to drug discontinuation or death.

No deaths were assessed as related to study drug in the sulbactam-durlobactam group. One death due to pneumonia was assessed as study drug related in the colistin group. We also see here on the right part of the slide the open-label Part B sulbactam-durlobactam data that was generally similar to the Part A sulbactam-durlobactam group.

Turning to specific common adverse events,

the most common adverse events in the phase 3 trial were consistent with the patient population and the classes of antibiotics in the treatment groups. Most patients in the trial experienced at least one adverse event. Without regard to causality, diarrhea, anemia, and hypokalemia were the most frequently reported events in the sulbactam-durlobactam group. In the colistin group, the most frequently reported events were anemia, acute kidney injury, diarrhea, and hypokalemia. Acute kidney injury was seen in 13 percent of patients treated with colistin compared to 4 percent in the sulbactam-durlobactam group.

Next, we'll turn to serious adverse events. Overall, there was a lower incidence of serious adverse events in the sulbactam-durlobactam group compared with the colistin group. This table shows the serious adverse events regardless of causality that occurred in two or more patients in any treatment group. Of the serious adverse events in Part A, the most common was septic shock. This occurred in the same number of patients in both

treatment groups. All other SAEs reported in the sulbactam-durlobactam group occurred in one or two patients.

Turning next to the primary safety objective of the trial, the incidence of nephrotoxicity was sulbactam-durlobactam and colistin based on the modified RIFLE criteria. This was the primary safety objective. This was considered a relevant measure given the frequency with which colistin is used in this population. Sulbactam-durlobactam achieved the primary safety objective, demonstrating a statistically significant lower incidence of nephrotoxicity compared with patients treated with colistin.

Adverse events in the renal and urinary disorders system organ class are consistent with the finding in the primary safety objective. Most of these events when occurring in the sulbactam-durlobactam group were mild or moderate in severity. In Part A of this study, 1 percent of patients in the sulbactam-durlobactam group had a severe event compared to 8 percent in the colistin

group.

In summary, sulbactam-durlobactam has demonstrated a safety profile similar to the established class of beta-lactam/beta-lactamase inhibitor combinations. In the clinical trials, sulbactam-durlobactam was generally well tolerated in severely ill patients, and no new safety signals were identified. In the phase 3 trial, sulbactam-durlobactam achieved the primary safety objective of significantly lower incidence of nephrotoxicity compared to colistin, commonly used in the treatment of *Acinetobacter* infections. The phase 1 and phase 2 safety data provides supportive information in characterizing the safety profile for sulbactam-durlobactam.

We acknowledge that the safety data set from this pathogen-focused development program is smaller than what is typically provided in traditional development programs. Given the seriousness of these infections, the limited available treatments, and the safety profile review, the benefit-risk profile is favorable.

Overall, the data support that if approved, sulbactam-durlobactam could be an important, well-tolerated treatment option for patients with these serious and life-threatening infections due to susceptible strains of *Acinetobacter*. Thank you, and I'll turn the presentation to Dr. Patrik Hornak.

Applicant Presentation - Patrik Hornak

DR. HORNAK: Good morning. I'm Dr. Patrik Hornak, and I'm on the faculty as an assistant professor of medicine at the University of Texas Medical Branch, where I'm actively involved in clinical Care, medical education, and research. In my infectious disease practice, I care for patients with serious infections due *Acinetobacter*, many of whom are afflicted with hospital-acquired or ventilator-associated pneumonia, including multidrug-resistant strains.

As a clinical ID specialist with a long career ahead of me, I expect that terms like "extensively drug resistant, pan resistant," and "difficult to treat" will probably grow more and

more common by the season. The development of new antibiotics generally has not kept pace with the growing threat of antibacterial resistance, and nowhere is this more accurate than with *Acinetobacter* infections. Thus, I'm excited to be here today to share my clinical experience with sulbactam-durlobactam.

In the current environment of rapidly increasing antimicrobial resistance and complex patient populations, both physicians and patients need new treatment options for drug-resistant bacterial infections. Those infections caused by *Acinetobacter* are some of the most difficult to treat. They consume vast healthcare resources and confer significant morbidity and mortality. As Professor Paterson reviewed earlier, our current treatment options for *Acinetobacter* infection are limited, and they all lack the type of clinical evidence that we physicians need to best inform our treatment decisions.

I want to walk you through a case from my own practice. This was a patient with

ventilator-associated pneumonia due to *Acinetobacter*, which we described in the Journal of Antimicrobial Agents and Chemotherapy in 2021. This case illustrates the challenge that we physicians frequently face caring for patients with serious *Acinetobacter* infections when there may be few or even no effective treatment options. Thankfully, my patient was fortunate to receive sulbactam-durlobactam through an expanded access program and experienced a positive outcome. Let me review the time course of treatment in greater detail.

She, like many others, acquired *Acinetobacter* pneumonia during a hospital admission for some other initial problem. My patient happened to be admitted for respiratory failure due to severe COVID-19 pneumonia and was in the ICU receiving mechanical ventilation. She initially did well at first, improving over several days. She had no other superimposed infectious process at the time and did well enough to be extubated on hospital day 13.

Unfortunately, she rapidly deteriorated soon after, and within 24 hours of extubation, she developed fevers, leukocytosis, respiratory distress, a significant productive cough, abnormal chest X-ray findings, which altogether supported a new diagnosis of ventilator-associated pneumonia. Her condition rapidly worsened to sensor septic shock and fulminant respiratory collapse, which required repeat intubation. And while a new diagnostic workup was being performed, the patient was started on empiric antibiotics with vancomycin and meropenem. Then the pulmonary respiratory culture results come back detecting *Acinetobacter*, and she remained intubated and still required a vasopressor for blood pressure support.

By day 16, our culture result showed a completely pan-resistant *Acinetobacter*, and our team attempts an optimized salvage regimen of high-dose ampicillin sulbactam, extended infusion meropenem, and polymyxin B; and despite these best efforts, our patient continued to worsen. Even after adding a fourth antibiotic, eravacycline, she failed to

show any signs of meaningful improvement.

At this point, the patient seemed destined for a disastrous outcome. Our team worked tirelessly, continuing to explore any and all treatment options, including those that were still under investigation, and this led us to sulbactam-durlobactam. We requested and quickly obtained the drug through the expanded access program.

We wanted to maximize our patient's chances, especially without any sensitivity results at the time, so we opted to use sulbactam-durlobactam within 24 hours of initiation of another antibiotic, cefiderocol, and we were thrilled when she demonstrated a clear and profound response after the addition of sulbactam-durlobactam, so profound, in fact, that her vasopressor requirement, fevers, tracheal secretions, and leukocytosis, all of which had been ongoing for 10 days, completely resolved in the next 72 hours. Two weeks later, the patient completed her sulbactam-durlobactam course without any incident

or adverse event, and was discharged from the hospital after 38 days. She ultimately recovered fully and without any relapse of her *Acinetobacter* infection.

I'd like to believe that I'll never see a case this challenging again in my career; however, that's highly unlikely, and in fact, in this era of rapidly increasing drug resistance amongst *Acinetobacter*, I expect to encounter more and more of these demanding and dangerous infections. Even though my patient had a positive outcome, many do not, and that is why I am so encouraged by the data presented today on sulbactam-durlobactam, and I look forward to having it available to treat my patients.

Thanks for your attention. I'll now turn the presentation back to Dr. Rege for concluding remarks.

Applicant Presentation - Shruta Rege

DR. REGE: Thank you, Dr. Hornak.

Looking at the snapshot of some of the efficacy data that Dr. David Altarac shared

earlier, the phase 3 results were robust, demonstrating clinically important benefits in patients with serious infections caused by *Acinetobacter*. Sulbactam-durlobactam met the primary efficacy, non-inferiority endpoint of 28-day all-cause mortality when compared to colistin. Clinical cure rates and microbiologic favorable rates were also consistently greater in the sulbactam-durlobactam group at all time points and in all analyses populations.

Regarding the safety profile, sulbactam-durlobactam was well tolerated and provides a clear benefit over the currently available treatment options for patients with infections due to *Acinetobacter*. Polymyxins like colistin, which was used in our phase 3 trial, have well-known risks of nephrotoxicity and neurotoxicity, and we just heard from Dr. Drew Lewis that sulbactam-durlobactam had a significantly lower incidence of nephrotoxicity when compared to colistin. Further, the treatment-emergent adverse events in the phase 3 trial were consistent with the expectations for

this population of critically ill patients who typically have many comorbidities.

In conclusion, with multidrug resistance increasing, the limited treatment options are simply inadequate to help patients survive and recover from the serious infections due to drugs resistant to *Acinetobacter*. When combined with the beta-lactam/sulbactam, durlobactam restores its intrinsic activity and efficacy against resistant strains of *Acinetobacter*.

The efficacy data for sulbactam-durlobactam for the proposed indication are from the randomized assessor-blinded, active-controlled phase 3 trial in patients with serious infections caused by carbapenem resistant *Acinetobacter*. Confirmatory evidence is provided from the robust in vitro and animal data, demonstrating activity of sulbactam-durlobactam against *Acinetobacter*. The safety profile is consistent with the beta-lactam/beta-lactamase inhibitor class, and no one expected safety signals that I identified during our development program.

Overall, the totality of data with sulbactam-durlobactam demonstrate a favorable benefit-risk profile for a pathogen-targeted therapy that has the potential to address the critical unmet need and help physicians better care for patients. Thank you. I'll now take your questions.

Clarifying Questions

DR. BADEN: Thank you for a terrific presentation, covering a lot of very important data.

We will now take clarifying questions for the applicant. To the panel members, please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again 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 will be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "This is all for my questions," so we can move on to the next panel member.

I see that Dr. Green has a question.

DR. GREEN: Yes. Thank you, Dr. Baden. This is Michael Green. I have two questions relating to resistance, and these likely go to Dr. Miller and probably also Dr. Altarac.

To Dr. Miller, she stated that they did not see spontaneous resistance to SUL-DUR in the laboratory, but I'm wondering if there was any effort to use selective methods in the laboratory to get emergence of resistance. Then the follow-up to Dr. Altarac resistance question is, we got data on the presence of resistance at onset of treatment and entering into the trial, but I'm wondering if there was any testing of subsequent isolates, particularly those that had positive microbiologic testing at the test-to-cure evaluation or subsequent isolates on treated patients down the

line. Thank you very much.

DR. REGE: Sure. I'll turn it over to Dr. Alita Miller to address both your questions. Thank you.

DR. MILLER: Alita Miller, Entasis. We did get some resistant mutants in the lab. We had to try real hard, but we did get some, and when we isolated those, we found that they mapped primarily to the target of sulbactam, which is PBP3 in *Acinetobacter*. So in surveillance studies, the resistance is also associated with strains that express metallo beta-lactamases. We didn't see any of those in our clinical trial, but we did find some of those in our surveillance studies.

For your second question about resistance emergence during the clinical trial, of the patients that received sulbactam-durlobactam, there are 105 in total. The vast majority had favorable microbiological outcomes, meaning those were either eradicated or presumed eradicated. There was one patient that did have increase in sulbactam-durlobactam MIC values over the course of the

study, and I'll show you that data.

This patient started out with an MIC value of 4 at the screen, and the infection was persistent. On day 7 it was an MIC of 32, and then on test of cure, it was an MIC of 8. So this particular isolate was also extensively drug resistant, and even though it was an MIC of 8, the infection was cleared by late follow-up.

We did characterize this isolate, and you can see that it's the same isolate that was infectious throughout the study. The only genetic difference that we found between the baseline isolate and this test-of-cure isolate was a mutation in a gene associated with the efflux, so we're continuing to study that, but we haven't found anything in particular that shows there's a difference in efflux potential between these isolates. Thank you.

DR. BADEN: Dr. Murphy?

DR. MURPHY: Richard Murphy, VA Medical Center. In the proposed indication, you're seeking approval for the drug in certain indications, but

it's not mentioned specifically to be used as part of combination therapy. However, in the clinical trial, all patients received the drug in combination with imipenem, and that makes sense because, frequently, this pathogen can be a colonizer, and there could be another active pathogen driving ventilator- or hospital-acquired pneumonia.

So my question is, what's the actual spectrum of the drug outside of *Acinetobacter baumannii* complex in the event that this drug was deployed accidentally or for another reason as monotherapy? Thanks.

DR. REGE: Sure. I will turn it over to Dr. Alita Miller to answer your question.

DR. MILLER: Alita Miller, Entasis. Sulbactam is what provides the targeted therapy against *Acinetobacter.* As we described, sulbactam has limited antibacterial activity against *Acinetobacter* and a handful of other strains. Durlobactam is a beta-lactamase inhibitor that also has some intrinsic activity against other bacteria,

primarily enterobacterales such as *E coli*. This activity is driven by inhibition of PBP2, so it's similar to drugs like selenium. So if sulbactam-durlobactam were administered by itself, you would get intrinsic activity of durlobactam against some species of enterobacterales. However, the intrinsic activity of durlobactam is unrelated to its beta-lactamase inhibitory activity, so durlobactam is able to restore beta-lactam activity against strains, whether or not they're susceptible to the intrinsic activity of durlobactam, if that makes sense. Thank you.

DR. MURPHY: So it would make more sense to seek an indication for the drug as combination therapy for these disease processes?

DR. MILLER: I'll let Dr. Altarac answer.

DR. ALTARAC: I will come back to Dr. Miller in a minute, but I think it's important, again, as you stated, that the combination of imipenem was done in the trial, in both arms of the trial, to cover these polymicrobial infections. We believe that the agent that is acting to treat the

underlying *Acinetobacter* infection is the sulbactam-durlobactam, and as a result, we're seeking an indication for *Acinetobacter* with sulbactam-durlobactam. And I think the data that we'd like to show, we'll go back to Dr. Miller to show you what combining carbapenems to sulbactam-durlobactam did in the lab. Thank you.

DR. MILLER: Alita Miller, Entasis. Just to answer the question about how much does imipenem contribute to the activity of sulbactam-durlobactam against *Acinetobacter,* we have this slide. This is characterization of the baseline isolates from the phase 3 trial. Again, it's the percent cumulative inhibition as the function of MIC. You can see here sulbactam-durlobactam is shown in the blue solid line with and without imipenem. If you add imipenem, it's the green solid line, and they're pretty much superimposed. That means that imipenem addition to sulbactam-durlobactam against *Acinetobacter* doesn't help or hurt its activity, and also a combination of sulbactam-imipenem or imipenem-durlobactam are less effective than

sulbactam-durlobactam. Thank you.

DR. MURPHY: Let me just leave with a final thought, is that we don't know how effective it would be as monotherapy because it hasn't been studied in that way, and I think that the way the clinical trial was designed made sense, but we don't know if it's effective alone. Thanks.

DR. BADEN: Thank you, Dr. Murphy.

So I'll ask the next question, and this is for Dr. Altarac and Dr. Lewis. In looking at the data, there's the efficacy benefit on mortality, 13 percentage points; there's also the nephrotoxicity at 24 points. How do we know that SUL-DUR is active versus colistin is harmful?

Can you help me tease out the benefit of the one versus the risk of the other as we try to ascribe the good outcomes to the benefit, where it may be substantial harm related to the comparator? Can we tease that out or can you help me understand that?

DR. REGE: Sure. I will turn it over to Dr. David Altarac to address your question.

DR. ALTARAC: David Altarac. Let me focus on your point about efficacy. We did select colistin as the comparator for this trial, as colistin was then, as it is now, a frequently used antibiotic for the serious and life-threatening conditions, and at the time of the trial, no other clear standard of care. But we do know that based on the literature review that we use to inform the non-inferiority margin, colistin-based therapies have mortality rates that range anywhere from 25-to-57 percent versus no therapy or delayed treatment therapies, which range from 65-to-87 percent; and therefore, colistin does work, although, as we know, it does have the known toxicities, which do not make it a favorite antibiotic for many clinicians.

So when we look at the known or the literature, which demonstrates a mortality rate that ranges 25-to-57 percent, and we look at the data from our clinical trial with rates overall that range from 19 percent, overall, to lower numbers, and other populations, and consistently

across populations, we do feel that we have demonstrated a clear efficacy of sulbactam-durlobactam on these types of infections.

With respect to safety, I'd turn that over to Dr. Lewis.

DR. LEWIS: Good morning. Drew Lewis Entasis Therapeutics. In looking at the the risky part of the equation for the benefit-risk, what we've demonstrated is t hat the side effect profile is similar to that of the established class of beta-lactam/beta-lactamase inhibitors, and number two, no new safety signals were identified. Thank you.

DR. BADEN: Thank you.

Dr. Perez?

DR. PEREZ: Thank you. I have a question regarding the polymicrobial infections that were shown here [indiscernible]. Do you have information on the co-pathogens that occurred in *Acinetobacter baumannii*, and then the outcomes thereof??

Thank you. This is for Dr. Miller or

Dr. Altarac.

DR. REGE: Sure. So just to clarify, you asked about the co-infecting pathogens in our phase 3 trial and the outcomes related to that. I'll turn it over to Dr. Alita Miller to answer your question. Thank you.

DR. MILLER: Alita Miller, Entasis. To answer your first question, the most common co-infecting, gram-negative pathogens in the trial were *Klebsiella* and *Pseudomonas*, and this slide shows the pie chart, basically a breakdown of the different species that were co-infecting in the CRABC mITT population. You can see most of them. Forty-four percent were *Klebsiella* species. The next most prevalent were *Pseudomonas*. We also had things like *Achromobacter, E. coli, Stenotrophomonas; Proteus*; and *Serratia*.

In terms of the outcomes, for the polymicrobial versus monomicrobial infections, we have that data slide, and I'll hand it over to Dr. Altarac.

DR. ALTARAC: David Altarac. When you look

at the monomicrobial infections at the 28-day all-cause mortality of the primary endpoint, in the sulbactam-durlobactam arm, monomicrobial was 17 percent compared to 35 percent in the colistin arm -- I'll bring that slide up now -- versus in the polymicrobial, it was 22 percent versus 26 percent. So in both monomicrobial and polymicrobial infections, sulbactam-durlobactam demonstrated a lower mortality rate than compared to colistin. Thank you.

DR. PEREZ: And that is irrespective of the pathogen?

DR. ALTARAC: Can you repeat the question, please?

DR. PEREZ: My question was whether this was irrespective of the co-pathogen that occurred in the setting of polymicrobial infections?

DR. ALTARAC: Yes, our assessment was that it was irrespective of the pathogen, the co-pathogen.

DR. PEREZ: Thank you.

DR. ALTARAC: Thank you.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Yes. Hi. Thanks. I'm not sure to whom this question is best addressed, but sulbactam has good penetration into the CSF. Is there any data on durlobactam distribution into the CNS, and is there any animal data on any propensity to induce seizures? Thank you.

DR. REGE: Sure. I will turn it over to Mr. John O'Donnell to answer your question. Thank you.

MR. O'DONNELL: Good morning. John O'Donnell, Entasis Therapeutics. In our pivotal GLP toxicology studies, we didn't see any evidence of CNS effects, including the safety pharmacology study in terms of any adverse events with penetration into the CNS. I will say in terms of distribution into CSF, we have not studied that directly with durlobactam, but we have had some experience with treating patients with CNS type of infections, and maybe Dr. Altarac could follow up with that.

DR. ALTARAC: David Altarac. We have seen

the product used in our expanded access program. The expanded access program, for the purposes of this discussion, is primarily related to those patients in our safety database; however, we did have one patient who did have a post-surgical hemicraniectomy, developed multidrug-resistant *Acinetobacter*, wound infection, mental status changes, and a presumed meningitis, who did receive sulbactam-durlobactam in combination with another antibiotic, and did not have any adverse events, completed treatment, and resolved their infection. Thank you.

DR. BADEN: Dr. Patel?

DR. PATEL: Good morning. Nimish Patel, UC San Diego. I had a question about the use of the drug, and I apologize if the detail was presented. My understanding is there's a 3-hour infusion q6, so over half the day is consumed just administering SUL-DUR.

Can you clarify how imipenem was sequenced? Was it given simultaneously or was it given sequentially with SUL-DUR in the trial?

DR. REGE: Sure. I will hand it over to Dr. David Altarac.

DR. ALTARAC: David Altarac. In the trial, it was not specified whether the imipenem had to be given at the same time points as the sulbactam-durlobactam, although it was likely that it was just based on how it's done in the clinic. So we did not specify that it had to be done that way. Imipenem was also dosed q6.

I would like to turn it over to Dr. Hornak, who can describe for you how it was done in the real world and how it might be used if approved.

DR. HORNAK: Patrik Hornak. For my patients that I use sulbactam-durlobactam for through the expanded access program, this patient was in the ICU and was receiving multiple other ICU type medications. He was in the ICU for the duration of their sulbactam-durlobactam course, which was 14 days, in addition to another antibiotics, and there were no issues from a pharmacy standpoint, from a nursing standpoint, medical standpoint with regards to overburdensome logistics or maintenance

of extra IV lines, et cetera. Thanks.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you, Dr. Baden. This is sort of a follow-up, and I had put the green check. I thought that's what we were doing to agree for a follow-up. But earlier when they talked about the co-pathogens, I was wondering whether the protocol allowed for additional treatments to be added to the regimen if a co-pathogen was identified that was resistant to imipenem-cilastatin.

For instance if you had a *Pseudomonas* that was carbapenem resistant, and you weren't expecting SUL-DUR to be effective against it, was the treating center allowed to add yet another agent to try to cover a co-pathogen? Thank you.

DR. REGE: Sure. I would like to hand it over to Dr. David Altarac to answer your question.

DR. ALTARAC: David Altarac. If the co-pathogen was another gram negative, it was not part of the protocol to add another agent; however, if the co-pathogen was gram-positive or a fungi, additional therapy for those infections was

allowed. Thank you.

DR. BADEN: Dr. Hilton?

DR. HILTON: Thank you. This is Joan Hilton, University of California San Francisco, biostatistics. I would like to ask a little more about slide CO-35. It's the sample size calculation.

I saw that there was an assumed 41 percent mortality rate in the colistin arm, but a 32.5 percent mortality rate was observed in the component of the study that we've focused on. Can you explain the difference in the assumed and observed mortality rates, and also, can you tell me what the original sample size calculation was? I know that you negotiated a new sample size with FDA part way through the study.

DR. REGE: I would like to turn it over to Dr. David Altarac to answer your question.

DR. ALTARAC: David Altarac. Actually, if we can bring up the colistin slide, again, we estimated the mortality rate based on what we read in the literature or what we know about the

treatment effect of colistin, which, as I mentioned earlier, ranged between 25 and 57 percent versus no treatment or delayed treatment, which have clearly much higher mortality rates. So based on this, the literature does show that the range, depending on the care within the institution, depending on other co-factors, depending on how they're treated, depending on how quickly antibiotic coverage is initiated, could determine rates anywhere within that range.

So again, a mortality rate in the colistin arm in the study of 32 percent is not unreasonable, especially in a well-controlled study, where patients are in an intensive care unit being monitored so closely and getting every opportunity to maximize their care a lower rate than what one would hypothesize based on the literature is not unexpected.

In terms of your question around the discussion on the non-inferiority margin, Entasis had approached the FDA early on, and looking at this literature did believe that a 20 percent

non-inferiority margin was acceptable and within spectrum, and consistent with the FDA guidance on unmet medical need for serious infections. Based on these estimates, FDA looked at the same literature and determined from their perspective that a 19-percent non-inferiority margin would be their preferred non-inferiority margin.

Entasis agreed with that, but then as the study was undergoing and COVID-19 challenges were upon us, we approached the FDA, had a discussion with them, and they agreed that going back to our proposed 20 percent non-inferiority margin would retain the statistical rigor of the trial, and we agreed the 20 percent non-inferiority margin and updated all of our statistical analysis plans well before completion of the study and any database block or analysis. Thank you.

DR. HILTON: Excuse me.

DR. ALTARAC: Sure. Go ahead.

DR. HILTON: I agree with your comments about the well-controlled trials probably explain why you're at the lower end, and I wonder if

restricting the literature to well-controlled trials might have been a better way to target that. But you didn't answer one part of my question, which was, what was the original sample size calculation? I know the number randomized in the observed study was 181.

DR. ALTARAC: Yes. So I will turn your question over to Dr. Close. Thank you.

DR. HILTON: Thank you.

DR. CLOSE: Nicole Close, Entasis. The power calculations and sample size was focused on the CRABC population. The original sample size for the CRABC population was a sample size of 126 subjects. With the information that Dr. Altarac presented about the non-inferiority, the discussions with the FDA, that 20 percent non-inferiority margin reduced our sample size to 120 in the CRABC population, and in the end, the trial did enroll 128 into the CRABC population.

DR. HILTON: Thank you.

DR. BADEN: Thank you.

We are at the time for a break. I suspect

there are many more questions from committee members. We can resume clarifications after we go through the remaining presentations, but first we'll take a 10-minute break. Panel members, please remember there should be no chatting or discussion of the meeting topic with other panel members during the break. We will resume at 10:59, in 10 minutes for the FDA's presentation.

Thank you. We're now on break.

(Whereupon, at 10:49 p.m., a recess was taken, and the meeting resumed at 10:59 a.m.)

DR. BADEN: It is now 10:59 and we will resume the meeting. We will now proceed with the FDA presentations, starting with Dr. Qi.

Dr. Qi?

FDA Presentation - Karen Qi

DR. QI: Good morning. I'm Karen Qi. I'm the statistical reviewer for this NDA. I'm going to present the efficacy assessment for sulbactam and durlobactam.

(Pause.)

DR. QI: Sorry. We're having some technical

issues here.

(Pause.)

DR. SHERWAT: Dr. Baden, this is Adam Sherwat. Could we have a couple of minutes? We have a couple of technical issues here.

DR. BADEN: Of course. We'll leave it to our AV crew to get this back on track.

DR. SHERWAT: Okay. Thank you.

(Pause.)

DR. QI: Sorry. Let me continue.

The proposed indication for sulbactam and durlobactam is for treatment of HABP and VABP that is caused by susceptible strains of ABC complex. The efficacy data to support the proposed indication was from a phase 3 trial, which was conducted in two parallel parts, Part A and Part B. Part A was the randomized investigator unblinded, assessor-blinded, non-inferiority portion. It compares sulbactam ABC and durlobactam with colistin for treatment of HABP, VABP, ventilated pneumonia, or bacteremia caused by ABC. Part B has a single arm for evaluation of sulbactam and

durlobactam for treatment of ABC-infected subjects who were resistant to colistin or who were ineligible for Part A due to other factors. Because Part B was single arm, efficacy assessment of sulbactam-durlobactam was based on Part A. I'm going to present the study design and efficacy results for Part A.

In Part A, subjects were randomized in a 1-to-1 ratio to receive either sulbactam and durlobactam, or colistin. Randomization was stratified by three factors: infection type, including HABP, VABP, VP, or bacteremia; baseline disease severity, including APACHE score, SOFA score, or qSOFA score; and by region, mainland China or the rest of the world. Subjects in both groups received imipenem or cilastatin as background therapy. The study duration was 7-to-14 days of treatment and 14 days of follow-up after the treatment.

The primary efficacy endpoint in Part A was 28 days all-cause mortality. This was assessed using a 20 percent non-inferiority margin. The

secondary efficacy endpoint included clinical cure and microbiological favorable assessment at 3 visits, including an end-of-treatment visit; the test-of-cure visit 7 days after the end of treatment; and late follow-up visit 14 days after the end of treatment.

To evaluate whether sulbactam and durlobactam was non-inferior to colistin for the primary endpoint of 28-day all-cause mortality, we need to determine whether sulbactam and durlobactam had an unacceptably higher mortality rate than colistin based on a prespecified NI margin of 20 percent. As shown in this figure, if the upper 95 percent confidence limits of treatment difference in mortality rate is below the margin of 20 percent, then sulbactam and durlobactam is non-inferior to colistin.

This table shows the result of the literature review conducted during the design stage to justify the NI margin in study with relatively high rate of HABP, VABP, or bacteremia due to ABC pathogen. The 28-day mortality rate for subjects

treated with colistin-based therapy was estimated to be 41 percent with the upper 95 percent confidence limit of 47 percent. The mortality rates for subjects treated with delayed or inadequate antibacterial therapy was estimated to be 76 percent, with the lower 95 percent confidence limit of 66 percent.

The estimate of the effect of a colistin-based regimen versus inadequate or delayed therapy, in terms of reducing mortality rates, was the difference, between 66 percent and 47 percent. This estimate was consistent with the difference in mortality rates between effective and ineffective antibacterial therapy justified in the FDA guidance documents on developing drugs for HABP and VABP. Therefore, considering the high unmet medical need for antibacterial drug to treat HABP, VABP, CRABC, and trial feasibility due to COVID-19 pandemic, an NI margin of 20 percent was used.

Multiple analyses population was used to analyze the efficacy endpoint and included the intent to treat, or ITT, population, which

consisted of all randomized objects in Part A. The microbiologically-modified ITT, or m-MITT, was a subset of ITT. It included the ITT subjects who received any amount of study drug and who had a baseline ABC organism isolated as the qualifying culture specimen, as confirmed by the central or local lab.

The primary efficacy analysis population was CRABC m-MITT, which was a subset of m-MITT. It included subjects who were in the m-MITT population and had HABP, VABP, VP, or bacteremia, and had a baseline ABC organism resistant to carbapenem but not to the study drug, and had a blood culture or respiratory samples collected 72 hours before randomization, and were not transferred to Part B.

A total of 181 subjects were randomized, with 92 subjects in the sulbactam and durlobactam group and 89 in the colistin group. These subjects were included in the ITT population. The m-MITT population included about 85 percent of the ITT subjects in the sulbactam and durlobactam group and 89 percent in the colistin group. The primary

reason for exclusion from m-MITT was some subjects were positive by BPP rapid test for ABC, but subsequently found to be culture negative by the central or local lab.

The CRABC m-MITT population included about 70 percent ITT subjects. The most common reason for exclusion from CRABC m-MITT was subjects were excluded from m-MITT due to BPP positive but culture negative. The second most common reason was the baseline ABC organism was resistant to colistin.

In the ITT population, 26 percent of sulbactam and durlobactam subjects and 35 percent of colistin subjects discontinued study treatment. The two most common reasons for discontinuation of sulbactam and durlobactam were adverse events and no growth of ABC, and the two most common reasons for discontinuation of colistin were adverse events and treatment failure. Twenty-two percent sulbactam and durlobactam subjects and 32 percent colistin subjects discontinued from the study. In both groups, the primary reason for discontinuation

from the study was death. Also, one subject per group was transferred to Part B because they were resistant to colistin.

This table displays some important demographic and baseline clinical factors. The average age was 62 years old for sulbactam and durlobactam subjects and 65 for colistin. The majority of subjects in both groups were males and were enrolled in the rest of the world other than mainland China. In terms of infection type, in total, only 3 subjects had bacteremia. Regarding baseline disease severity, 73 percent of subjects in the sulbactam and durlobactam group and 69 percent in the colistin group had APACHE score between 10 and 19 or SOFA score between 7 and 9, or qSOFA score of 2.

For the primary analysis, sulbactam and durlobactam were shown to be non-inferior to colistin for the primary endpoint of 28-day all-cause mortality in the CRABC m-MITT population. The mortality rate was 19 percent for sulbactam and durlobactam versus 32 percent for colistin. The

treatment difference was negative 13.2 percent, with the upper 95 percent confidence limit for a difference of 3.5 percent. This was below both the 20 percent NI margin specified for this trial and the 10 percent NI margin specified in the FDA guidance for general HABP/VABP indication. The analysis excluded 3 subjects who did not have data for 28-day survival status. All were due to withdrawal of consent.

To evaluate the impact of missing survival status at day 28 and receipt of prohibited medication before day 28 on the primary endpoint, we conducted the sensitivity analyses. We considered subjects who missed survival status or who received prohibited medication as events in the sulbactam and durlobactam group and non-events in the colistin group; therefore, our analyses are relatively conservative.

This table shows the results for CRABC m-MITT and ITT populations. The upper 95 percent confidence limit for 28-day all-cause mortality rates were below 10 percent in all three

populations. Thus, the sensitivity analysis provided similar conclusions to the prespecified primary analysis.

For the secondary endpoint of clinical cure, the cure rates for sulbactam and durlobactam were higher than colistin on end-of-treatment, test-of-cure, and late follow-up visits. There was no prespecified statistical testing for this endpoint to control for false positive from multiple comparisons, but the treatment difference and end of treatment and test of cure were nominally significant.

The secondary endpoint of microbiological favorable assessment included microbiological eradication and presumed eradication. Microbiological favorable assessment was higher for sulbactam and durlobactam at each visit, and the treatment differences were nominally significant in end-of-treatment and test-of-cure visit. The differences in favor of sulbactam and durlobactam at all visits were driven by presumed eradication, which was based on clinical response.

In summary, Part A in the phase 3 study demonstrated that sulbactam and durlobactam was noninferior to colistin for a primary endpoint of 28-day all-cause mortality in the CRABC m-MITT population, as the upper 95 percent confidence limit for the treatment difference in mortality was 3.5 percent, meeting both 20 and 10 percent margins. About 96 percent of subjects in the CRABC m-MITT had either HABP or VABP, and only 3 subjects had bacteremia. Consequently, we concluded that the sulbactam and durlobactam was non-inferior to colistin for treatment of HABP or VABP, caused by CRABC.

This is the end of my presentation. Thank you. Now I would like to turn the presentation to Dr. Ghosh.

DR. SHERWAT: Dr. Baden, hi. This is Adam Sherwat. If you could give us just 2 or 3 minutes to be able to switch our slide deck, that would be great.

DR. STEVENSON: Yes. Hi. Good morning. This is Takyiah Stevenson speaking, DFO. Yes,

Apologies. We're going to take a quick five-minute break to address technical issues. Thank you.

DR. BADEN: So we'll resume at 11:20. Thank you.

(Pause.)

DR. KIM: Hi, Dr. Baden. This is Peter Kim. We're ready to start when you're ready.

DR. BADEN: Perfect. So the technical issues are resolved, so let me ask Dr. Ghosh to continue with the agency's presentations. Thank you.

FDA Presentation - Mayurika Ghosh

DR. GHOSH: Good morning. My name is Mayurika Ghosh, and I'm a clinical reviewer in the Division of Anti-Infectives, FDA. I will present the clinical safety assessment for new drug application sulbactam and durlobactam.

Sulbactam is a beta-lactam antibacterial and beta-lactamase inhibitor. Durlobactam is a non-beta-lactam beta-lactamase inhibitor. Sulbactam has intrinsic activity against *Acinetobacter* species. The proposed indication is treatment of hospital-acquired bacterial pneumonia

and ventilator-associated bacterial pneumonia caused by susceptible isolates of ABC complex in adults. The proposed dose is 1 gram sulbactam and 1 gram durlobactam co-packaged together, administered intravenously every 6 hours for a duration of 7-to-14 days, as guided by the patient's clinical status.

The safety data for sulbactam and durlobactam was derived primarily from the phase 2 complicated urinary tract infection and the single pivotal hospital-acquired bacterial pneumonia and ventilator-acquired bacterial pneumonia phase 3 study.

The phase 2 study was randomized 2 to 1 to sulbactam-durlobactam and placebo. All 80 subjects, including the 53 subjects on the sulbactam-durlobactam group, received background imipenem-cilastatin therapy to cover for co-infecting pathogens in patients with polymicrobial *Acinetobacter* infections in the sulbactam-durlobactam group. No *Acinetobacter* infections were enrolled in this phase 2 study;

therefore, data from this study was used to assess safety of sulbactam-durlobactam.

The phase 3 study consisted of a comparative part, Part A, where subjects were randomized 1 to 1 to sulbactam-durlobactam and colistin with background independent cilastatin therapy. Part A was comprised primarily of HABP, VABP subjects. Part B of the phase 3 study was non-randomized and included 28 subjects with inclusion criteria of colistin-resistant pathogens, complicated urinary tract infections, and surgical post-traumatic infections.

These 28 subjects received sulbactam-durlobactam with background independent cilastatin therapy. The study drugs were not masked for logistic reasons, and the treating physician and other healthcare providers were not blinded in the trial, except for the outcome assessor who evaluated criteria for clinical outcomes, conducted causality assessment for adverse events, and assessed clinical signs and symptoms at study visits. The safety population

consisted of predominantly white and Asian subjects. About 70 percent of the subjects were males.

This slide gives you an overview of the size of the clinical safety database. Durlobactam up to 8 grams was studied in phase 1 subjects and 10 subjects received sulbactam and durlobactam at the proposed dose and duration. Fifty-one subjects in phase 2 and 97 subjects in phase 3 received sulbactam and durlobactam at the proposed dose and duration.

The median duration of treatment was approximately 8 days in Part A and 10.5 days in Part B of the phase 3 study. In total, 181 subjects received the intended dose and 158 subjects received the intended dose and duration of sulbactam and durlobactam. There were 12 subjects who received sulbactam-durlobactam under the expanded access program after failure of multiple salvage regimens.

There were no deaths in phase 1 or phase 2 studies. The mortality rates on the

sulbactam-durlobactam arm at 26 percent were numerically lower than colistin at 35 percent of the phase 3 study. The deaths were related to underlying comorbidities, complications in critically ill subjects, or progression of the presenting pneumonia without apparent biologic plausibility or causal assignment to sulbactam and durlobactam. The most common etiologies of death in both sulbactam-durlobactam and colistin groups were septic shock and sepsis. The mortality rates were generally consistent with those in HABP/VABP trials and in *Acinetobacter* infections reported in the literature.

This slide gives an overview of the adverse events in the phase 3 safety population. The overall incidence of treatment-emergent adverse events was 88 percent in the sulbactam-durlobactam arm and 94 percent in the colistin arm. There were lower incidences of serious adverse events, 40 percent versus 49 percent, and drug-related, treatment-emergent adverse events, 13 percent versus 30 percent, in the sulbactam-durlobactam arm

compared to colistin.

There were 24 deaths on sulbactam-durlobactam and 30 deaths on the colistin arm. Four deaths were noted in Part B of the study. There was one subject with related TEAE of anaphylaxis, which led to treatment discontinuation with sulbactam and durlobactam. A greater proportion of subjects in both arms experienced severe TEAEs, but moderate and severe TEAEs were less frequent in the sulbactam-durlobactam arm as compared to colistin. In Part B, 9 subjects had a serious adverse event, and of them, one subject had a drug-related serious adverse event.

This slide gives you an overview of selected treatment-emergent adverse events occurring at more than 5 percent incidence in the safety population of the phase 3 study. Of note, diarrhea, hypokalemia, and thrombocytopenia occurred at more than 5 percent in the sulbactam-durlobactam arm, as well as abnormal liver function tests. Acute kidney injury was higher in the colistin arm, about 36 percent, compared to sulbactam and durlobactam

arm, which was 5.5 percent. The most common drug-related, treatment-emergent adverse event in subjects who received sulbactam-durlobactam was liver function tests and diarrhea.

Hypersensitivity, pseudomembranous colitis, convulsions, acute kidney injury, and drug-related hepatic disorders were adverse events of special interest, which were monitored during the clinical treatment program. Hypersensitivity reactions were more frequent in the sulbactam-durlobactam group at 16.5 percent compared with the colistin group at 11.5 percent, which would be expected with penicillin derivatives.

The most common drug-related reaction was rash. One subject who received sulbactam-durlobactam had anaphylactic shock. This subject had treatment discontinued and treated with steroids. The *C. difficile* colitis was noted in both groups and less frequently on sulbactam-durlobactam. The incidence of seizure was higher in the colistin arm, 6 subjects, 7 percent, compared with sulbactam-durlobactam arm, which was

one subject at 0.8 percent.

In conclusion, the safety database was limited; however, the safety profile of sulbactam-durlobactam is consistent with the pharmacologic class. Hypersensitivity reactions were more frequent in the sulbactam-durlobactam group. Diarrhea, including *C. difficile* infections were noted among both treatment groups. Liver function tests elevations were comparable between treatment groups, and no specific hepatotoxicity signal was noted. No additional safety signals were noted from the phase 2 study.

I would again like to thank the advisory committee for their participation in today's meeting, and thank you for your attention. I will now invite Dr. Simone Shurland to provide the clinical microbiology assessment for this application. Thank you.

FDA Presentation - Simone Shurland

DR. SHURLAND: Thank you, Dr. Ghosh.

My name is Simone Shurland, and I will present the clinical microbiology assessment of

sulbactam-durlobactam. *Acinetobacter baumannii* has the ability to develop resistance through several diverse mechanisms. Both intrinsic- and acquired-resistance mechanisms have very limited options for treatment of multidrug-resistant ABC isolates. This may be due to *Acinetobacter* ability to exchange genetic material, which are encoded on extra-chromosomal DNA, such as plasmids, transposons, and insertion sequences that give this bacterial an advantage to adapt and develop rapid resistance mechanisms to many classes of antibacterial agents. Current treatment options for ABC isolates are limited due to high resistant rates of resistance, including the first-line agents such as carbapenems. These resistant organisms have been associated with very poor outcomes.

An important feature of *Acinetobacter* species is the intrinsic resistance to multiple antibacterial agents. The most common resistant mechanism in *Acinetobacter* species is the production of beta-lactamases intrinsic to a majority of ABC

isolates or the AmpC beta-lactamases, which is chromosomally encoded cephalosporinases, referred to as the *Acinetobacter* derived cephalosporinases or ADCs.

Such beta-lactamases have a low level of expression when expressed within certain sequence next to the AmpC gene increases beta-lactamase production, causing resistance to penicillin such as ampicillin, cephalosporins, and the carbapenem-ertapenem. More importantly, the major mechanism of carbapenem resistance in ABC isolates is the production of Ambler class D beta-lactamase, often referred to as oxacillinases or OXAs. Less common carbapenemases found in *Acinetobacter* are the class A such as *Klebsiella pneumonia carbapenemase* or KPC. And depending on the region, the class B, or often referred to as metallo beta-lactamases, like the New Delhi metallo beta-lactamase, often referred to as NDMs.

Overexpression of bacterial efflux pump can also decrease or impede the drug penetration to its target by accumulating the drug in the periplasmic

space. The most common efflux pump found in *Acinetobacter* is the AdeDE efflux pump, which affects trimethoprim, fosfomycin, and to some extent the aminoglycosides, chloramphenicol and fluoroquinolones. Also in concert with all these mechanisms of resistance discussed, *Acinetobacter* showed low permeability of some antibacterial agents through its outer membrane due to the expression of conductance of porins like OmpA.

Similar to beta-lactams, sulbactam has a beta-lactam core that is able to covalently bind to penicillin-binding proteins, the enzymes required for bacterial cell wall synthesis. It is often used as a class A beta-lactamase inhibitor as in the formulation of ampicillin-sulbactam. As stated earlier, the presence of the ADCs often inactivate ampicillin. Most of the activities are attributed to sulbactam, which inhibits the penicillin-binding proteins PBP1 and PBP3.

Durlobactam is a novel, non-beta-lactam/beta-lactamase inhibitor that does not contain a beta-lactam core, though durlobactam

binds to a catalytic site of the serine beta-lactamases, resulting in opening the cyclic urea ring of susceptible beta-lactamases. Durlobactam alone does not have activity against the ABC isolates, and as shown by the applicant, durlobactam inactivates ABC isolates expressing serine beta-lactam patients, including class A, class C, and class D. Durlobactam does not have any activity against the MBLs.

This graphical presentation shows the minimum inhibitory concentration through MICs of sulbactam, shown in gray, and the MICs of the combination of sulbactam-durlobactam, shown in green. The activity of sulbactam alone had MIC modal values of 16 milligrams per liter, whereas the addition of durlobactam at a fixed concentration of 4 milligrams per liter lowered sulbactam value to about 1 to 2 milligrams per liter, which is at least an 8-to-16 fold shift in the sulbactam MIC value.

Approximately 98.2 percent of the ABC isolates based on these surveillance studies were

shown to have sulbactam-durlobactam less than 4 milligrams per liter, as the applicant has shown. There were no difference in sulbactam-durlobactam activity against different species that make up the ABC grouping, nor did the MIC differ by infection source or over the period of study time.

In different resistance genotype subpopulations, sulbactam-durlobactam maintained activity against carbapenemases associated with meropenem-resistant isolates and ESBL-producing isolates. Isolates classified as colistin non-susceptible, as well as multidrug resistant, defined as isolates that remains susceptible to one or two antimicrobial categories, sulbactam-durlobactam showed MICs less than 4 milligrams per liter.

The applicant has shown in the global surveillance and resistance studies that isolates that had sulbactam-durlobactam with MICs greater than 4 milligram per liter correlated with amino acid changes near the active site of sulbactam or PBP3 in *Acinetobacter*. Since these changes likely

affect sulbactam binding to its target, changing the relative concentration of durlobactam would not be expected to fully restore sulbactam's susceptibility.

In addition, as discussed earlier, durlobactam is not active against isolates that express NDM-1 or any other MBLs. Isolates that encode the MBLs show that sulbactam-durlobactam MIC values were greater than 32 milligrams per liter, demonstrating no significant shift in the MIC for sulbactam when tested alone. It is likely that there will be multiple factors that will contribute to higher sulbactam-durlobactam MIC values, including isolates that produce 1, 2, or even 7 beta-lactamases at different and varying degrees of expression levels, or in combination with PBP mutations or other resistant mechanisms such as efflux pumps. However, based on the applicant's global surveillance studies, it shows that 2-to-4 percent of the ABC isolates had sulbactam-durlobactam MICs greater than 4 milligrams. It was recommended that the applicant evaluated isolates

in and outside the susceptibility range in in vitro studies and animal models of infection studies.

Though the applicant has evaluated the activity of sulbactam-durlobactam in murine thigh or lung infection models against at least 10 *A. baumannii* isolates, these isolates were well characterized based on its beta-lactamase activity, as well as other resistant mechanisms. The tested isolates had sulbactam-durlobactam MICs that ranged from 0.5 to 16 milligrams per liter and sulbactam MICs of 2 to 64 milligrams per liter. The models showed that durlobactam alone demonstrated minimal to no activity, and sulbactam administered at a fixed concentration and varying concentrations of durlobactam showed a dose proportional reduction in bacterial burden.

In the next few slides, I will show some examples of at least two different ABC isolates with mechanisms of resistance patterns for sulbactam-durlobactam. This graphical presentation shows the results of two isolates tested in the neutropenic murine thigh infection models. Animals

were infected by muscular injection of an inoculum of 10^5 or 10^8 CFUs into the dorsal thighs. Treatment commenced at 2 hours post-infection. In these models, subcutaneous injections of a fixed concentration of sulbactam and varying concentrations of durlobactam were administered every 3 hours for up to 24 hours. At the end of the study, animals were humanely euthanized, and the bacteria burden was enumerated from the infected thigh.

Untreated animals at the start of treatment showed at least a 1-log increase in CFUs, as shown in the graphical presentation on the Y-axis. The green bars above the line show an increase in growth and bacteria, and bars below the line show a decrease in CFUs or increased killing of bacteria. As a positive control, animals were treated with 40 milligrams per kilogram of colistin, which showed greater than a 2-log decrease in CFUs, depending on the isolate.

The graph on the left evaluated the ARC 3486 strain, which has a class C or ADC-30; class A,

TEM-1; and two class D's, OXA-66 and OXA-72. The isolate had a sulbactam MIC of 32 milligrams per liter and a sulbactam-durlobactam MIC of 1 milligram per liter. Durlobactam alone dosed at 15 mgs per kg showed an increase in CFUs, almost similar to the untreated animals. Incremental increasing in durlobactam concentration showed a dose proportional reduction in bacterial burden.

The graph on the right shows an isolate ARC5950, which contained a class C, ADC-11, and two class D's, OXA-23 and OXA-69, as well as mutation in the PBP3, which affects sulbactam resistance. The sulbactam MIC was 64 milligram per liter, and the sulbactam-durlobactam was 4 milligrams per liter. As shown in the graphic, higher sulbactam doses at 150 mgs per kg alone and durlobactam at 50 mgs per kg alone was not sufficient to reduce the bacterial load.

As compared to ARC3486, treatment of animals infected with ARC5950 strain not only required a higher sulbactam dose at 150 mgs per kgs, as well as an increase in the durlobactam concentration to

show a dose proportional reduction in the bacterial burden.

Similar results were shown in in vitro hollow fiber infection model against the same two strains. The model simulated steady-state unbound plasma concentration of 1 gram sulbactam and 1 gram durlobactam, administered every 6 hours over a 24-hour period. The Y-axis shows the average CFUs and the X-axis shows the change in CFUs over time. Against the ARC3486, as shown in this graphic, the purple or mauve line shows the growth control. The red line shows the ARC isolate when treated with 1 gram sulbactam alone, demonstrating no difference in growth when compared to the growth control. The blue line shows the combination of 1-gram sulbactam and 1 gram durlobactam, showing greater than 3-log bacteria killing, demonstrating bactericidal activity.

Similar bactericidal activity was observed when sulbactam-durlobactam was used in combination with meropenem or imipenem. In fact, the killing curve lines were on top of each other, suggesting

no difference in bacterial killing between the different combinations tested. Against the ARC5950 strain, the purple and mauve lines show the growth control. The red line shows isolates treated with 1 gram sulbactam alone, demonstrating no difference compared to the growth control. The blue line shows the combination of 1 gram sulbactam and 1 gram durlobactam, showing greater than 2-log killed up to 10 to 12 hours, and then a regrowth that occurred.

A limitation was the study was done in an in vitro system, which eliminates the innate killing mechanisms as if it was done in an animal study. It is assumed that the overgrowth of isolates may be due to the presence of the PBP3 mutation, which durlobactam is unable to restore sulbactam binding to its target. It is important to note that all isolates in the phase 3 trials, as shown by the applicant, had sulbactam-durlobactam MICs less than 4 milligrams per liter.

I thank you for your attention. Dr. Tracey Wei will present the clinical pharmacology

assessment.

FDA Presentation - Xiaohui Wei

DR. WEI: My name is Tracey Wei. On behalf of the clinical pharmacology review team from the FDA, I will present the clinical pharmacology assessment on this NDA of sulbactam-durlobactam.

This slide highlights the key PK characteristics of sulbactam and durlobactam. Both sulbactam and durlobactam penetrate into the lung with the ratio of total drug AUC in epithelial lining fluid, ELF, to plasma of 0.5 for sulbactam and 0.37 for durlobactam in healthy human subjects.

Excretion is the primary elimination pathway for both sulbactam and durlobactam. Renal function had a significant impact on the PK of sulbactam and durlobactam compared to human subjects with normal renal function who have creatinine clearance at or above 90 mL per minute. The dose normalized AUC is approximately 2-fold higher in subjects with moderate renal impairment and approximately 4-fold higher in subjects with severe renal impairment; therefore, dose adjustment is needed in patients

with renal impairment.

In terms of PK-based drug-drug interaction, results from a phase 1 study demonstrated no interaction among sulbactam-durlobactam imipenem-cilastatin in healthy subjects. Results from in vitro studies suggest that sulbactam and durlobactam are both substrates of OAT1 transporter, a renal organic anion transporter to uptake the substrates from the blood into renal proximal tubular cells. Hence, the concomitant administration of OAT1 inhibitors such as probenecid will increase the drug exposure in plasma.

Clinical pharmacology assessments include the evaluation of the proposed dose regimens, but reviewing the probability of PK/PD target attainment for sulbactam-durlobactam, the assessment of renal function-based dose adjustments, and the assessment of the effect of body weight on the PK of sulbactam and durlobactam.

Sulbactam and durlobactam PK/PD targets were determined from murine thigh and lung infection

models using a collection of 10 *A. baumannii* isolates. Among them, 9 isolates are sulbactam and carbapenem resistant. Consistent to other beta-lactams, the percentage of the time during a dosing interval, that frees sulbactam plasma concentration, remains above MIC and was identified to be the PK/PD driver for the efficacy of sulbactam, and a magnitude of 50 percent is associated with 1-log kill in the murine infection model against the resistant *A. baumannii* strength.

For durlobactam, the free drug AUC from dosing to 24-hour post-dose to MIC ratio was identified to be the PK/PD driver to restore the bactericidal activity of sulbactam, with a ratio of 10 associated with 1-log kill and a ratio of 30 associated with 2-log kill against the resistant *A. baumannii* strain.

The proposed dose regimens is 1 gram sulbactam and 1 gram durlobactam given every 6 hours by IV infusion over 3 hours, for 7-to-14 days, in patients with creatinine clearance between 45 to 129 mL per minute. Dose adjustments

are required for patients with a creatinine clearance less than 45 mL per minute and for patients with a creatinine clearance at or above 130 mL per minute.

Dose selection was facilitated by performing the probability of PK/PD target attainment, PTA, analysis, using the joint sulbactam and durlobactam PK/PD targets to achieve at least 1-log kill against the resistant *A. baumannii* strain. In this PTA analysis, simulated patients were generated to resemble the distributions of demographic variable of the phase 3 patient population with ABC infection. PTA analysis was conducted at a proposed renal function-based dose regimen based on unbound plasma concentration or total drug concentration in epithelial lining fluid, ELF.

The curves in the figure show the percentage of the simulated patients who achieved the PK/PD targets across a range of MIC values. The PTA results indicate that the applicant's proposed dose regimen can generate drug concentration in plasma or ELF to achieve the PK/PD associated with 1-log

kill from a list of 90 percent of simulated patients at MIC value up to 4 microgram per mL. MIC up to 4 microgram per mL covers the MIC levels of greater than 98 isolates from global surveillance study in the phase 3 study.

Drug exposures were estimated at the proposed dose adjustment in the simulated patients, representing each of eight renal function categories covering creatinine clearance from 0-to-200 mL per minute. As shown in this figure for sulbactam and durlobactam, respectively, the predicted plasma AUC of sulbactam and durlobactam at a steady state were generally comparable across renal function categories and were within the range of exposures for subjects with normal renal function.

PTA at a proposed dose adjustment was also conducted in the simulated patients from each of eight renal function categories, based on free drug plasma concentration or total drug concentration in ELF. As shown in these figures, the proposed dose adjustments resulted in at least 90 percent PTA in

achieving PK/PD targets corresponding to 1-log kill at MIC up to 4 micrograms per mL across each renal function category, supporting the proposed dose adjustment by renal function.

The population PK covariate analysis identified the body weight to be the statistically significant predictor of the variability in clearance in central volume distribution for sulbactam-durlobactam, and sulbactam and durlobactam exposures decreased as the body weight increased. Based on the observed Cmax and AUC values from phase 2 and phase 3 patients, this table summarizes the fold changes in the mean AUC and the Cmax values. Compared to those from patients with body weight from 51 to 90 kilograms, Cmax and AUC levels on day 3 were approximately 2-fold higher in patients with body weight lower than 50 kilograms and approximately 25 percent reduction in Cmax and AUC on day 1 was observed in patients with a body weight greater than 90 kilograms.

The number of patients with body weight less

than 50 kilograms is limited from the phase 3 study, but higher exposures observed in the low body weight subjects is not considered to be a safety concern since the incidence of the rare adverse events and the treatment discontinuations, due to adverse events following sulbactam-durlobactam treatment, was similar between the patients with a body weight lower than 50 kilograms and the patients with a body weight greater than 50 kilograms from the phase 3 study.

Since the lower drug exposures in subjects with a high body weight might lead to reduced efficacy, PTA was conducted in the simulated subjects at various body weights, ranging from 35-to-150 kilograms, as well as at three body mass index categories across each renal function group, based on the proposed dosing regimen.

The figures on the slide show the representative PK results from patients with normal renal function. In general, the PK/PD targets of sulbactam and durlobactam associated with 1-log kill achieved at least 90 percent of simulated

patients at MIC up to 4 micrograms per mL, including those subjects in the highest body weight and from 120 kilograms to 150 kilograms, either based on the free plasma concentration or total drug concentration in ELF across the various renal function groups.

To streamline dose regimens of sulbactam-durlobactam, the applicant further revised the dose adjustments by standardizing the doses to 1 gram sulbactam and 1 gram durlobactam in all renal function categories and adjusting the dosing frequency for patients with a creatinine clearance at or above 130 mL per minute and for patients with a creatinine clearance less than 30 mL per minute groups so that the predicted drug exposure from each renal function category are still comparable to those from patients with normal renal function.

Taking the dose amount to 1 gram sulbactam and 1 gram durlobactam across all renal function groups will allow the use of one standard dosing kit in all patients and simplify the process of dosing preparation and drug administration. The

applicant's proposed revision in dose adjustments is still under our review.

In summary, results of population PK and probability of PK/PD target attainment analysis generally support the proposed dose regimens in the patient population for the target indication. The applicant's proposed revisions on the dose adjustments in patients with altered renal function is under our review.

This concludes the presentation from the FDA. Thank you for the participation of all the advisory committee members. Thank you for your attention, and I will turn it over to the chairperson.

Clarifying Questions

DR. BADEN: Thank you. I'd like to thank all of the agency presenters for, once again, presenting a lot of data from many different angles and making it very accessible and understandable.

We will now take clarifying questions for FDA presenters. Panel members, please use the raise-hand icon to indicate that you have a

question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your questions 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 my questions," so we can move on to the next panel member.

I will just note to the committee and to the community that we will have 15 minutes of Q&A with the agency till 12:15. We will break for lunch. At 1:00, we will have the open public hearing session. When that is concluded, we will resume with clarifying questions for both the applicant and agency, but we need to carefully manage the time to allow the different elements to be represented in this meeting and discussion.

Dr. Siberry, first question, please.

DR. SIBERRY: Thank you, Chair, and I think this question is for Dr. Qi.

I noticed that there was almost double the number of participants in the comparison arm who were aged 75 and older. Not surprisingly, they had the highest mortality rate, and I wanted to see if there was a way to understand how that imbalance in the age, with a much higher number and proportion in that greater than 75 group, could have distorted the apparent point estimate and confidence interval for the difference in mortality between the arms, and if there's some way to estimate what that difference would be if you had the same background age band structure. Thank you.

(Pause.)

DR. QI: This is Karen Qi. I'm a statistical reviewer. So yes, there's some imbalance in terms of age distribution between the two treatment arms. This is a subgroup analysis by age. As you see here in the first block, you see a patient below 65 years old and above 75 years old.

The mortality rate for sulbactam-durlobactam is numerically lower than colistin. Between the 65 and 75-year-old subgroup, the mortality rate for sulbactam-durlobactam was higher than colistin, but you see the sample size in this subgroup was small. It's inconclusive.

I hope I answered your question.

DR. SIBERRY: Thanks, Dr. Qi. I think you've reviewed that, and I just want to confirm that from your perspective, the relatively high number of people in the greater than 75 and the relative high number of deaths in that group, especially in the colistin arm, aren't leading to what looks like a more favorable performance of the study drug than might actually be the case if those age distributions were better matched.

DR. QI: Yes.

DR. SIBERRY: Okay. Thanks. That's all. Thank you.

DR. QI: You're welcome.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you. Michael Green. This

is also for Dr. Qi.

It's just that I wondered -- and maybe I missed this in my preparation reading. Can you provide us the definition of presumed eradication? On your slide, on page 25 of the FDA presentation, a substantial number of the SUL-DUR group had presumed eradication compared to colistin, but I'm wondering what that means since it does impact the superior aspect or at least saying a more favorable outcome. Presumed eradication, how is that defined? Thank you.

DR. IARIKOV: Hi. It's Dmitri Iarikov, cross-discipline team leader of this application. I turn this question over to Dr. Shurland.

DR. SHURLAND: I will attempt to answer the question, but I will defer to the applicant. Presumed eradication means that they did not get an isolate, and based on the patient's feeling, function, and survival, it was based on clinical outcome. But again, I will defer to the applicant.

DR. GREEN: So just to clarify -- and then hopefully in the afternoon when we do clarifying

questions for the applicant, they can confirm this -- these are individuals that don't have a follow-up culture, but because they did well clinically, we presume that they had eradication, but it doesn't mean that they had an endotracheal aspirate culture that doesn't grow it. It means that they didn't get the culture.

(No response.)

DR. GREEN: I guess it's better that we'll just have to have the applicant address this question.

DR. BADEN: I will ask the applicant, if their mic is on, to give Dr. Green a targeted answer.

DR. REGE: That is correct. Thank you.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Thanks again, Chair. This question I think is for Dr. Wei.

I saw that the FDA proposed dosing for creatinine clearance greater than 130 is 1 gram per kilo q4 hours. If that's still a 3-hour infusion,.

I wanted to ask whether it wouldn't make sense to make that a continuous infusion, since you'll barely have time to take down one before you have to put up the next one to start it, if I'm understanding the q4-hour/3-hour duration. Thanks.

DR. WEI: Yes. Thank you. Yes, good question. We also took this into consideration when we recommended duration to the every 4-hour infusion. But considering that the targeted patients are very sick patients in the ICU, patients most of the time are on multiple IV infusion lines, so I think that may be supported for this proposed dose regimen. But I will defer to our clinical reviewer if they have more clinical experience or practice experience for this question, but thank you.

DR. SIBERRY: Thanks very much.

DR. BADEN: Any further comment from the clinical reviewer to Dr. Siberry's question about the infusion duration?

DR. IARIKOV: Hi again. It's Dmitri Iarikov. I think it's a good question, and it

might be more beneficial under some circumstances to have continuous infusion, but I don't think it's been tested in the trial. So it's probably an issue and a question for additional discussion, if a pump for continuous infusion would be more beneficial and practical in certain settings. Over.

DR. BADEN: Thank you.

I'll ask the next question, and then we have Dr. Hunsberger on deck; and to the other panel members, please do use the hand icon.

These safety data, Dr. Ghosh, it looks like there was one anaphylaxis, and it's a small number. And whether that's out of the 60 or the under 200 who have received the target dose and interval, we know that anaphylaxis hypersensitivity is a problem with beta-lactams, but in such a small number, how should we think about that on the safety standpoint? That is a severe allergic reaction, and is it a 1 percent rate, or a 0.5 percent rate? I know the numbers are small, but the degree of hypersensitivity seemed a little higher than what

at least I'm used to for beta-lactams.

DR. IARIKOV: And this is a question to Dr. Ghosh?

DR. BADEN: Ghosh or to any of the agency who would like to comment. It's the safety issue; is how should we think about the hypersensitivity in the anaphylaxis, given the small numbers?

DR. IARIKOV: Let me try to answer this question. Hypersensitivity is a known reaction associated with beta-lactams. All patients received imipenem as a background, and it's also a beta-lactam, so there are two beta-lactams.

It's a well-known safety data on sulbactam. It's been for many years. The drug is not known to be specifically associated with anaphylaxis compared to other beta-lactams, but it's a recognized adverse reaction. Whether durlobactam has an increased risk of anaphylaxis, it's just hard to answer overall. We have some experience from the phase 2 data. We have some experience from phase 1 data and, in general, anaphylaxis would be expected with the initial dose. You don't

need to have sometimes proposed dosage duration.

So in terms of anaphylaxis, it might be somewhat more reassuring as compared to 150 patients, but it's going to be investigated in the postmarketing setting through pharmacovigilance, for instance. So yes, it's a good question, but additional data might provide more clarity on this.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. I wanted to follow up on Dr. Siberry's question about the age effects. It is a little odd that in the 65 to 75, and then older than 75, the mortality kind of goes in opposite directions. It could be attributed to other covariates and how those groups are made up.

So I'm wondering if you did any kind of logistic regression where you controlled for other covariate effects to see if there was still that discrepancy in the age groups once you control for other covariate effects.

DR. IARIKOV: Thank you for the question. I will turn it over to our statistical team.

Dr. Daniel Rubin, the statistical team leader, will address this question.

DR. RUBIN: Hello. I'm Dan Rubin. I'm a secondary statistical reviewer for FDA. Thank you, Dr. Hunsberger, for your question.

I think we viewed these results as due to mainly noise from chance variation, but to specifically answer your question, we did not specifically look at other potential covariates that might be influencing these results, but thank you for that suggestion.

DR. HUNSBERGER: Thank you.

DR. BADEN: I have several more questions, but I want to give my colleague ample time to ask as well.

One aspect of the data -- the pivotal phase 3 trial, granted it was small, 120 in the final analytic set -- is a single individual was enrolled in the U.S. How does the agency look at those types of data and on those types of inclusion in relation to practice patterns in the U.S. where there may be different background care, and does it

have implications in generalizability?

Granted, it's a very difficult infection to identify, as the applicant has demonstrated, so it is heroic work to be able to identify 100, 150, 180 individuals who may be appropriate to enroll, but we do know there are tremendous variations in background care. So how does the agency look at that issue, and how should the committee think about it in relation to generalizability to broad use in the US?

DR. IARIKOV: Thank you for the question, Dr. Baden. In general, use of data from foreign sites might be acceptable to support an application when there are sufficient similarities in the disease process, pathogens, clinical care, et cetera, and across geographic regions that enrolled in the trial. We believe that in terms of *Acinetobacter*, HABP/VABP infections, there's sufficient similarity to leverage the data from foreign sites.

DR. BADEN: Thank you.

Given that it is 12:15, or 12:14 and soon to

be 12:15, we will break for lunch.

Dr. Green, you are noted, and after the OPH session, we will resume clarifying questions to both the applicant and the agency, and I encourage the panel members to prepare those questions.

So we will now break for lunch. We'll reconvene sharp at 1:00 p.m. Eastern time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene at about 12:50 to ensure you are connected before we reconvene at 1:00 p.m. Thank you. We are now on the lunch break.

(Whereupon, at 12:16 p.m., a lunch recess was taken, and the meeting resumed at 1:00 p.m.)

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

(1:00 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:00 p.m. Eastern time, and we shall resume the advisory committee meeting. We will begin with 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 relationships that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant'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 this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance on 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, and 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.

Speaker number 1, please unmute and turn on

your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have five minutes. Please go ahead, speaker number 1.

DR. MERCURO: Hello. My name is Nick Mercuro. I'm an infectious disease pharmacist at Maine Medical Center. First, I'd like to thank the committee for allowing me to share my perspective and experience with sulbactam-durlobactam. I don't have materials to share. I'll just be reading my testimony, and I have no conflicts of interest to disclose, and I've not received any funds to speak here.

My background in ID includes a doctoral degree in pharmacy, four years of residency and fellowship, three of which were specifically in infectious disease, and several years of practicing as an ID pharmacist and adjunctive clinical faculty at teaching institutes and medical centers. Every day I review microbiologic and therapeutic data with patients, as well as clinicians, on

antimicrobial properties, optimal selection, dose duration of therapy, and failure to recognize risks in presence of multidrug-resistant pathogens, and subsequently initiate an optimal antibiotic because of enormous consequences for patients.

Sulbactam-durlobactam feels a critical need for patients, as the failure and toxicity rates associated with antibiotics; therefore, carbapenem-resistant *Acinetobacter* infections are unacceptable.

I'd like to review a patient's case that highlights the importance of reliable antimicrobials against MDR *Acinetobacter*, and while these indications of sulbactam-durlobactam in this case doesn't pertain to pneumonia as we discussed today, we found the role of sulbactam-durlobactam to be essential in this critically ill patient with a neurosurgical infection that Dr. Altarac briefly alluded to today in the Q&A session of the clinical data.

Last year, an elderly female suffered a traumatic fall overseas leading to a subdural

hematoma. She was hospitalized in Europe and underwent the hemicraniectomy. The patient subsequently developed a subgluteal food collection, and that required a drain to be placed. She was then transferred to our hospital in the U.S. Neurological status remained poor, and the patient demonstrated nuance at heart failure, and several days into therapy in her hospital stay, she developed fever, increased size of fluid collection, and worsening mental status. She was empirically started on nichomycin, cef-taz [ph], avibactam, and on [indiscernible], given the concern for infection caused by a multidrug resistant pathogen.

The patient was taken to the OR for incision and drainage of the surgical site. Food was cultured and gram stain showed gram-negative rods. Molecular diagnostics identified in OXA-producing carbapenemase for *Acinetobacter baumannii.* The patient was then switched to polymyxin and cefiderocol. Final susceptibility showed that the *Acinetobacter* was only susceptible to cefiderocol

and intermediate to colistin and minocycline. At this point, we filed an EIND for sulbactam-durlobactam, again, as promising preliminary results of the ATTACK trial for *Acinetobacter* infection, and we were also concerned of the safety and efficacy of the current regimen based on the patient's clinical state and published literature.

Her mental status remained poor. Leukocytes, creatinine, and BUN began to rise. She was having oxygen desaturation caused by a large pleural effusion. The polymyxin was then discontinued after 3 days, given the concern for toxicity, and low likelihood of being beneficial, given the site of infection. The subgluteal collection had continued to increase, and it was tapped through the [indiscernible] with significant inflammation of about 1700 leukocytes.

It was consistently documented that this patient's prognosis was highly guarded due to nonverbal and unable to follow commands. Once sulbactam-durlobactam was approved after a few days, she was initiated on a combination with

cefiderocol and minocycline, based on susceptibility and synergy testing that was performed at the Entasis laboratory, with a planned 28-day course, which was eventually extended to 42 days.

We elected to use its most potent combination, which demonstrated an MIC of 0.5 milligrams per liter since it was studied in combination in the trial with another beta-lactam and for a more prolonged course for the osteomyelitis presumed central nervous infection. After 5 days of this combination, leucocytosis begin to normalize, and she was becoming more interactive.

After the second week she was answering varying questions and was oriented to self and place. After a month, she continued to make significant progress and was able to be transferred out of intermediary care. By the time of discharge, she was ambulatory and conversive, nearly back to her baseline mental state with no signs of septic pathophysiology. No adverse events

were suspected to be directly attributable to sulbactam-durlobactam or cefiderocol, although we believed she developed side effects related to polymyxin, vancomycin, and minocycline. She was discharged to rehab, where it is documented that she had made remarkable recovery and continues to progress.

While conclusions can't be made from a single case report, and multiple and antimicrobials were used in this particular case, I do feel that if sulbactam-durlobactam was not available, they likely would have either succumbed to this infection or suffered from debilitating consequences of progressive neurosurgical infection or antibiotic-related harms related to either polymyxin or other antimicrobials.

Our pipeline's in desperate need of an agent with reliable activity in efficacy against multidrug-resistant *Acinetobacter* infection. I think this case highlights the potential importance of sulbactam-durlobactam as an option even for off-label use. Thank you for your time.

DR. BADEN: Thank you.

Will speaker number 2 please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have five minutes. Thank you.

DR. MALEK: Good afternoon, esteemed chairperson and advisory committee members. My name is Alexandre Malek. I'm an assistant professor of medicine in the Division of Infectious Disease at LSU Health, Shreveport Louisiana. I want to thank FDA for allowing me time and giving me the opportunity today to share my personal and independent clinical perspective. I do not have a financial relationship with the sponsor or its competitors, and I'm not being compensated for my current brief testimony.

I want to share my experience with the FDA committee regarding the use of sulbactam-durlobactam as a cornerstone treatment for ventilated-associated pneumonia with invasive disease septicemia, secondary to extensively

resistant *A. baumannii* complex. Our patient was a 44-year-old male who presented with sustained burn injury, involving full-thickness burns covering more than 70 percent, up to 90 percent, of the total body surface area, and was intubated upon admission. The patient has a prolonged hospital course in the intensive care unit, which was complicated by ventilator-associated pneumonia and bacteremia, and skin and soft tissue infections, again, related to carbapenem-resistant *A. baumannii*.

Our patient developed multiple organ failure and was on renal replacement therapy, CRRT. Despite being on the standard treatment for carbapenem *A. baumannii*, polymyxin, and cefiderocol-based regimen, the bacterial strain becomes intermediate to polymyxin and resistant to cefiderocol. Under the emergency investigational new drug application, EIND 163424, we used sulbactam-durlobactam as compassionate, along with high-dose tigecycline 100 milligram twice a day and meropenem, and subsequently, meropenem was transitioned to cefiderocol.

Our patient was in septic shock and required two pressors to maintain his blood pressure. Both pressors were discontinued in 36 hours after initiating the sulbactam-durlobactam-based antibiotic regimen. Of interest, our patient was dependent on CRRT for 23 days and was weaned off on day 9 of investigational antibiotic treatment. The dose of sulbactam-durlobactam was adjusted according to the creatinine clearance and CRRT as instructed by Entasis Therapeutics' protocol.

During the treatment course, our patient developed nausea and increased LFTs, AST, and ALT, but remained less than 3 times the upper normal limit, and had thrombocytopenia at 37,000. The codes was deemed multifactorial in origin, and tigecycline high dose was considered the most likely culprit agent. Patient has clinically improved, and the antibiotic treatment was discontinued after 23 days of investigational antibiotic therapy after amendment of the protocol. The patient was discharged from the hospital to a rehab center and remains alive and recovering.

In summary, the beneficial effect of the use of sulbactam-durlobactam-based regimen in this case were the following: controlled the septicemia and cleared the bacteremia, which has impacted and protected the kidney function; expedited the removal of the indwelling hemodialysis catheter and reduced catheter-related complication, in particular in the setting of extensive burns; expedited the discharge from ICU; and has certainly impacted on survival. Thank you.

DR. BADEN: Thank you for sharing.

Speaker number 3, please unmute and turn on your webcam. Please begin and introduce yourself. State your name and any organization you're representing for the record. You have five minutes.

DR. BONOMO: Thank you very much for this opportunity. My name is Dr. Robert Bonomo. I am a professor of medicine, pharmacology, molecular biology, and bioinformatics at Case Western Reserve University. I'm an infectious diseases physician with both interests in clinical, as well as basic

molecular sciences of resistance. I have 25 years of background in antimicrobial resistance.

My laboratory's had the privilege to test more than 200 beta-lactamase inhibitors from industry, as well as from the private sector. I've published 153 manuscripts on *Acinetobacter,* looking at the different mechanisms of resistance, and my laboratory has received financial support from Entasis for some of the work we did; from Vernatorx; from Merck; and Lockhart, all in the area of preclinical testing of beta-lactamase inhibitors. I've also worked with the IDSA guidance on the treatment of multidrug-resistant infections, as well as worked with ESCMID guidelines on the treatment of multidrug-resistant infections.

My experience with compounds dates way back when it was in its preclinical stages, and I've watched very carefully as the field has developed, and most recently with the results of the ATTACK trial. Our laboratory did some of the fundamental studies looking at the kinetics and molecular

biology of the interactions of durlobactam with its targets both in the cephalosporin ASA [ph] *Acinetobacter,* as well as the OXA beta-lactamases. We were able to test 72 highly drug-resistant strains from legacy collections, where the combination of sulbactam-durlobactam compared extremely favorably.

I think those studies set the groundwork by which the subsequent five phase 1 trials, and phase 2, and the phase 3 ATTACK trial were conducted. I was very pleased with the results of the ATTACK trial showing how much better sulbactam did than comparative clinical therapy. The patients did well clinically. They did a lot better than the comparator. There was less adverse side effects and there was significant microbiologic, as well as clinical cure.

I think at no other time -- with the emergence of multidrug-resistant *Acinetobacter* occurring, according to reports of the CDC, an increasing importance as a result of COVID -- is that we have better therapies available to treat

our patients with this drug. I think overall it would be a very, very important addition to our therapeutic armamentarium, particularly for this pathogen that has a significantly higher mortality rate and is significantly much more difficult to treat than any other gram-negative pathogen. Thank you.

DR. BADEN: Thank you.

Speaker number 4, please unmute and turn on your webcam. Introduce yourself. Please state your name and any organization you're representing for the record. You have five minutes.

DR. NAZINITSKY: Hi. My name is Allison Nazinitsky. I'm an MD. I'm an infectious disease physician. I work for myself. I do mostly telemedicine. I cover a lot of hospitals across the United States and have 15 state licenses. I do not have any financial disclosures, and I am speaking simply because I had a bad outbreak of pan-resistant *Acinetobacter* at one of the hospitals I covered and have lost several patients, and was able to use this drug as compassionate use for one

of our patients, and he is doing well, and I have no financial disclosures.

Let me get to my screen here. I don't know why it won't let me get back to my screen.

Well, my patient, he came in. He's a 73-year-old male. He was discharged to a nursing facility after a catastrophic stroke and had been there for about a month, and came back in with a stage 4 sacral decubitus ulcer and was septic; was taken to the operating room and debrided and diverted, and had a G-tube placed for feeding and nutrition.

Our initial cultures did grow polymicrobial flora, including a pan-resistant *Acinetobacter,* and due to formulary issues, we had him on a combination of antibiotics initially, and continued to progress, and had multiple debridements. We had VRE pan-resistant *Acinetobacter* and several other gram-negative organisms. Over the course of several more debridements, the *Acinetobacter* became the predominant organism, and I reached out to get compassionate use for this drug, and we started a

combination of therapies, including eravacycline, sulbactam-durlobactam, and we actually did continuous infusions of cefepime, and this was due to formulary issues at this very small hospital that I was covering.

Over the course of the next 4 weeks, with aggressive wound care, and aggressive nutrition, and offloading, we did 4 weeks of therapy. He did have a breakthrough VRE bacteremia about 1 week into our therapy, and I added linezolid, and after about a 6-week hospitalization and 4 weeks of our combination therapy, he was discharged back to a different nursing facility, and we got a photo on Easter Sunday that he's doing well and he's improving clinically.

We did not have any other major drug side effects during this treatment course. The only issue we ran into is we did have that breakthrough VRE bacteremia, and after another debridement, his cultures -- a week after the VRE bacteremia, they did another bedside debridement, and his cultures were actually negative. They did not grow the

Acinetobacter, just some other organisms. So we had a microbiological response as well after a combination approach.

So after having several patients pass away from this unfortunate pan-resistant organism, it was wonderful to have a therapeutic modality that I truly believe saved this patient's life, and that's why I'm here speaking today.

DR. BADEN: Thank you.

Will speaker number 5 please unmute and turn on your webcam. Begin and introduce yourself. Please state your name and any organization you're representing for the record. You have five minutes.

MS. RELKO: Good morning. My name is Consuelo Relko, and I do not have any financials for anybody. Good morning to the FDA.

Thank you for allowing me to testify my story. It all started on August 3, 2020. I was in the hospital for 85 days, up to October 27 2020, and I was in three different hospitals. Today I can speak, walk, and take care of myself. You'd

never know by looking at me now how far I came. If it weren't for my son, daughter, and husband fighting for me, I would not be here.

I sort of remember being in the hospital and could not talk, walk, and was kind of out of it. There were too many machines and too much medication. My doctor had given up hope for me. They had nothing more to offer. It was a new disease, and my son, and daughter, and husband, however, never gave up on me. They wanted to transfer me to a different hospital, but my doctor would not release me. My doctor thought that I would not make it.

My daughter and son in fighting, transferred me -- through argument -- to a different hospital. They wanted a new opportunity for me to fight and get a chance to send me to a different hospital. Thank God they won. My son had to pay $10,000 to transfer me by plane and ambulance almost 400 miles away to another hospital. The move, as expensive as it was, saved my life. I remember laying in my bed at the new hospital. Even though I was out of

it, I barely remember my new doctor. He said he would try to give me a new medication that was not made for most of the patients yet, then things turned around, and I got the medicine, and started to get better.

Several of my life [indiscernible] -- but it was a long time before I was independent again. I did not know if I was able to walk again, and talk again, any eat and drink. I was transferred to a rehab center to get better. I went through hell and came back. I wonder why so many people have passed away and left the kids and little ones, but why I was able to get better.

I have decided it was because I had people fighting for me. Even though I was out of it, my daughter, and son, and husband fought to get me to a new hospital. My doctor joined the fight to get me the medicine. Without all them, I would not be here. I was a miracle, and I think God for it, but not every patient has so many people fighting for them. I'm here today to ask you to join the fight and help other people who are sick as I was and

need this medication. Thank you. Sincerely, Consuelo Relko.

DR. BADEN: Thank you for sharing.

Will speaker number 6 please unmute and turn on your screen. Begin and introduce yourself. Please state your name and any organization you're representing the record. You have five minutes.

MS. O'TOOLE: Hi, everyone. My name is Rebecca O'Toole, and I am from Fort Washington, Pennsylvania. Thank you so much for allowing me to speak today. I have no conflicts of interest, and I'm representing myself. I also have no financial disclosures.

I am passionate about the development of new antibiotics designed to fight multidrug-resistant infections because I have witnessed the life-saving power that they wield. About two years ago, my mom fell into septic shock due to an unknown antibiotic-resistant bacterial infection, and she spent over a month in the ICU on several different forms of life support. Luckily, thanks to her amazing international care team and the life-saving

power of antibiotics, she is still with us today.

As a pharmacy student, I am proud to advocate for the development of novel antibiotics and proper use of our existing therapies to help other patients just like my mom. Infections caused by the carbapenem-resistant *Acinetobacter* are a major threat to the health and safety of hospitalized patients. These bacteria frequently colonize healthcare facility services and are responsible for multiple outbreaks in hospitals and nursing homes. They cause a variety of infections, including bloodstream infections and serious pneumonias.

Acinetobacter is also one of the most antibiotic-resistant bacteria in clinical medicine because it has developed resistance to one of our last lines of defense, a class of antibiotics called carbapenems. *Acinetobacter* can also develop resistance to multiple antibiotics classes at the same time, which further complicates treatment. *Acinetobacter* that are resistant to multiple antibiotic classes are known as multidrug resistant

and extensively drug resistant.

Recent work completed by the Providence VA Medical Center and the University of Rhode Island evaluated the clinical outcomes of patients with *Acinetobacter* infections across the national VA health system. Clinical outcomes such as death in the hospital and longer hospital stays were worse in patients with multidrug-resistant infections versus non-multidrug-resistant *Acinetobacter* infections, and outcomes were worse among patients who had carbapenem-resistant *Acinetobacter* infections versus non-carbapenem-resistant *Acinetobacter* infections.

Other work also completed by the Providence VA Medical Center team and the University of Rhode Island looked back at all *Acinetobacter* cultures collected as part of normal clinical practice from VA patients who were treated in VA hospitals, long-term care facilities, and outpatient clinics nationally from 2010 to 2018. They used their data to describe carbapenem resistance, multidrug resistance, and extensive drug resistance in their

national collection of almost 20,000 *Acinetobacter* clinical cultures. The most common source of resistant *Acinetobacter* infections was the lung. Among lung cultures, carbapenem resistance was seen in 43 percent of cultures, multidrug resistance was seen in 49 percent of cultures, and extensive drug resistance was seen in 21 percent of cultures.

While the overall incidence of *Acinetobacter* cultures consistently decreased by about 12 percent per year throughout the study period, multidrug-resistant *Acinetobacter* and carbapenem-resistant *Acinetobacter* remain common. In 2018, carbapenem resistance was seen in 28 percent of *Acinetobacter* cultures collected in VA hospitals and 36 percent of *Acinetobacter* cultures collected in VA long-term care facilities. Multidrug resistance was seen in 31 percent of *Acinetobacter* cultures collected in VA hospitals and 36 percent of cultures collected in VA long-term care facilities. Based on their data, better treatment options are necessary to improve clinical outcomes in patients with these resistant

infections.

The compilation of work done at the Providence VA Medical Center demonstrates that multidrug-resistant and carbapenem-resistant *Acinetobacter* infections should be a focus of stewardship efforts in drug development. Ensuring that carbapenem resistance does not spread to other organisms is also a priority. By effectively treating carbapenem-resistant infections, we can preserve the effectiveness of carbapenems and limit the spread of carbapenem resistance among other organisms.

Based on available information regarding sulbactam-durlobactam, if it is approved, it will provide a new, potentially life-saving avenue of treatment for carbapenem-resistant *Acinetobacter* infections to a population that currently does not have many treatment options to pick from. I am hopeful that if approved, this medication will provide life-saving treatments across the country and positively impact appropriate patients and their families. Thank you so much for your time.

Clarifying Questions (continued)

DR. BADEN: Thank you for sharing.

This concludes the open public hearing portion of the meeting. We'll no longer take comments from the audience, but we greatly appreciate the six OPH speakers and their diverse, varied viewpoints to help inform our deliberations and thought processes.

We will now go back to clarifying questions for both the applicant and the agency. Please display M1 slide 5. To panel members, please use the raise-hand icon to indicate that you have a question, and remember to put your hand down after you've asked your question. 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 question with,

"That is all for my questions," so we can move on to the next panel member.

Panel members, please raise your hands.

Dr. Stevenson, did the applicant have a comment they wanted to make as we resume our clarifying question session?

DR. STEVENSON: Hi, Dr. Baden. I believe so, yes.

DR. BADEN: Dr. Rege?

DR. REGE: Thank you, Dr. Baden. We just wanted to clarify a point, and I would like to call on Mr. John O'Donnell to discuss that.

MR. O'DONNELL: Good afternoon. Dr. Shurland presented some work with the in vitro hollow fiber infection model at Entasis with a few representative strains. We just want to clarify that the PB3 mutant, ARC5950, that was utilized in this study, has an MIC of 8 mg per liter, not as opposed to 4. So based upon that data set, we believe that the time course that you can observe with that study in the panel I've shown here is representative of SUL-DUR activity, but with an MIC

that's slightly outside of the susceptible range. We do see in vivo that these strains are readily treatable, and we see very good cidal killing against these strains even though they have the PB3 mutants. Thank you.

DR. BADEN: Thank you for clarifying.

To both the applicant and the agency, if discussion comes up where you can bring in clarifying information, please let me know so we can understand the issues as clearly as possible because there is much depth and complexity here.

Dr. Green?

DR. GREEN: Thank you, Dr. Baden. This is Michael Green. I think my question can be both with the sponsor, and perhaps with the sponsor's speaker, Dr. Paterson, if he's still available, but then I'm interested in the agency's response.

One of the challenges we have in looking at these data is that it's really a small study. Maybe that's even the reason why the AMDAC has been asked to opine on this. But even in this small study, if I understood the presented data

correctly, approximately 1 patient in the SUL-DUR treatment arm did evolve resistance on treatment; that's 1 patient for less than 100 treated patient courses, which might be 1 percent.

So what do we think about the durability of efficacy of SUL-DUR, if it's approved, given the data as we have it available at this time? Thank you.

DR. REGE: Sure. I would like to call on Dr. David Paterson.

DR. PATERSON: Thank you. David Paterson. Thank you very much, Professor Green, for the comment, and I think it's important to firstly put all of this into a little bit of context.

First of all, we know that *Acinetobacter* infections in the United States have a very high mortality, so when we've looked at data from the NIH-sponsored OVERCOME study, in people from the U.S., 27.9 percent who had *Acinetobacter* and were treated with colistin either as combination therapy or monotherapy died within 28 days. Maybe apart from out-of-hospital cardiac arrest, I do not know

any other disease process that kills almost 30 percent of Americans once it occurs. So I think live, die, heal, function, survive, survive is the most important aspect in our discussions.

Next, really, is looking at the microbiological issues, and when we have looked at cefiderocol, tetracycline derivatives, and of course colistin-based therapies, all of those we've seen emergence of resistance during therapy, and we know that with any antibiotic, this is something that we're going to see over time. So I think it is something that needs surveillance, but it also needs to be put into context that it will only be seen in survivors. Almost a third of people who die of *Acinetobacter* infections who are treated with colistin will never have the opportunity, of course, to develop subsequent infections that are resistant because they're, unfortunately, no longer alive. So I think that's our biggest priority, but it is certainly something that needs to be addressed, of course, during the course of an antibiotic's lifespan. Thank you.

DR. BADEN: Thank you. I will recognize myself.

As Dr. Murphy said early in clarifying questions to the applicant, this medication will be used in combination; not SUL-DUR, but in combination with other antibacterials, given the nature of the infection these patients have is likely to be complex, and *Acinetobacter* may be a very important organism but may not be the exclusive organism. An interesting attribute of SUL-DUR, despite its impressive activity against resistant organism *Acinetobacter*, it's fairly selective.

So how do we think about this in terms of the combination used with other antibacterials in this study, or as imi-cilastatin? But one may imagine it being used with beta-lactam/beta-lactamase inhibitors of other flavors. The multiple beta-lactamase inhibitors, do we need some guidance in how to use this agent with other combination antibacterials, especially other beta-lactamase inhibitors? Any data on the safety

or any guidance on how we should be thinking about that, any data to guide us? To the applicant, to the agency.

DR. REGE: We would like to call on Dr. David Paterson again.

DR. PATERSON: Thanks very much. It's David Paterson. This is such a clinically important question, but it's pretty much a data-free zone, unfortunately. I do know that the sponsor has looked at the potential of combination therapy in vitro. Clearly, sulbactam-durlobactam is going to be a high target for antimicrobial stewardship programs across the country and across the world because we want to preserve it. How it is used in practice is going to very much be determined by our guidelines, but I would like Dr. Miller to review the company's in vitro testing for combinations because that could be quite informative for us. Thank you.

DR. MILLER: Alita Miller, Entasis. I do have a slide to summarize the studies that we've done in vitro in combination with sulbactam-

durlobactam. We basically did these in checkerboard assays with a wide variety of different agents. They're listed here. These are gram-negative agents, so I won't read them off, but it did include ceftazidime-avibactam, as well as a number of gram-positive agents, antifungals, and metronidazole. And we didn't actually see any effect on any of these agents, either on the activity of sulbactam-durlobactam or the reverse, that sulbactam-durlobactam affected the activity of these agents against their target organisms. So just based on this in vitro alone, we don't see any worrying signals.

DR. BADEN: But to follow up -- thank you -- on the efficacy side, there's no data to be worried that there's interference. But how about on the toxicity side if somebody's on ceftaz-avi or pip-tazo, and for other organisms of concern in a polymicrobial infection, and on SUL-DUR, do we have toxicity or side effects that we have to be mindful of? And maybe we have no data yet, and this will be something that requires active monitoring if

this is authorized or approved, but we are in novel territory in terms of combination antimicrobial use in complicated patients, whereby mechanism, there may be overlap that we have to better understand.

Am I capturing some of the issues properly? It sounds like there are not data to inform us, at this point.

DR. REGE: That is correct.

DR. BADEN: And I don't know if the agency has any comment on this type of use because this is very likely to be used with many different antimicrobial combinations, including other beta-lactamase inhibitors.

DR. IARIKOV: Thank you, Dr. Baden, for that question. I'll turn it over to our clinical reviewer, Dr. Ghosh.

DR. GHOSH: Hi. This is Mayurika Ghosh, clinical reviewer, Division of Anti-Infectives, FDA. The question was whether a combination of sulbactam-durlobactam with other beta-lactams or concomitant antibacterials could result in certain toxicities?

The data that is in the application shows that the subjects were on several concomitant medications, and as you know, in the comparative Part A of the phase 3 study, both arms had background imipenem therapy. Now, the Part B, which was the open-label part, had only sulbactam and imipenem-cilastatin, and the safety profile was reviewed earlier in the day.

The 12 subjects who were on the expanded access program, they were on multiple salvage regimens -- imipenem, cefoperazone, cefiderocol, ceftazidime-avibactam, and several antimicrobials, both recently approved, as well as older beta-lactam/beta-lactamase inhibitors. And again, these are very critically ill patients in the intensive care unit, and about 6 patients of the 12 subjects had an outcome of death, and 8 patients cured their infections.

There was nothing that was noted in the narratives of the patients which showed that it was out of the ordinary. Now, we do think about the combination of beta-lactam/beta-lactamase

inhibitors, we think about bone marrow suppression, and we think about other effects on organ systems, but certainly those would be something to be monitored down the road. Certainly, this is a very small database, but there was nothing that was suggestive of bone marrow suppression or anything of that nature. Thank you.

DR. BADEN: Thank you.

Dr. Hilton?

DR. HILTON: Yes. Thank you. I wonder if the follow-up time of this study is actually adequate, and I wonder if there might be subsequent follow-up data.

I'm looking at the FDA slide 24 that shows the test-of-cure rates at three different time points, and I see that they're diminishing in both treatment arms, but the treatment effect by this endpoint is also diminishing with time, and that caused me some concern, then I see similar findings when I look at the microbiological endpoint. So I just wonder if we've really seen the full story. Thank you.

DR. BADEN: Any responses from the applicant on the longer term follow-up or do we have what the study was designed to capture?

DR. REGE: Sure. I would like to call on Dr. David Altarac to answer your question.

DR. ALTARAC: David Altarac, Entasis. What I'd like to bring up now is a comparison of our trial compared to some recently completed other trials in similar populations. What you can see in these trials, including our trial, REPROVE -- which was ceftazidime-avibactam versus meropenem and CREDIBLE-CR -- is that this finding that you're describing is seen throughout. These types of trials, it's not an unusual finding. It is by nature, as you go further out, the probability of a patient succumbing to their underlying disease process increases. But what I think is most meaningful, again, is that our findings are consistent with these other findings, but we have demonstrated at 28 days, and 14 days, and in various other endpoints that sulbactam-durlobactam did achieve the primary efficacy objectives. Thank

you.

DR. BADEN: If no follow-up, then Dr. Hardy.

DR. HARDY: Hi. This is Dr. David Hardy from Los Angeles. I just want to touch back on a point that Dr. Baden made earlier in our discussion, and my questions are both to the applicant as well as to the agency.

It was a bit of a surprise to me to see that only one of the study participants from the ATTACK phase 3 trial was in the U.S., with the majority being from China and from Europe. Was there a strategy or a reason that you were using to enroll most of the patients in this study ex-US?

DR. REGE: We did, and I'd like to call on Dr. David Altarac again to answer your question.

DR. ALTARAC: David Altarac, Entasis. Our strategy to enroll in this trial, which was a global trial, was to enroll equally in any geography for which there were sites that were open. We had 5 sites that were open in the United States. Those sites reflected various geographies within the United States, as well as reflected the

diversity of the country. These sites were in Chicago, Memphis, Shreveport, Cincinnati, and Houston. The challenges with enrolling in this trial were mainly focused on the underlying condition, which you can't predict. You don't know when you're going to have a case of multidrug-resistant *Acinetobacter*, so our strategy was to maximize the probability that we would find those infections by selecting these sites, and they included sites in the U.S., as well as global.

It is important to note that in our overall development program, which included our phase 1, phase 2, and phase 3 trials, over 20 percent of the participants were from the United States, so we tried to make sure that it represented the U.S. and used those data to inform decisions moving into the the phase 3 trial. And the numbers that you see in the enrollment in our study are reflective both of the global epidemiology of multidrug-resistant *Acinetobacter*, which is highest in Asia Pacific, Eastern Europe, and Latin America, followed by North America.

Then finally, as you may know, experts at the FDA published an article in 2021, Part [indiscernible] et al., where they described the four most recent phase 3 clinical trials, and in their data, our demographics were consistent with enrollment in those trials as well. So overall, our strategy was to be equally selective in all countries. Thank you.

DR. HARDY: Thank you very much.

I guess just to go back to the question that Dr. Baden opened, my question is to the agency to say does the epidemiology of this medical problem, being much less apparently in the U.S., affect in any way the decision-making process by the FDA or the question to the committee?

DR. IARIKOV: Thank you for the question. FDA approves drugs to be used in the United States, so we'll always pay attention to adequate representation and the possibility to extrapolate collected data to the U.S. population. We also looked at this closely, and we believe that, based on resistant patterns observed in *Acinetobacter*

isolates, and based on standards of clinical care that were used in the trial to enroll subjects, we feel confident that these data would be extrapolatable to the United States population, but there are probably more -- it's not a single explanation why sometimes it's more difficult, and it's a subject for another conversation why it might be more difficult to enroll in the clinical trials in this serial population in the United States. But back to the data that we have, we think they do reflect current epidemiology and standards that would be used in the United States.

DR. HARDY: So you do believe that this still represents a large unmet need in the U.S., as well as internationally.

DR. IARIKOV: Yes, we do believe, but acknowledge that, fortunately, the number of patients with carbapenem with *Acinetobacter,* including multidrug-resistant *Acinetobacter*, in the United States proportionally may be lower than in other geographies. And again, it's a fortunate finding, but we do have patients. And for the

individual patient, it's absolutely an unmet medical need, thinking about the mortality, and it's very hard to predict how resistance will spread and emerge.

DR. HARDY: Thank you.

DR. BADEN: Thank you.

I see Dr. Murphy has a checkmark we are not using at this time, but I assume that's a raised hand and you have a question; so please, and then we'll get back to the other raised hands.

DR. MURPHY: Thanks, Dr. Baden. It's a follow-up for Dr. Hardy's question.

The sad irony, I guess, is that the burden of MDR bacterial infections is probably greatest in countries that are least equipped to identify them and treat them. So excuse me, as this is a little bit beyond the purview of the FDA, but I have to ask, has the sponsor thought about access to the drug in low-income countries outside of the U.S., Europe, that otherwise will find this to be unaffordable? Thanks.

DR. REGE: Sure. I would like to call on

Dr. David Altarac to answer your question.

DR. ALTARAC: David Altarac. We are fully committed to providing sulbactam-durlobactam to patients in need globally. We actually have enrolled 2 patients in our expanded access program in Europe and made that drug available, and we'll continue to look at opportunities to provide drugs outside of the United States if the drug is approved, and we'll be looking to work with partners to facilitate further development in other countries, but we don't have any specific plans at this time and are focusing on the United States. We do have an ongoing application pending with our partner, Zai Laboratory, for review and approval in China, but beyond that, we are looking at other opportunities to make the drug available. Thank you.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: Thank you, Chair. I think this question will be for the pharmacology speakers from the applicant and the agency.

In the applicant's presentation, I note that

there would be no required dose adjustments for weight, and then in the agency review, I think there were 10 participants who fell into the 35-to-under-50-kilo body weight group, but the pharmacokinetic modeling suggested that PK targets would be met and that there wouldn't be concerned for toxicity.

So I just wanted some confirmation that based on who was represented as participants in that modeling, is the suggestion that no dose adjustment is needed for a weight of at least 35 kilos or some different minimum? That's my question.

DR. REGE: I would like to call on Dr. Kajal Larson to answer your question.

DR. LARSON: Kajal Larson, Entasis. Based on our population PK model, which included data from phase 1, 2, and 3, we did look at the effect of weight on PK exposures, as well as other covariate effects and demographics, but body weight was not a clinically relevant covariate in the model, and we do not expect any dose adjustment

based on weight.

DR. SIBERRY: And I'm sorry. What lower weight limit do you mean by that? Down to 20 kilos, or 30 kilos, 35?

DR. LARSON: We had looked down to the exposures that we had captured in the model, and we will try to get you the exact data shortly. Thank you.

DR. SIBERRY: Great. Thank you so much.

Perhaps the agency can comment if they had a lower weight that went into their analyses for what they thought would be covered by the available data modeling or both? Dr. Wei perhaps.

DR. WEI: Thank you. Based on our review of the data submitted by the applicant, just based on the summarized data, I think the body weight is at 35 kilograms at the lower limit, but my pharmacometrics colleague, Dr. Xiaolei Pan, if she can also provide input from her pharmacometrics review.

DR. PAN: Hello. I think the body weight is from 35 kg and higher, but what we see is that for

patients with lower body weight, they have higher exposure. Also, from an efficacy endpoint, we don't have much issue, so that's more of a consideration from a safety perspective. But I think from the safety aspect, we don't see too much safety concern.

DR. SIBERRY: Okay. That's very helpful, and I'll just end by saying I think it's helpful to think maybe about using this down to 35 kilos rather than down to an arbitrary age of 18, that which is a social event, not a biologic event. And for treating severe disease for which there may not be any alternatives, that just may give some reassurance and guidance to pediatricians faced with adolescents who have these. I've noted at least one 18 and one 19 year old were reflected among the participants, which was good to see.

Thanks very much, Chair.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you, Dr. Baden. This is a question for the sponsor, I think for Dr. Altarac.

I'm wondering if you did any analysis looking at differences in outcome based on the primary reason for the initial hospitalization. We know that many of these infections are nosocomially commonly acquired in people that were admitted for other reasons. And in particular, a lot of the study was done during the COVID pandemic, and we know that this organism was a particularly horrible problem as a secondary cause of pneumonia during that pandemic, and it may be that outcomes are different when you are in hospital and have other underlying problems that then are associated with infection. Thank you very much.

DR. REGE: Yes. I would like to call on Dr. David Altarac to answer your question.

DR. ALTARAC: David Altarac. I'm not sure this answers your question. We didn't do specific analyses looking at comorbid conditions that were underlying the hospitalization or presumably led to their hospital-acquired or ventilator-associated pneumonia, so I don't think that's totally answering your question, but we do show that there

were, in many of these patients, multiple and significant comorbid conditions in both the sulbactam-durlobactam arm, and what we show in this slide is that they were generally comparable between the two treatment groups.

DR. BADEN: Thank you.

I'd like to just ask a question of the agency that I asked of the applicant at the beginning. Do you have any techniques to help us understand how much of the benefit we've seen is due to the benefit of SUL-DUR versus negative attributes of its comparator, colistin, or are we left with a sum total integration of benefit? Is there any way to tease apart benefit-risk, given that the different agents have different characteristics in both spaces?

(Pause.)

DR. BADEN: Thank you, Dr. Rubin, for being willing to take on my impossible to answer question, but I would be grateful for your perspectives.

DR. IARIKOV: Could you confirm that you see

the slide that we're projecting?

DR. BADEN: No, I see the two of you at the podium. We can always use our mind's eye if you're not able to have technology be our friend.

DR. IARIKOV: Okay. Let's try one more time. What about now?

DR. BADEN: Yes, a slide has come through.

DR. IARIKOV: Okay.

DR. RUBIN: Thank you for that question, Dr. Baden. It's a difficult question, but in terms of teasing out the benefit over colistin as attributed to efficacy due to rather than a possible harm from colistin, I guess I would like to share some of the data we used for the non-inferiority margin justification. Here are mortality rates for patients treated with colistin-based therapy or in combination with carbapenems.

Is it possible to go to backup slide 10? And here are mortality rates for patients treated with inappropriate therapy or delayed treatment, and the non-inferiority margin was basically a

comparison of mortality between colistin-based regimens and delayed or inadequate therapy. And based on that analysis, we thought that there would be a fairly dramatic impact of colistin over not giving anything or giving inappropriate therapy. So we did think that colistin had some benefit over the absence of therapy.

That being said, it still is kind of difficult to tease out your question. I think mortality encompasses both efficacy and safety, and it's obviously very important, and was one reason why it was chosen for the primary efficacy endpoint, but I'm not sure if we can say more than that. I don't know if my colleagues have anything to add. Thanks.

DR. IARIKOV: We don't have anything to add to Dr. Rubin's response. Thank you.

DR. BADEN: Dr. Rubin, thank you. That was incredibly helpful because it's an impossible question. Just like creating the non-inferiority margin is based on characteristics that you just discussed, which are imperfect, but it's the best

we can do, so thank you for sharing the thought process.

Dr. Sidberry?

DR. SIDBERRY: Thanks very much. This is a focus question for both. I noted that preclinical studies and repro-tox studies were described as reassuring, so I just want a confirmation from the applicant that they didn't see any reason to withhold this drug from a pregnant person who was in need of it like a non-pregnant person would be, and that the agency didn't see any reason that we needed to consider language discouraging use in pregnancy if criteria was otherwise met. Thanks.

DR. REGE: Sure. I would like Mr. John O'Donnell to discuss the nonclinical data.

MR. O'DONNELL: John O'Donnell, Entasis Therapeutics. We did indeed do a full battery of reproduction toxicology studies and developmental toxicology studies, and found no findings, and this is up to a limit dose of 1,000 mg per kg in all of these studies. We currently are in the middle of doing our juvenile toxicology studies in suckling

pups and rats, so we're doing this in preparation for our pediatric development for the program. But based upon the nonclinical safety data set, we see no issues with regard to reproductive toxicology. Thank you.

DR. IARIKOV: I'd like to invite Dr. McMaster, a pharmacology-toxicology reviewer for this NDA.

DR. McMASTER: Good afternoon. I would like to note that we have looked at the data, and we're going to add to the label some descriptions of delayed ossifications that we saw in some of the rat studies. These are developmental delays and malformations, but we will add that to the label. Thanks.

DR. SIBERRY: Thanks for that. And just to clarify before you go, will that be enough to discourage use where otherwise deemed needed in pregnancy?

DR. IARIKOV: We wouldn't comment on the ongoing labeling language. It continues to be under review, but we definitely will look at all

these issues. Thank you.

DR. SIBERRY: Thanks very much. Thank you, Chair.

DR. BADEN: Just to amplify Dr. Siberry's point, and I don't want to discuss anything about the labeling, but data such as that, that may influence the labeling, would be important to get in the public domain so that thoughtful people have a chance to understand the strength of the evidence and the imperfections in the evidence as they try to make tough clinical decisions in managing patients with very difficult infections.

So thank you for sharing that, and look forward to as much data being in the public square as possible when complete.

Dr. Green?

DR. GREEN: Thank you, Dr. Baden. This is actually a follow-up to your previous question which you asked of both the sponsor, but more recently of the agency. And to the agency, I wonder if we are able to get at some of Dr. Baden's query about benefit of SUL-DUR as opposed to

avoidance of colistin by looking at the Part B data, where the 28-day mortality endpoint was essentially the same and no one got colistin. So they seemed to mass up SUL-DUR in Part B and Part A.

Does that really help us to understand that it is efficacy from the drug rather than avoidance of toxicity from colistin or at least a substantial component?

DR. IARIKOV: Would you like the agency to respond or the applicant would take it?

DR. BADEN: Dr. Green --

DR. GREEN: No, I asked the question to the agency.

DR. BADEN: The agency. Okay, to the agency.

DR. IARIKOV: Oh, to the agency. Again, I'm inviting my statistical colleague, Dr. Rubin.

DR. RUBIN: Thank you for the question. It's an interesting analysis approach, but I would say that by and large in our analyses, we did not emphasize Part B just because there was no

randomized comparison. And in particular, there was no randomization between subjects in Part A and subjects in Part B, and due to the complexities of the patients and possible confounding, we thought that it would be difficult to interpret those types of comparisons. Thank you.

DR. BADEN: Thank you.

I have one last targeted question and last call to my panel members, so please raise your hand to clarify information.

My targeted question to either the applicant or agency -- and it's something that Dr. Swaminathan mentioned earlier -- has to do with penetration two key sanctuary sites, the CNS, the prostate. Are there data that can help us understand how this penetrates certain sanctuary sites so that we can understand the potential use if infection occurs in those spaces? And obviously, sulbactam, there's a much bigger experience, but for the newer agent.

To the applicant, you're on mute.

DR. REGE: Can you hear us now?

DR. BADEN: Yes.

DR. REGE: I would like to call on Mr. John O'Donnell to answer your question.

MR. O'DONNELL: John O'Donnell, Entasis Therapeutics. The evidence we provided is mainly in our nonclinical data sets. As you know, with the lung model, we've utilized our neutropenic model in mice looking at pneumonia. We've also looked at the neutropenic thigh model as more of an indicator in terms of distribution for other sites of infections, particularly soft tissue skin structure and other potential sites of infection. So we believe these models are pretty robust. They've been used throughout the history of anti-infectives, quite frankly.

We are looking to understand drug concentrations at these sites. We have looked at ELF concentrations both in mice and humans in ELF, and we also look at concentrations in the urine. So in terms of distribution and potential use for other indications, we feel we're gathering more and more data to understand the actual drug

concentrations at these types of infections, but we have a pretty good understanding from the main models that we have, in neutropenic thigh and lung, as far as adequate distribution of both sulbactam and durlobactam into tissues, and potentially for other sites for indications. Thank you.

DR. BADEN: Thank you.

If this is to move forward, I would encourage the applicant to generate the analogous human data when possible for sanctuary sites, but one can only generate those data when the opportunity arises, but that kind of information will be useful as we think about potential use in complex infection.

DR. REGE: Thank you.

DR. BADEN: Any other questions from panel members?

(No response.)

DR. BADEN: Seeing none, then we'll now proceed with the charge to the committee from Dr. Peter Kim.

Dr. Kim?

Charge to the Committee - Peter Kim

DR. KIM: Good afternoon. My name is Peter Kim. I'm the director of the Division of Anti-Infectives in the Office of Infectious Diseases at CDER, FDA, and I will be providing the charge to the committee, but first some considerations to frame the question, so some key considerations.

As you have heard this morning and during our discussions this afternoon, this is a streamlined development program targeting a high unmet need pathogen. Part A of the phase 3 trial demonstrated that sulbactam-durlobactam was non-inferior to colistin for 28-day all-cause mortality in the CRABC m-MITT primary analysis population that mainly consisted of HABP/VABP patients. The safety profile of sulbactam-durlobactam appears to be generally consistent with other beta-lactam/beta-lactamase inhibitor drugs; however, the safety data set is limited to less than 200 patients who received sulbactam-durlobactam at the proposed dose and duration.

And now the question for the committee, please vote yes or no to the following. Is the overall benefit-risk assessment favorable for the use of sulbactam-durlobactam for the treatment of patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex organisms? If yes, please provide your rationale. If no, please provide your rationale and describe what additional studies or trials are needed. Thank you.

Dr. Baden, I'll now turn it back over to you.

Questions to the Committee and Discussion

DR. BADEN: Thank you, Dr. Kim.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We'll now proceed with the question to the committee and panel discussion. I'd like to remind public observers that while this meeting is open for public observations, public

attendees may not participate, except at the specific request of the panel.

Dr. Stevenson will provide the instructions for the voting.

DR. STEVENSON: Thank you, Dr. Baden.

This is Takyiah Stevenson, DFO. We have one question, which is a voting question. Voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote.

After the chairperson has read the voting question into the record and all questions and discussions regarding the wording of the vote question are complete, we will announce that the voting will begin. A voting window will appear where you can submit your vote. There will be no discussion during the voting session. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. Please note that once you click the submit button, you will not be able to

change your vote.

Once all voting members have selected their vote, I will announce that the vote is closed. Please note there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room. 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 a list, and each voting member will state their name and their vote into the record. You should also address any subparts of the voting question which includes the rationale for your vote.

Are there any questions about the voting process before we begin?

(No process.)

DR. STEVENSON: Since there are no questions, I will hand it back to Dr. Baden, and we can begin.

DR. BADEN: Okay. The voting question reads as follows. Is the overall benefit-risk assessment favorable for the use of sulbactam-durlobactam for

the treatment of patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii* complex organisms? If yes, please provide your rationale. If no, please provide your rationale and describe what additional studies are needed.

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.

DR. STEVENSON: We will now move non-voting participants to the breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

DR. BADEN: Thank you. We'll now go down the list --

DR. STEVENSON: I'm sorry, Dr. Baden. One

moment.

DR. BADEN: Please.

DR. STEVENSON: There are 12 yeses, zero noes, and zero abstentions.

I'm handing it back to you, Dr. Baden. Thank you.

DR. BADEN: Thank you.

We'll now go down the list and have everyone who voted state their name and vote into the record. You should address the subparts of the voting question, including your rationale if you voted no -- which did not happen -- but if you voted yes, you can still add what additional data would be highest priority to generate.

We'll start with the first person on the list. Dr. Green?

DR. GREEN: Yes. Thank you, Dr. Baden. This is Michael Green. I voted yes, and this decision was really driven by the clear clinical need for an effective treatment for an organism that's often extremely drug resistant, if not pan resistant. I think there is no real doubt that

at least in comparison with colistin-based therapy, but in combination with imipenem-cilastatin, in a population with either either hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia, that outcomes were improved, particularly 28-day mortality.

Clearly, there are concerns with the relatively small size of the study population, which impacts our ability to fully understand the safety profile and signal, but I agree that it seems beta-lactam-based analysis is appropriate, but I hope that the company would be mandated to continue to capture safety data going forward, even if it gets approval for this indication.

I also think there's a great need to enforce surveillance for development of resistance, and if and when it occurs, to try to understand it, and also how easily it might be spread. As was mentioned by one of the speakers -- I think actually from the public comment -- I think clearly this is an important target for antimicrobial stewardship, particularly to protect the durability

of this very needed agent, and I even wonder if the FDA might discuss, as they're thinking about labeling, whether at some point we should be encouraging stewardship type language into our labels as a novel strategy to help support stewardship.

I do have a concern regarding the microbiologic cure, particularly when they include those that had no test as a cure. Many patients that have endotracheal tube or tracheostomy in play will get better critically but still have the organism present, which would represent an ongoing reservoir for recurrent infection in that patient or spread to others, especially if it becomes resistant. And I would hope that in the labeling language that that language and illusions towards efficacy, based on microbiologic data, be limited to those where they have evidence, and not those where absence of test is assumed to be a positive result just because the patient did fine.

Then my last point would be to support the comment made by Dr. Sidberry, to think about

approval based on weight rather than age, given that there are teenagers and actually younger children who also can have pan-resistant infection with this organism and who would need to have benefit, and could use that approval, encouraging them to give it to them as well, as soon as possible. Thank you very much.

DR. BADEN: Thank you.

Dr. Murphy?

DR. MURPHY: I see a global unmet need for drugs with action against highly resistant *Acinetobacter*. The efficacy and safety data are reassuring. I was concerned that the number of patients studied was small, but this is a difficult disease process to study, and it's very unlikely that the efficacy is lower than colistin, a drug that's clearly less safe.

Since it was proven efficacious only as combination therapy, it should not be used as monotherapy in most situations, as we really have no idea how it would perform as monotherapy, and the FDA should consider this in the labeling. In

real life, in actuality, it'll be used with a variety of companion drugs, and we need to track safety in patients receiving various combination therapies that include sulbactam-durlobactam. Thank you.

DR. BADEN: Thank you.

Dr. Hardy?

DR. HARDY: Hi. This is Dr. Hardy from Los Angeles. I voted yes, and just --

DR. BADEN: We're not able to hear you. Your connection --

DR. HARDY: -- have already said about this drug being used in combination with [inaudible].

DR. BADEN: Dr. Hardy, it may be best if you turn off your video. We're not able to hear you.

DR. HARDY: -- at least one other broad-spectrum antibiotic. Mechanisms have been also covered very well. I was a bit concerned, as I mentioned during the discussion, that it was so difficult to find patients for this trial in the U.S., where, at least in my experience, this has been a major problem in intensive care units for

many years. But I think it does certainly address a very great unmet need, and it's good to see that this kind of drug is being developed, and that's the reason I voted yes. But continued safety monitoring will need to be done as the FDA normally does, but particularly because of the small number of patients involved in this trial, and most of them being outside the U.S., where standards of care oftentimes are different than what happens in the U.S., the FDA still has an important job to do with this medication. That's it.

DR. BADEN: Thank you.

DR. HARDY: Thank you.

DR. BADEN: Dr. Block?

DR. BLOCK: Hi. Yes, because without this agent, the alternative for a significant portion of patients could be death. But I would add additional active surveillance, the point being that in an adverse event, a surveillance program similar to V-Safe that we did with COVID, which we needed to roll out before we tested it as much as we wanted to -- I still remember when Trovan was

launched, trovafloxacin, and we had over 5,000 patient exposures at the time of approval. It was the largest trial of its time, and we were all surprised as heck when we started seeing liver failure with its use post-approval. But with ongoing active surveillance like we had with V-Safe, we're all making well-informed decisions with very up-to-date data that's available to us. Thank you.

DR. BADEN: Thank you.

Dr. Patel?

DR. PATEL: Good afternoon. I think the applicant did a really good job presenting their data. The data looked very strong for *Acinetobacter.* I think some of the things that the applicant should consider in their phase 4 plan is looking at other infection types. It's very clear, based on the OPH testimony, that there are other infection types where the drug could potentially be useful and also trying to figure out whether there's a way to hit that PTA without giving a 3-hour infusion, whether it be a load or something

else.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: George Siberry, USAID. I voted yes for many of the same reasons expressed. If you look at these mortality rates from the study, it reminds you how starkly high the risk of death is in patients who get these infections, and that's the reason for this expedited, my vote, yes. In this limited data set, I think that they met the criteria well enough. I didn't see any major problems to suggest that it was at least as efficacious as colistin, and it's certainly much friendlier to kidneys to use than that.

I do think that there should be some enhanced surveillance because we have such a limited data set in terms of safety, at least for the durlobactam component, and I'd like to make sure that we don't have any barriers to use in pregnancy but that we also collect safety and PK information in pregnant people of this drug as we go forward. Thanks very much.

DR. BADEN: Thank you.

Dr. Perez?

DR. PEREZ: Yes. Thank you. Federico Perez from Cleveland. I voted yes, and I claim [indiscernible] all the comments from before because this is an organism of critical importance in terms of public health and because of the incredible difference that the availability of this compound will make for the individual patients who have to suffer infection by *Acinetobacter baumanni* complex in a landscape where therapeutic options are extremely limited. The trial itself demonstrates the shortcomings of colistin in terms of its limited efficacy and nephrotoxicity.

Adding to what has been said, I would also say that durlobactam is a [indiscernible], meaning that it's a beta-lactam [indiscernible], and we collectively have accumulated experience with this drug, negative infections, and have learned about the mutations but also the benefits on overall safety. And notwithstanding this, there clearly are many areas where questions remain.

To what has been said about safety, I would emphasize the challenge of managing the co-pathogens in these typically polymicrobial infections and the intricacies of the different combinations that become possible. They have to be sorted out both in terms of safety, but also efficacy. In this aspect, I would be very interested in seeing what durlobactam adds to other beta-lactams in terms of activity against organisms like *Pseudomonas aeruginosa* as part as pan resistant and [indiscernible]. Thank you very much.

DR. BADEN: Thank you.

Dr Hunsberger?

DR. HUNSBERGER: This is Sally Hunsberger. I voted yes. The study clearly met the primary endpoint, and the secondary endpoints were all very consistent, so I think that was really crucial. One thing I think would be very important would be to do some logistic regression analyses so that you could understand the treatment benefit while controlling for other covariates. That could also

help with potentially using this treatment for younger children. But everything else people have said, I totally agree with, so I don't have anything more to add.

DR. BADEN: Thank you.

Dr. Baden Lindsey Baden. I voted yes. Several key observations, it's a very small data set, which is probably why the committee was called together and has made all of us a little uncomfortable; however, this is a tremendous unmet need. It's an impressive mortality benefit. It does have some unique attributes, this agent, in terms of its spectrum of activity, which is advantageous and concerning at the same time, so we have to better understand how best to use it for treating polymicrobial infection with polymicrobial pharmacy.

The safety database is very thin, as has been mentioned, and real-world data will need to be collected to augment our understanding of safety. Lots more data are needed: other sites of infection; other comorbid conditions; other organ

insufficiency; other polypharmacy; other populations. So we need to know much more; however, it did demonstrate important efficacy in a target population that is an unmet need, so I voted yes. Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. Sankar Swaminathan here. I voted yes. This is a disease with very high morbidity and mortality, and the current available treatment, as has been pointed out, has significant toxicity and other issues. The possibility of uncommon side-effects is, I think, not ruled out by the limited study set that we have available, so postmarketing surveillance will be essential to identify these and to understand what the risk factors for those are, as well as drug-drug interactions, given the number of drugs that these patients are likely to be on, not just antibiotics.

But I also think that this type of data really is not going to be obtained in perspective randomized trials, given that there won't be a

placebo-controlled trial, and some of the things we're looking for in a fairly uncommon disease, at least in the U.S., will only become apparent after some significant use in the community. But I also think there's a possibility that it will have potential utility in collecting data on CNS penetration and its efficacy in CNS infections, which occur. And where colistin has very poor CNS penetration, it opens the door, at least, to possible treatments of CNS infections, so that's why I voted yes.

DR. BADEN: Thank you.

Dr. Hilton?

DR. HILTON: Joan Hilton. I voted yes because I was very impressed by the 19 percent versus 33 percent mortality rates, combined with the relatively good safety data. I did have some concerns. There are about 30 percent of randomized subjects who were not included in the primary analysis, and I think that an alternative might have been to use the post-randomization confirmation of the disease as a baseline covariate

and do a formal ITT analysis instead. But that said, the loss of a 30 percent really bothered me, but I was really glad that both the sponsor and the FDA also did ITT analyses of the primary endpoint, and they hardly changed at all, so that was quite convincing to me.

The last thing that I'm concerned about is I think that rather than using a 28-day mortality endpoint, a survival time to event outcome would have been much more powerful and informative, and also might pick up the trends that we saw in the declining efficacy of the secondary variables during the study period. That's it. Thank you.

DR. BADEN: Thank you.

Dr. Walker?

DR. WALKER: Hi. Dr. Roblena Walker, and I echo the sentiments of all of my colleagues. I voted yes due to the great clinical need for the resistance of this particular pathogen that has aided in decreased mortality rates, specifically among patients who are presented in such cases. I do agree that ongoing safety surveillance is

needed, but overall, I believe the applicant presented the data. And to the individuals who provided public feedback, I think that was well received as well. Thank you.

DR. BADEN: Thank you.

So I'd like to summarize the comments. Twelve panel members, all 12 voted yes. The benefit-risk assessment is favorable. Several elements went into the summative discussion. Tremendous unmet need and impressive mortality benefit has led to a strong view that this agent has a place in treatment; however, there is much more we need to know. A very small sample size, so the safety database needs to be expanded; perhaps a V-Save for some other mechanism that the agency can leverage to better collect more data, the agency and the applicant, because it's in all of our interests to collect the additional data to understand how best to use this medication.

The issue of emergent resistance needs to be monitored as well. Some aspects of the data presented could benefit from some reflection,

including the microbiologic endpoints and how to assess the test of cure. Some of the analytic issues raised by our statistical colleagues, in terms of other analyses that can help us better understand the data from a formal ITT, to risk factor, to logistic regression, time to event.

I don't think any of these in what we've seen changes the primary finding, but allows greater insight into what we learn. We need to, as this gets rolled out, if it gets rolled out, understand how this agent behaves in the U.S. hospital environment and how it is used in combination antimicrobial therapy, with other agents besides imipenem.

Practical issues need to be weighed such as how it's delivered, and if it's delivered 3 out of 4 hours in certain patients, do we need to think through certain delivery features to make sure that how we deliver it makes sense to patient care and patient flow. Additional data on sites of infection, penetration, and raised by some of the members, how this beta-lactamase interacts with

other organisms that have a beta-lactamase, is worth better understanding. But overall, the risk-benefit ratio was seen as favorable.

I will open it to any other panel members if I missed any core concepts in the summation for the agency.

(No response.)

DR. BADEN: If not, then I would like to, before we adjourn, make a few comments, and then ask the agency to make a few closing comments.

I would like to thank both the agency, and the applicant, and the open public hearing speakers for sharing a tremendous amount of data and real-world wisdom about this infection and the unmet need. The committee valued all of the shared information and greatly appreciated the tremendous amount of information shared in such an easy-to-understand manner, so thank you.

Now let me ask the FDA if you have any final comments.

DR. SHERWAT: It's Adam Sherwat. I wanted to also thank you very much and the committee for

all of the help today. We greatly appreciate your time and the effort at the AC, and your input will be strongly considered in our deliberations, and thank you again.

Adjournment

DR. BADEN: Thank you.

So then I will now adjourn the meeting. Thank you all.

(Whereupon, at 2:52 p.m., the meeting was adjourned.)