FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Wednesday, August 8, 2018

8:30 a.m. to 1:31 p.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

**Meeting Roster**

**DESIGNATED FEDERAL OFFICER (Non-Voting)**

**Lauren D. Tesh, PharmD, BCPS**

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Office of Executive Programs, CDER, FDA

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DAIP, OAP, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

**Call to Order**

**Introduction of Committee**

DR. BADEN: It's 8:30. We shall get started. Even though the agenda is not as full as prior, I think if we can stay on schedule, we'll all benefit, and I don't think anyone will be upset.

Good morning. I'd first like to remind everyone to please silence your cell phones and any other devices that you have not already done. I would also like to identify the FDA press contact, Theresa Eisenman. If you're present, please stand. She's always available even if we don't see her. My name is Dr. Lindsey Baden. I'm the chairperson of the Antimicrobial Drugs Advisory Committee and I'll be chairing this meeting. I'll now call this meeting to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA on my far left.

DR. FARLEY: Good morning. John Farley,

deputy director of the Office of Antimicrobial Products.

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

DR. TOERNER: Joe Toerner, deputy director for safety, Division of Anti-Infective Products, CDER, FDA.

DR. HENNESSY: Good morning. I'm Sean Hennessy talking into a loud microphone. I do pharmacoepidemiology research at the University of Pennsylvania.

DR. SWENSON: Erik Swenson in the Department of Medicine and the Division of Pulmonary Diseases at the University of Washington.

DR. EVANS: Scott Evans, pulmonary medicine at the University of Texas, MD Anderson Cancer Center.

DR. BRITTAIN: Hi. I'm Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases, NIH.

DR. SCHAENMAN: Joanna Schaenman, infectious

diseases, David Geffen School of Medicine at UCLA.

DR. DASKALAKIS: Demetre Daskalakis, infectious diseases, deputy commissioner for disease control at the New York City Department of Health.

DR. HONEGGER: Jonathan Honegger, pediatric infectious disease, Nationwide Children's Hospital, Ohio State University.

DR. TESH: Lauren Tesh, designated federal officer.

DR. BADEN: Lindsey Baden, infectious diseases, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School in Boston.

DR. WEINA: Peter Weina, infectious diseases, Walter Reed National Military Medical Center.

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

DR. GRIPSHOVER: Barbara Gripshover, adult infectious diseases from University Hospitals,

Cleveland Medical Center at Case Western Reserve University.

DR. LO RE: Vincent Lo Re, Division of Infectious Diseases, Department of Biostatistics, epidemiology informatics at the University of Pennsylvania.

DR. OFOTOKUN: Igho Ofotokun, infectious diseases, Emory University, Atlanta.

MS. D'AGOSTINO: Emma D'Agostino. I'm the consumer rep, and I'm in the Department of Biochemistry at Emory.

MS. NELKIN: Tina Nelkin, patient representative.

DR. CALHOUN: Good morning. I'm Bill Calhoun, professor and vice chair of medicine at the University of Texas Medical Branch in Galveston, Texas, pulmonologist and allergist by training.

DR. FLOYD: James Floyd, general internal medicine and epidemiology at the University of Washington.

DR. PROSCHAN: I'm Michael Proschan. I'm a

statistician at the National Institute of Allergy and Infectious Diseases.

DR. S. GREEN: Good morning. I'm Stuart Green. I'm the acting industry representative at today's meeting.

DR. BADEN: Thank you. Dr. Proschan, your mic is still on -- or, sorry, Dr. Calhoun. My depth perception needs some help.

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

We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in

the open forum of the meeting.

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

I'll pass it to Dr. Lauren Tesh, who will read the conflict of interest statement.

**Conflict of Interest Statement**

DR. TESH: The Food and Drug Administration is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

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

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

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential

financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and their primary employment.

Today's agenda involves discussion of new drug application 209816 for omadacycline tablets, and 209817 for omadacycline injection, sponsored by Paratek Pharmaceuticals, Inc. for the proposed indications for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections.

This is a particular matters meeting during which specific matters related to Paratek Pharmaceuticals' new drug applications 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 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. Stuart Green is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Green's role at this meeting is to represent industry in general and not any particular company. Dr. Green is employed by Merck and Co.

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

FDA encourages all other participants to

advise the committee of any financial relationships they may have with the firm at issue. Thank you.

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

**FDA Opening Remarks**

DR. NAMBIAR: Thank you, Dr. Baden.

Good morning, everybody, and welcome to today's meeting of the Antimicrobial Drugs Advisory Committee. We're here to discuss NDA's 209816, 209817, omadacycline injection and tablets.

The applicant for these new drug applications is Paratek Pharmaceuticals. The product has qualified infectious disease product designation for three indications: community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, and uncomplicated urinary tract infection. These NDAs were granted priority review as the product has QIDB designation.

The two proposed indications are as follows, CABP caused by the following: gram-positive, gram-negative, and atypical microorganisms --

won't go through the list of organisms -- and ABSSSI caused by the following gram-positive and gram-negative microorganisms.

The proposed dose includes a loading dose and a maintenance dose with the option of either intravenous or overloading and maintenance intravenous or oral as well. The proposed duration of therapy is 7 to 14 days.

In addition to phase 1 trials, the development program included two phase 3 trials in adults with acute bacterial skin and skin structure infections, study ABSI 1108, and study ABSI 16301. One phase 3 trial was conducted in adults with CABP 1200, a legacy phase 2 study and a truncated phase 3 trial in patients with complicated skin and skin structure infections, which was the name of the indication previously, which currently we refer to as ABSSSI.

The studies ABSI 1108 and CABP 1200 allowed for switch from intravenous to oral omadacycline, while ABSI 16301 evaluated oral omadacycline only.

The phase 3 ABSSSI trials were randomized,

double-blind, noninferiority trials where omadacycline was compared to linezolid. The design of the trial was generally consistent with the FDA ABSSSI guidance. After a minimum of 3 days of blinded IV therapy, there's an option to switch to oral therapy in one of the studies.

The primary analysis population was modified intent-to-treat and the primary endpoint was early clinical response, defined as patient being alive and having a 20 percent or greater reduction in lesion size 48 to 72 hours after therapy was initiated. The prespecified noninferiority margin was 10 percent.

In both trials, omadacycline was noninferior to linezolid for the primary endpoint and the prespecified NI margin was met. Consistent results were seen for the key secondary endpoint, which was clinical response at a post-treatment evaluation 7 to 14 days after treatment was completed. Consistent results were also seen in subgroups of interest.

The phase 3 CABP trial was a randomized,

double-blind, NI trial where omadacycline was compared to moxifloxacin. The design of the trial was, in general, consistent with the FDA CABP guidance. After a minimum of 3 days of blinded IV therapy, there was an option to switch to oral therapy. The primary analysis population was the intent-to-treat population.

The primary endpoint was early clinical response assessed 72 to 120 hours after treatment was initiated. And this assessment was based on improvement in symptoms of pneumonia, such as cough, sputum production, pleuritic chest pain, and dyspnea. The prespecified NI margin was 10 percent.

In this trial, omadacycline was noninferior to moxifloxacin. The clinical success rates in the omadacycline, 81 percent compared to 82.7 percent in moxifloxacin, a treatment difference of 1.6 and the lower bound of the confidence interval of minus 7.1.

Key secondary endpoint assessed was the investigator assessment at a post-treatment

evaluation 5 to 10 days after completion of treatment. Clinical success rates were similar between the two treatment arms.

Thirty-day, all-cause mortality was higher in the omadacycline arm. There were 8 deaths, 2.1 percent compared to the moxifloxacin arm. There were 3 deaths, 0.8 percent. Subgroup analyses showed that response rates were numerically lower in some subgroups of interest, for example patients over 65 years of age and those with PORT class IV.

In terms of the safety assessment, there were no significant differences in adverse events between the treatment groups. With oral omadacycline, there was a higher incidence of nausea and vomiting.

Infusion site reactions, primarily extravasation, was reported with IV omadacycline in one of the skin trials. And as I've noted, there was an imbalance in the 30-day all-cause mortality in the CABP trial.

So as Dr. Baden mentioned, today's an

abbreviated day compared to our regular advisory committee meeting, so we will have presentations by the applicant followed by time for clarifying questions. We have one presentation by the FDA, by Dr. Toerner, who's the deputy director for safety in the division and also the cross-discipline team leader for this application. Dr. Toerner will cover both the efficacy and safety presentation.

There will be time for clarifying questions. After the open public hearing, we will have questions for the committee.

We have two voting questions for the committee. We are seeking your input on the following. Has the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of acute bacterial skin and skin structure infections?

If you voted yes, please provide any recommendations for labeling, and if you voted no, please discuss additional studies or analyses that are needed.

The second question is if the applicant has

provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of community-acquired bacterial pneumonia. If you voted yes, please provide any recommendations for labeling, and if you voted no, please discuss additional studies or analyses that are needed. Thank you.

DR. BADEN: Thank you, Dr. Nambiar.

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

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

you at the beginning of your presentation to advise the committee if you do not have 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 Paratek Pharmaceuticals' presentations.

**Applicant Presentation - Evan Loh**

DR. LOH: Good morning, Mr. Chairman, members of the advisory committee, and members of the FDA. Antibiotic resistance is a global problem of tremendous importance to all of us. New antibiotics with clinically important efficacy and safety advantages blended with other important attributes are needed in order to ensure that physicians have therapeutic options that can cure infections and save lives.

I'm Evan Loh, chief medical officer of Paratek. We are pleased to have the opportunity to work with you today to bring to patients a new

antibiotic treatment option, omadacycline, for community-acquired bacterial pneumonia, CABP, as well as acute bacterial skin and skin structure infection, ABSSSI.

Omadacycline, an aminomethycycline, is a next-generation tetracycline. Omadacycline's chemical structure is designed to restore tetracycline efficacy by circumventing the bacterial resistance that limits the clinical efficacy of older-generation tetracyclines.

The specific omadacycline structural modifications at the 7 and at the 9 position circumvent the two most common and clinically relevant tetracycline-specific mechanisms of bacterial resistance, efflux and ribosomal protection.

Omadacycline's key pharmacokinetic properties include an elimination half-life between 14 to 16 hours, which supports once-daily dosing; oral bioavailability of approximately 35 percent with equivalent once-daily IV and oral exposures; and no dose adjustments for age, gender, renal, or

hepatic impairment.

Drug-drug interaction potential is low, an important attribute for the elderly population who often present with polypharmacy for multiple comorbidities; a steady-state plasma AUC exposure between 11 and 12 microgram hours per mL that provides an AUC-to-MIC ratio above the target MICs for relevant skin and pneumonia pathogens; low protein binding of approximately 20 percent that is not concentration dependent.

This translates into higher free drug concentrations, facilitating tissue penetration. Omadacycline penetrates into human lung epithelial lining fluid at concentrations approximately 50 percent greater than in plasma.

Omadacycline is potent against relevant pathogens for the indications of focus today. The in vitro activity of omadacycline against common ABSSSI and CABP pathogens, including resistant strains, is shown here from surveillance studies in approximately 123,000 isolates.

A total of 27 phase 1 to phase 3 studies are

included in the current NDA, enrolling more than 3300 patients and healthy volunteer subjects. Of those, a total of 1,947 patients were exposed to omadacycline, of which nearly 1100 were exposed in the pivotal phase 3 program.

The dose rationale for omadacycline is based on PK/PD data. The PK/PD index associated with the efficacy of tetracyclines is the AUC-to-MIC ratio. The magnitude of the AUC-to-MIC ratio associated with omadacycline efficacy was identified using in vitro and in vivo infection models with relevant skin and pneumonia pathogens. Monte Carlo simulations support proposed omadacycline dosing regimens for patients with CABP and ABSSSI.

Results of these analyses demonstrated percent probabilities of PK/PD target attainment that exceeded 90 percent at the upper margins of the MIC distributions for clinically important skin and pneumonia pathogens, including Streptococcus pneumoniae, Haemophilus influenzae, as well as Staphylococcus aureus.

High percent probabilities of PK/PD target

attainment were consistent with the high omadacycline efficacy rates demonstrated in the phase 3 CABP and skin trials.

The loading dose and maintenance regimens for the OPTIC, OASIS I, and OASIS II trials are summarized here. Dr. Anita Das will discuss them in more detail during the efficacy review.

Following this introduction, Dr. Keith Kaye will describe the important unmet needs for new antibiotics in ABSSSI and CABP. Dr. Anita Das will show that all three pivotal studies demonstrated noninferiority efficacy to the comparators, linezolid for ABSSSI and moxifloxacin for CABP.

I will show that omadacycline is safe and well tolerated. Dr. Eric Mortensen, an expert in pneumonia and pneumonia-related mortality will show that the benefit-risk assessment is favorable for both indications. Evan Tzanis, chief development officer at Paratek, will moderate the question-and-answer session. All of the external speakers have been compensated for their time and travel. None have a financial interest in Paratek nor in the

outcome of this meeting.

Now, here's Dr. Kaye to address unmet need. Dr. Kaye?

**Applicant Presentation - Keith Kaye**

DR. KAYE: Good morning. I am Dr. Keith Kaye, the director of research in the Division of Infectious Diseases at University of Michigan Medical Center. I'm actively involved in clinical care, antibiotic research, and stewardship.

In my infectious diseases practice, I am often faced with patients who may be infected with drug-resistant pathogens and patients who present with comorbidities or allergies, which make choosing the right antibiotic complicated.

Antimicrobials are losing their effectiveness due to increasing antimicrobial resistance and dissemination of resistant pathogens. Thus, discovery of new agents to fight antimicrobial-resistant infections is a priority focus of FDA. Antibiotic resistance to frequently-used antibiotics occurs naturally over time, sometimes necessitating use of older antimicrobials

that may be associated with safety and tolerability limitations.

According to the Centers for Disease Control, every year, 2 million patients acquire serious infections with resistant bacteria, and 23,000 people die as a direct result of these infections. Novel antibiotics with good safety profiles are needed to address these emerging resistance challenges.

The incidence of skin infections requiring hospitalization has increased almost 900,000 hospital admissions annually, which has coincided with the emergence of community-acquired MRSA. MRSA is often resistant to multiple classes of antibiotics and is on the World Health Organization priority pathogen list for new antibiotics.

Antimicrobial resistance is associated with ineffective empiric therapy and results in delayed implementation of effective antibiotic treatment. These delays can result in treatment failure, increased length of stay, increased duration of treatment, and recurrent skin infections.

New agents with the appropriate spectrum to treat MRSA skin infection have been developed, most of which are available only in intravenous formulations. The only recent oral agents developed to treat MRSA are oxazolidinones and delafloxacin, both of which are associated with safety concerns, including drug-drug interactions, C. difficile risk, and toxicity limitations. Additional oral options are needed.

Another common infectious disease that has been impacted by antibiotic resistance is community-acquired pneumonia or CAP. CAP is the most common infectious disease leading to hospitalization and mortality among all age groups and, together with influenza, is the eighth leading cause of death in the United States.

The all-cause 30-day mortality in hospitalized patients exceeds 10 percent, with higher rates of mortality in subpopulations such as the elderly and those with severe pneumonia. Hospitalization rates of pneumonia are increased in older populations and in populations with certain

comorbid conditions, including COPD, heart failure, and diabetes.

The most common bacterial pathogen is Streptococcus pneumoniae, which due to increasing antimicrobial resistance is classified by the Centers for Disease Control as a serious threat. Increased rates of antimicrobial resistance in Streptococcus pneumoniae have been observed in beta-lactams, macrolides, and older-generation tetracyclines.

In addition, although MRSA is an infrequent cause of pneumonia, it has been associated with severe disease and requires consideration when choosing empiric therapy.

High rates of resistance among pneumonia pathogens are associated with ineffective empiric therapy, resulting in an increased risk for treatment failure, mortality, and prolonged duration of hospitalization. Current treatment is largely empiric and guidelines recommend coverage for typical and atypical pathogens. Guidelines recommend beta-lactams, fluoroquinolones, and

macrolides, but these classes have known allergy safety and resistance limitations.

Beta-lactam allergy limits the use of first-line ceftriaxone treatment while the fluoroquinolones have a boxed warning and several safety concerns, including tendonitis, tendon rupture, and neurologic toxicities.

In addition, FDA recently strengthened warnings regarding mental health side effects and serious blood sugar disturbances. Fluoroquinolones and cephalosporins are also associated with an increased risk for C. difficile infection, which in patients with pneumonia is associated with increased 30-day and 1-year mortality. Thus, clinicians are in need of new oral agents for pneumonia to address limitations of current treatment options.

To summarize, antibiotic resistance is a constant and growing concern and has been recognized by the World Health Organization as one of the biggest threats to global health. Skin infection and pneumonia are serious diseases which

often involve resistant pathogens and frequently occur in older populations with underlying comorbid conditions.

In the current environment of increasing antimicrobial resistance and complex patient populations, there is an urgent need for new antibiotics that will provide clinicians with safe and effective therapeutic options that are active against resistant pathogens.

Ideally, these therapies would be available in both intravenous and oral formulations, which would facilitate transitioning patients from the hospital.

Thank you. I will now turn things over to Dr. Das, who will discuss efficacy.

**Applicant Presentation - Anita Das**

DR. DAS: Thank you, Dr. Kaye.

My name is Anita Das, and I'm the statistician for the phase 3 omadacycline program. I've been involved with the development of antibiotics for over 10 years, including working with the Foundation of the National Institutes of

Health on development of endpoints in ABSSSI and CABP. I will present the efficacy results showing that omadacycline was noninferior to the comparator in all three phase 3 studies.

The two phase 3 studies, ABSSSI, are OASIS-1 or 1108, which was an IV-to-oral study, and OASIS-2 or 16301, which was an oral-only study. Both studies have similar designs. They were randomized, comparator controlled, double dummy, blinded, noninferiority studies utilizing a 10 percent noninferiority margin, consistent with the FDA guidance.

In OASIS-1, patients received a minimum of 3 days of IV therapy and could be switched to oral if prespecified criteria were met for a total of 7 to 14 days of treatment. In OASIS-2, patients received all oral therapy for a total of 7 to 14 days of treatment.

Consistent with the FDA guidance, the primary efficacy endpoint was early clinical response at 48 to 72 hours post first dose in the modified intent-to-treat population. To be

considered an early clinical success, patients must have been alive and had at least a 20 percent reduction in lesion area without receiving rescue anti-bacterials.

The secondary endpoints were investigator's assessment of clinical response at a post-treatment evaluation occurring 7 to 14 days after the last day of treatment in the modified ITT and clinically evaluable or per-protocol populations. A clinical success of PTE was defined as the patient was alive, and the investigator determined that the infection had sufficiently resolved such that no further anti-bacterial therapy was required.

For safety, patients were followed from time of consent to the final follow-up visit, which occurred between days 30 and 37. Both studies enrolled patients with a wound infection, cellulitis/erysipelas, or major abscess. The infection had to be at least 75 centimeters squared. Patients also had to have evidence of a systemic response to the infection.

For OASIS-1, patients could not have

received anti-bacterial treatment within the 72-hour period prior to the first dose of test article. However, for OASIS-2, a single dose of a short-acting anti-bacterial was allowed in up to 25 percent of patients. For both studies, patients could not have used a topical anti-bacterial agent continuously within the 72-hour period prior to the first dose of test article.

In both studies, treatment groups were well balanced with respect to demographics. The majority of patients were male and between 18 and 45 years of age. The median lesion area of about 300 centimeters squared was well above the minimum lesion area of 75 centimeters squared required for enrollment.

In OASIS-2, over 50 percent of patients had a wound infection and very few patients received a prior anti-bacterial. In both OASIS-1 and OASIS-2, omadacycline was found to be noninferior to linezolid in the modified ITT population. In both studies, outcome rates in the omadacycline group were high at 85 percent or greater.

The lower bound of the 95 percent confidence interval was minus 6.3 in OASIS-1 and minus 0.2 in OASIS-2, both of which were well within the margin of noninferiority of 10 percent.

Clinical success rates based on the investigator's assessment at the PTE visit in both the modified ITT and CE populations were high, similar between treatment groups, and consistent between studies.

In the pooled data, 84 percent of omadacycline and 80 percent of linezolid patients with a pathogen were an investigator-assessed clinical success at PTE. High clinical success rates at PTE were also observed for common ABSSSI pathogens, including MRSA, with clinical success rates of 84 percent for omadacycline and 82 percent for linezolid.

Several other subgroup analyses were conducted. Pooled data are shown on this slide with early clinical success shaded in gray and investigator's assessment of clinical success at PTE presented in the unshaded rows. Regardless of

infection type or lesion size, omadacycline and linezolid had high and similar response rates.

Data from OASIS-1 and OASIS-2 demonstrate that omadacycline meets the standard of substantial evidence of efficacy for the treatment of adults with ABSSSI. In both studies, omadacycline was noninferior to linezolid for the primary outcome of early clinical response.

In addition, the investigator-assessed clinical success rates were high and similar between treatment groups at the PTE visit and for each of the most common and clinically relevant ABSSSI pathogens, including MRSA. Efficacy is maintained for both early clinical response and investigator's assessment of clinical response at PTE in subgroups based on infection type and lesion size.

The community-acquired bacterial pneumonia study, OPTIC or 1200, was an IV-to-oral study in which robust efficacy was demonstrated. OPTIC was a randomized comparator-controlled, double-dummy, blinded, noninferiority study utilizing 10 percent

noninferiority margin as agreed to with the FDA. In this study, patients received a minimum of 3 days of IV therapy and could be switched to oral if prespecified criteria were met, for a total of 7 to 14 days of treatment.

As indicated in the FDA guidance, the primary efficacy endpoint was early clinical response at 72 to 120 hours post-first dose in the ITT population. An early clinical success was defined as the patient being alive with improvement in at least 2 of the 4 cardinal CABP symptoms, no worsening of any of the 4 symptoms and no receipt of a rescue anti-bacterial.

Improvement was considered a decrease by at least one category of severity, assessed as absent, mild, moderate, and severe, and worsening was considered an increase by at least one category of severity.

The secondary endpoints were the investigator's assessment of clinical response at the post-treatment evaluation, occurring 5 to 10 days after the last treatment day in the ITT and

CE or per-protocol populations. A clinical success at PTE was defined as the patient was alive, and the investigator determined that the signs and symptoms of CABP had resolved such that no new anti-bacterial therapy was required.

For safety, patients were followed from time of consent to the final follow-up visit, which occurred between days 30 and 37.

To be enrolled in the study, patients had to have radiographically confirmed pneumonia and a PORT risk class of II, III, or IV. The protocol limited enrollment of PORT II to no more than 15 percent of patients. Patients were required to have at least 3 days of IV treatment. In addition, patients were required to have at least 3 of the cardinal CABP symptoms, 2 abnormal vital signs, and at least 1 clinical sign or laboratory finding associated with CABP.

Patients were excluded from the study if they received more than 1 dose of a potentially effective systemic anti-bacterial within 72 hours of first dose with the exception that a single dose

of a short-acting anti-bacterial was allowed in no more than 25 percent of patients.

Additionally, patients known or suspected to have hospital-acquired or healthcare-associated pneumonia or evidence of septic shock were to be excluded.

Treatment groups were balanced with respect to demographics. The majority of patients were male with a mean age of approximately 61 years. Twenty percent of males in both treatment groups were greater than 75 years. Eighteen percent of patients had COPD or asthma and about 45 percent of patients were current or former smokers.

The study population represents patients with moderate to severe CABP who require hospitalization. The majority of patients had a PORT risk class of III, with 28 percent of patients with a PORT risk class of IV. About a quarter of patients presented with a multi-low-bar pneumonia, and bacteremia was present in approximately 4 percent of patients.

Omadacycline was found to be noninferior to

moxifloxacin for the primary endpoint of early clinical response. Outcome rates in both treatment groups were high at approximately 82 percent. The lower bound of the 95 percent confidence interval was minus 7.1, which was well within the protocol-specified margin of noninferiority of 10 percent.

Secondary endpoints of investigator's assessment of clinical success at the PTE visit in both the ITT and CE populations were high and similar between treatment groups. The consistency in success rates between the early time point and at the PTE visit demonstrated durable clinical response.

Fifty percent of patients had a CABP pathogen isolated from a respiratory or blood sample or detected by urinary antigen or serology. In this population, 89 percent of omadacycline and 87 percent of moxifloxacin patients were an investigator-assessed clinical success at PTE.

For the most common causative pathogens, including Streptococcus pneumoniae, Haemophilus influenzae, and the atypical pathogens, similar

clinical success rates at PTE between treatment groups were seen.

Efficacy was analyzed by subgroups, which categorized patients by risk of mortality. In both treatment groups, high clinical success rates by PORT risk class were seen for early clinical response and investigator's assessment of clinical response, including those patients with the highest risk of mortality, PORT risk class IV.

In patients 75 years or older, high and similar clinical success rates were observed between treatment groups for early clinical response and at PTE.

The modified ATS minor criteria and SMART-COP are used to classify patients by severity of CABP. For early clinical response, there is a numerical difference between omadacycline and moxifloxacin for patients with at least 3 of the ATS minor criteria. However, the clinical success rates are within the expected variability given the small sample size.

Early clinical success rates for patients

with at least 3 of the SMART-COP risk criteria were 80 percent for the omadacycline group and 82 percent for the moxifloxacin group. At PTE, investigator-assessed clinical success rates in both subgroups are high and similar between treatment groups, demonstrating that omadacycline has efficacy in more severe CABP patients.

To further explore the early efficacy of omadacycline and the mortality risk and severity subgroups, clinical failure due to receipt of a rescue anti-bacterial and stabilization of vital signs were examined. In all subgroups, very few patients in the omadacycline and moxifloxacin groups received a rescue anti-bacterial.

In addition, the rates of stabilization of vital signs at the ECR time point were at least 80 percent in both treatment groups. Both measures of efficacy indicate that patients were responding at the early clinical response time point.

Data from the OPTIC study demonstrates that omadacycline meets the standard for substantial evidence of efficacy for the treatment of CABP.

Omadacycline demonstrated noninferiority to moxifloxacin for the primary outcome of early clinical response and high success rates at PTE based on the investigator's assessment.

Clinical success rates at PTE for target CABP pathogens were also high and similar to those observed for moxifloxacin. Early clinical response and investigator assessment of clinical response results were consistently observed across subgroups with higher mortality risk or higher severity.

In conclusion, data from the three phase 3 studies show that omadacycline is effective for the treatment of ABSSSI and CABP. Consistent efficacy results for both early clinical response and investigator assessment of clinical response at the PTE visit were found across the indications and demonstrate durability of response.

The efficacy results persisted in subgroup analyses based on severity measures and by pathogen. These studies have shown substantial evidence of the efficacy of omadacycline.

Thank you. Dr. Loh will now present the

safety data.

**Applicant Presentation - Evan Loh**

DR. LOH: Thank you, Dr. Das.

I'm Evan Loh, and I've been in my role as chief medical officer since 2012. I'm an internist and cardiologist in clinical practice for nearly 20 years at the Brigham and Women's Hospital and also at the University of Pennsylvania Health System, where I was the medical director of the heart failure and cardiac transplantation program, as well as director of the coronary care unit.

I'm pleased to have the opportunity to provide this safety overview for omadacycline across the entire phase 3 development program. This large safety database contains over 1900 healthy volunteers and patients exposed to omadacycline.

Of the total exposed, 1,073 were from the three large pivotal phase 3 studies, resulting in exposures of more than 700 patients to the IV formulation and more than 900 patients to the oral formulation of omadacycline. In each of the

pivotal phase 3 studies, mean duration of therapy was between 8 to 10 days and similar between omadacycline and the respective comparators.

The safety overview will demonstrate that omadacycline is safe and well tolerated. The data safety monitoring committee chaired by Steven Opal, Brown University, was in place for the pivotal IV to oral OASIS-1 and OPTIC studies to monitor benefit-risk.

For today's presentation, we will focus on disposition, adverse events, and mortality. The rates of treatment completion and overall study completion were approximately 90 percent in both the skin and pneumonia studies. Approximately 50 percent of patients experienced at least 1 TEAE, and these will be reviewed on subsequent slides.

There were low and similar rates of patients who experienced serious adverse events and of patients who discontinued test article for TEAEs. Mortality rates were low across the skin and pneumonia studies.

In the phase 3 skin studies, the most common

adverse events observed with omadacycline were nausea and vomiting, which were mild to moderate in severity and not treatment limiting. The difference in rates between omadacycline and linezolid was due to the higher rates of nausea and vomiting observed in the oral loading dose period on days 1 and 2 in the OASIS-2 trial.

Nausea and vomiting rates were lower on the list of TEAEs in the OPTIC study. The most common adverse events observed with omadacycline in the OPTIC trial were elevations in transaminases, which were generally low in amplitude, asymptomatic, and not treatment limiting.

Diarrhea occurred at a rate of 8 percent in moxifloxacin and in 1 percent of omadacycline patients. Eight cases or 2.1 percent of moxifloxacin patients had Clostridium difficile infection. To date, no cases of Clostridium difficile infection have been reported in omadacycline-treated patients.

The mortality rate in the pooled safety population was low and similar between omadacycline

and comparators. Overall, 10 omadacycline and 7 comparator patients died in the clinical development program with low rates observed in each of the phase 3 studies. The difference in rates between omadacycline and comparators across all studies is 0.2 percent with a 95 percent confidence interval of minus 0.4 to 0.9.

Across all of the skin studies, the mortality rate is 0.2 percent for omadacycline ad 0.3 percent for linezolid. In the pivotal phase 3 ABSSSI studies, 1 omadacycline and 3 linezolid patients died. One patient in each treatment group died from an illicit drug overdose. 2 linezolid patients died from cardiac causes, including a cardiac arrest and a myocardial infarction.

In the OPTIC study, there were 12 patients who died, 8 in the omadacycline treatment arm and 4 in the moxifloxacin treatment arm. The rate difference is 1.1 percent, with a 95 percent confidence interval of minus 0.7 to 2.8.
1 moxifloxacin death occurred more than 30 days after the first dose of study drug. Therefore, if

considering 30-day all-cause mortality, there were 8 omadacycline and 3 moxifloxacin patients who died.

To understand the numerical difference in mortality rates in the OPTIC study, Paratek conducted a systematic examination to determine if there was a possible causal relationship between omadacycline treatment and mortality. We also endeavored to fully understand if there could be a lack of efficacy or a safety signal associated with the numerical differences in mortality.

First, we asked whether the rates observed in OPTIC were similar to or different from contemporary randomized phase 3 CABP studies. Contemporary registration trials in pneumonia from 2009 to the present have reported mortality rates that range from 0.8 percent to 3.2 percent.

From the top of the slides to the bottom, the mortality rates are arranged from the highest to the lowest by investigational treatment arm, which are represented by the black solid dots, while the comparator treatment arms are represented

by the open circles.

The omadacycline mortality rate in OPTIC falls in the middle of the range at 2.1 percent. The moxifloxacin mortality rate was 1.0 percent. Importantly, because of the low frequency event rates, we examined the specific cause of mortality on a case-by-case basis.

All 12 deaths observed in the OPTIC study occurred in patients over the age of 65. Three patients over the age of 75 died in each treatment group. No particular pattern in terms of the timing or the causes of death were observed within the treatment groups. The causes of death are not unexpected in patients hospitalized with community-acquired bacterial pneumonia.

Three of the omadacycline mortality cases have evidence for early efficacy. These 3 cases were clinical cures, discharged to home, and then readmitted with diagnoses that were distinct from their indexed pneumonia. All deaths occurred more than 6 days following treatment completion.

Omadacycline 5 was a 68-year-old patient who

was discharged and readmitted 6 days later with a fatal stroke in a setting of atrial fibrillation not treated with systemic anti-coagulation.

OMC6 was a 90-year-old patient with a prior history of myocardial infarction and severe aortic stenosis, who was discharged and readmitted 1 day later with an acute myocardial infarction. The patient had sudden cardiac decompensation and died from cardiogenic shock 5 days later.

OMC8 was an 86-year-old patient who was discharged and readmitted 6 days later with a de novo contralateral, hospital-acquired pneumonia that progressed to pulmonary failure and death.

Given the clinical evidence of early efficacy in these 3 cases, mortality does not appear to be related to the indexed pneumonia, nor to treatment with omadacycline.

Of the remaining mortality cases, there were 5 omadacycline-treated patients and 2 moxifloxacin-treated patients who died while hospitalized with their indexed pneumonia. The etiology of deaths appeared to fall within either of two categories.

One category is cardiac and vascular, 3 omadacycline versus 1 moxifloxacin, or progression of the indexed pneumonia, 2 with omadacycline and 1 with moxifloxacin.

Let's review the cardiac and vascular cases in patients who died during hospitalization for the indexed pneumonia. OMC2 was a 76-year-old patient clinically stable on day 2 with cardiac risk factors who suffered from an unwitnessed cardiorespiratory arrest.

Electrocardiographic assessments post-omadacycline infusion on day 1 and pre-omadacycline infusion on day 2 did not demonstrate any increases in heart rate nor in QTc, thus making it unlikely that there was a substrate for proarrhythmia. The investigator considered pulmonary embolism as a potential cause of death.

OMC3 was a 66-year-old patient with COPD who had a fatal MI on day 2. He had stable vital signs with no changes in heart rate or QTc on day 2 observed prior to his fatal event.

OMC4 was a 72-year-old patient with a known

large thoracic aortic aneurysm who on day 9 had the sudden onset of severe chest pain and shortness of breath, followed by cardiovascular collapse and death, a clinical syndrome consistent with aortic dissection or rupture.

Given the underlying cardiovascular comorbidities in these patients, none of these deaths were unexpected nor appear related to omadacycline.

Next, let's review the cases of progression of pneumonia. OMC1 was a 67-year-old with pneumococcus, cultured from both blood and sputum, who died from overwhelming pneumococcal sepsis, having received only 1 dose of omadacycline. It is unlikely that any antibiotic would have impacted this outcome.

OMC7 was a 74-year-old who presented with a polymicrobial multi low-bar pneumonia. On day 5, omadacycline treatment was discontinued and meropenem was initiated. Despite appropriate antibiotic therapy for the pathogens cultured, the clinical course progressed to sepsis, multisystem

organ failure, and death. Mortality from the progression of pneumonia is not an unexpected clinical outcome in patients hospitalized with pneumonia.

We also wanted to examine whether a lack of efficacy was driving the small numerical difference in mortality. We observed that omadacycline non-responders were similar to, if not lower than, moxifloxacin non-responders at the ECR, end-of-therapy, and PTE time points. Similarly, we also observed a lower rate of rescue antibiotic use in omadacycline-treated patients at all of these time points.

Beyond the day 1 to ECR time window, new mortality events that occurred within the ECR-to-EOT time window and within the post-EOT time window appeared balanced. Within day 1 to ECR time window, there were 3 omadacycline patients who died. All 3 of these patients died on day 2.

There was a single case of progression of the incident pneumonia. That was the pneumococcal sepsis case that I just previously described. The

remaining 2 omadacycline patients died from cardiovascular etiologies that were unrelated to omadacycline treatment as previously reviewed. Therefore, these data allow us to conclude that a lack of efficacy does not explain the numerical difference in mortality with omadacycline.

In order to determine if there was a background rate of an adverse event or a group of adverse events that were driving the observed numerical difference in deaths, we examined serious TEAEs between treatment groups.

Serious TEAEs occurring at a greater than or equal to 1 percent frequency by system organ class are presented here. Serious TEAEs were low and similar between omadacycline and moxifloxacin overall. When the 12 deaths from these SOC categories are excluded, as shown in the right-most two columns, a small difference in respiratory disorders remains. However, when looking at the preferred terms for respiratory failure, there is no imbalance noted.

Therefore, there is no background rate of an

SAE or grouping of SAEs that suggest a safety signal that explains the numerical difference in mortality with omadacycline.

We have thoroughly investigated the data, and we conclude that the small numerical difference in mortality observed in the OPTIC trial is likely to be a chance event. The mortality rates are low and consistent with in-contemporary phase 3 randomized CABP studies.

The review of the mortality cases provided no basis for a causal link to treatment. There is no evidence for a lack of efficacy or safety signal linked to mortality. The deaths appear related to underlying comorbidities or progression of the index pneumonia.

In conclusion, TEAE and SAE rates were similar to comparator with low treatment discontinuation rates. Nausea and vomiting were the most common adverse event, which were mild to moderate and not treatment limiting.

No cases of Clostridium difficile were reported in omadacycline-treated patients. No

clinically meaningful post-baseline changes in laboratory values, vital signs, and electrocardiograms were observed. There's a low proarrhythmic risk potential for omadacycline.

Liver transaminase increases were transient, of low amplitude, and generally asymptomatic. No Hy's law cases were observed. Mortality rates were low, similar to comparator, and consistent with expected rates and causes in both the skin and pneumonia studies. In conclusion, omadacycline is safe and well tolerated.

Now, I would like to introduce Dr. Eric Mortensen, who will discuss benefit-risk.

Dr. Mortensen?

**Applicant Presentation - Eric Mortensen**

DR. MORTENSEN: Thank you for the opportunity to address this advisory committee today. I am Eric Mortensen, an internal medicine physician with almost 20 years of research and publishing in the area of infectious diseases, pneumonia, and mortality after pneumonia.

I still see patients regularly who are

struggling with both of the infections under discussion today. As you've heard from Dr. Kaye, the need for new treatments for these infections is urgent. Like many of you in practice, I experience a frustration of a limited array of options for these infections.

While we thank the FDA for prioritizing antibiotic development, we still have an acute need for new and improved treatment options. The urgency is greatest in CABP.

We have been waiting almost 20 years for a new antibiotic with both IV and oral options. During that time, we have seen increasing bacterial resistance in patients coming from the community with pneumonia. Our primary antibiotic options in CABP are limited to quinolones or combination therapy. The most common pairing is a cephalosporin and a macrolide.

While there is a substantial need for antibiotics active against resistant strains, they need to be both effective and safe. With safety in mind, I performed a comprehensive assessment of the

mortality results in the CABP study. In my evaluation of this data, I paid particular attention to the post-treatment cure results as they most reflect the clinical goals for antibiotic therapy.

Patients' symptoms early in the hospital course can vary. Normally, we assess clinical stability by examining both symptoms and objective measures, including vitals and signs of infections like white blood cell count. These signs of clinical stability have been demonstrated to better predict clinical cure.

During my review of the cases, I have not seen any safety issues or lack of efficacy in the omadacycline arm. The mortality rates are low and the causes of death are consistent with what I see in my clinical practice. I also do not see an imbalance in the adverse events that would precede mortality, such as non-fatal myocardial infarction or respiratory failure.

During my review, I found three cases that demonstrated progression of the pneumonia, 2 on

omadacycline and 1 on moxifloxacin. Therefore, I do not believe that efficacy is driving the numeric differences in mortality. My review finds no causal link between the treatment assignments and mortality.

Regarding the risks of omadacycline, they were overall similar to other members of the tetracycline class. There were no new or unexpected events. Nausea and vomiting were the most commonly observed events and were not associated with discontinuation.

To maximize bioavailability, oral omadacycline should be taken with water after fasting for 4 to 6 hours. As a once-per-day treatment, this should not be a barrier to patient compliance. There is no data in patients requiring long-term treatment, pediatric patients, or the immunosuppressed.

Finally, as described in the briefing documents, the development of bacterial resistance to omadacycline was not seen. However, resistance monitoring post-approval is necessary. These risks

are outweighed by the benefits.

Omadacycline is active against many resistant pathogens. It has been demonstrated to be noninferior to linezolid for serious skin infections and moxifloxacin for community-acquired bacterial pneumonia. As with all tetracyclines, there is low potential for C. difficile infections with no C. difficile infections identified during the development program.

Omadacycline has both IV and oral formulations that require only once-daily dosing. It meets the need for an IV and oral antibiotic for serious skin infections in CABP. There were also no significant drug-drug interactions. There are no dose adjustments that need to be made in those with renal or liver impairment.

These features of omadacycline are particularly important to those of us who treat geriatric patients admitted with serious skin infections and pneumonia.

The benefits of omadacycline are clear. It's potent against resistant strains that are

increasingly prevalent in the community. It has demonstrated clinical efficacy as an empiric treatment. The risk profile is consistent with what we see for the tetracycline class. It was generally well tolerated.

Therefore, the benefits substantially outweigh the risks for both indications, and this will make a real difference for our patients. It gives physicians a new flexible treatment option.

Thank you. Now, Evan Tzanis will moderate the sponsor Q&A team.

**Clarifying Questions**

DR. BADEN: Thank you, and I'd like to thank the applicant for quickly covering a lot of data from many studies and thousands of patients, very much appreciated. Before we move into the clarification question segment, I just wanted to remind the committee, some of whom are new members, that the format that I prefer to do is we start a theme. And if you want to build -- if you have questions, let myself or Lauren know.

Once we ask a question, if you have a

follow-on, let me know so that we can build on a theme and try to develop the themes as much as possible.

So we will start, and please remember to state your name for the record before you speak. Please direct the question to a presenter or Evan will guide the response from the applicant. So we'll start with Dr. Calhoun.

DR. CALHOUN: Thank you. Bill Calhoun. I have a couple of clarifying questions here. One of the measurement tools for symptomatic improvement defines early clinical success. So I understand that tool is a patient-reported outcome with categories of absent, mild, moderate, and severe.

So my question is, is there any language around those categories that help patients determine where their symptom might lie? I can imagine that might differ patient to patient, and it might even differ within patient. And are these categorizations independent of placebo effects?

MR. TZANIS: Thank you. I'll actually ask Dr. Das to specifically address the symptom scales

used to assess early clinical response.

Just to clarify before she comes up here, the ECR is actually physician assessed, so it's not a patient self-assessment tool. Dr. Das was involved in the development of the ECR criteria.

Dr. Das?

DR. DAS: Yes. Can we please have slide 1 up? This slide provides for each of the 4 cardinal CABP symptoms: cough, pleuritic chest pain, shortness of breath, and sputum production, the definitions that we had in the protocol for absent, mild, moderate, and severe.

So we did train the investigators on using this tool, using it as outlined here. There's no way, really, to assess the placebo effect in this study. And as we stated, it's not really a PRO in the sense of a validated patient-reported. It's investigator discussing with the patient their symptoms and also for certain symptoms, assessing it themselves.

DR. CALHOUN: The table, if I recall correctly, was in the briefing document. So as I

was looking at it, I was a little concerned that the differentiation of moderate and severe was a challenge. So in that regard, the fraction of people who had severe symptoms, who had efficacy demonstrated by a change to moderate, might be interesting to take a look at.

DR. BADEN: If no follow-ons, Dr. Gripshover?

DR. GRIPSHOVER: I just had a question. I noticed that in your proposed indication for skin and soft tissue, you said, Staph aureus including with bacteremia, and I wondered if you could show us some data on that. Bacteremia Staph aureus is a more serious infection.

MR. TZANIS: Absolutely. Dr. McGovern can review the bacteremia data with you. Overall, it was a relatively low event rate of bacteremia, but we have that data for you.

Dr. McGovern?

DR. McGOVERN: Thank you. Paul McGovern. I'm an infectious disease physician and vice president of clinical affairs at Paratek. There

were only a few bacteremias in either the OASIS-1 or OASIS-2 study. We're still waiting for the slide. There were only 2 failures among the bacteremic patients with Staph aureus, one in OASIS-2, which was a patient with MSSA and Strept sanguinis, who on day 3 received pip/tazo and vancomycin and nafcillin. Day 3 cultures were positive.

There was 1 patient in OASIS-1 who also had bacteremia. It was a mono-equivalent infection with MSSA, and day 1 and day 2 cultures were positive. The patient received ceftriaxone and vancomycin starting on day 3.

So if we can bring slide number 1 up, the slide shows the overall ECR responses by patients who were bacteremic and not bacteremic. If you concentrate on the middle portion of the graph, you can see there were only 11 patients in the omadacycline treatment group in OASIS-1 that were bacteremic, 7 of which were clinical successes. And in the linezolid arm, you had 8 of 9 who were successes at ECR.

If you bring up the PTE responses now, slide 2 up, you can see at PTE, we had 9 of 11 or 81 percent that were successes, and all of the linezolid, 9 out of 9, were successes at PTE assessment.

DR. BADEN: Which organisms?

DR. McGOVERN: It was predominantly Staph aureus.

DR. BADEN: Dr. Swenson, a follow-on?

DR. SWENSON: I'm sorry. It's not a follow-on. I don't know. How should we let you know whether it's a follow-on?

DR. BADEN: What you just did. If you have a regular question, you can just get our attention.

Anyone else have a follow-on? Dr. Honegger?

DR. HONEGGER: A question about duration -- can you give duration of bacteremia time to clearance with study drug versus the comparators in both skin and pneumonia infections?

MR. TZANIS: Dr. McGovern?

DR. McGOVERN: So we only had the 2 failures as I mentioned earlier with the Staph aureus

bacteremia. We'll have to actually look at the data and get you the time to bacteremic clearance.

However, I will point out, in many cases where the baseline blood cultures were positive, not all patients had follow-up blood cultures done. We'll get that data.

DR. BADEN: You can prepare that data, and after the break, we can look at it in the second half of the morning.

MR. TZANIS: So specifically just to make sure, we just want to see the time to clearance of the bacteremia?

DR. BADEN: It would be useful to see the organisms to see which ones were failures and then time to clearance.

MR. TZANIS: Very good.

DR. BADEN: Dr. Gripshover? Microphone.

DR. GRIPSHOVER: And duration of treatment as well? Because another question I had is that you have a flexible treatment period of 7 to 14 days.

DR. BADEN: The duration of treatment and

then understanding the two failures.

MR. TZANIS: Absolutely. We'll get that at the break.

DR. BADEN: Thank you.

Another follow-on? Dr. Floyd?

DR. FLOYD: This is about the cure rates in the bacteremia patients. I've reviewed this in the briefing materials from the sponsor and from the FDA, and there were discrepancies. And I could not understand what accounted for the differences.

So if either the sponsor or the FDA would care to explain why there are discrepancies in the cure rates and which numbers to refer to you, that would be helpful.

DR. BADEN: I think it is best to address that after the agency's presentation, and then we can have any synthesis of data. And we'll revisit this with the sponsor, clarifying agency's presentation, and then we'll make sure that that query is fully resolved.

Next is Dr. Lo Re.

DR. LO RE: In terms of trying to better

understand the mortality outcomes from the OPTIC study, can you provide for the OPTIC study for community-acquired bacterial pneumonia the ECR and PTE results stratified by use of short-acting anti-bacterial bacteremia, which you said there was 3.9 to 4.6 percent, and the type of bacteremia, and the presence of baseline diabetes?

MR. TZANIS: So we actually have the data for you that shows you received a prior antibiotic use, not specifically by bacteremia. Dr. Das can review that data with you.

DR. DAS: Can I have slide 1 up, please? This slide shows you the outcome rates at ECR for patients with and without prior anti-bacterials. As you can see in the patients with anti-bacterials, the outcome rates are 88 percent and 82 percent versus 79 percent and 83 percent in those patients with no prior anti-bacterials.

If we now look at PTE for these same patients -- slide 2 up, please -- slide 2, what we show for this, again, is PTE. And we have very high and similar between the two treatment groups,

both for receipt of prior and no prior anti-bacterial rates above 85 percent in both treatment groups.

I can also provide you the data for diabetic patients. Slide 3, please. This shows ECR in the diabetic and the non-diabetic patients. And then the small subgroup of patients with diabetes, there is a numerical difference, 76 percent versus about 86 percent, and similar in the non-diabetic patients at 82 percent.

But when we go to the PTE outcome for these patients, which would be slide 1 up, please, the treatment difference is well within the expected variability at this time point, with diabetic patients having about an 86 percent success rate in the omadacycline and 87 in moxifloxacin, and again very high outcome rates in the non-diabetic group.

MR. TZANIS: We don't specifically have the data with the short-acting antibiotics for the bacteremic data.

DR. LO RE: Do you have the PTE and ECR results by bacteremic status?

MR. TZANIS: We do, yes.

DR. LO RE: And the type of bacteremia?

DR. DAS: Can I have slide 2, please? The type of bacteremia -- let me just address that because this slide does not show the pathogens -- is overwhelmingly Strep pneumo. There are 15 and 18 patients with bacteremia; 11 of the 15 and 11 of 18 are Strep pneumo patients.

So again, at ECR, we'll see there's 10 of 15 or 67 percent versus an 89 percent outcome rate. When you get to PTE, a higher outcome rate with 73 versus 83 in this small subgroup of patients

DR. BADEN: Use your microphone.

DR. M. GREEN: Yes. Hi. Mike Green. Do you have confidence intervals or statistical analysis on those differences?

DR. DAS: For bacteremia specifically or for all of them?

DR. M. GREEN: For the last slide you just had up.

DR. DAS: For the bacteremia, no. We can try and get those for you after the break. But

what the small --

DR. M. GREEN: Thank you.

DR. DAS: -- very small numbers, the 15 and the 18 patients, we would expect the confidence intervals to be very, very wide.

DR. BADEN: Thank you. And it is a follow-up?

DR. EVANS: I think it's a follow-on because we just asked about the diabetes in those patients. And in those failures, do we know if there was a difference -- in the patients who failed due to what appeared to be progressive lung infection, is there a difference in underlying chronic lung disease between groups, or did you identify a signal for pre-existing chronic lung disease in the mortality in the treatment arms?

MR. TZANIS: So specifically, we'll address that from the efficacy perspective response rates as it relates to the history of COPD or asthma, and then I'll ask Dr. McGovern to address some of the failure data.

DR. DAS: So let me address one of your

questions regarding the diabetics. So in the diabetic patients, most of the reasons for failure at the early time point are the no improvement in CABP symptoms or worsening of one CABP symptom. Only one patient in the omadacycline group and no patients in the moxifloxacin group received a prior anti-bacterial.

So it's difficult to really say at ECR that those patients are failing. They haven't improved with their CABP symptoms, but by the time they get to PTE, we're seeing a higher outcome rate at PTE and very similar between treatment groups.

We can show you outcomes by COPD and asthma, but not specifically for the diabetic patients. So that would be slide 2 up, please. This slide shows both ECR endpoints as well as the PTE, and on the right-hand side is the mild to moderate COPD and asthma patients.

Again, at ECR, we have a 76 versus an 83 percent outcome rate. And then when you get to PTE, the outcome rates are high at 81 percent for omadacycline and 85 percent for moxifloxacin.

DR. BADEN: Dr. Proschan, a follow-on?

DR. PROSCHAN: No. Sorry.

DR. BADEN: Then we have Dr. Floyd.

DR. FLOYD: Yes. This question is about the effect of the drug on heart rate. I saw in the sponsor's briefing materials results from, I think, phase 1 or phase 2 studies. And there was a fairly potent chronotropic effect compared to I think a fluoroquinolone, another drug that has some proarrhythmic effect.

Have there been any investigations as to the mechanism of how this drug increases heart rate or any explanation for those findings?

MR. TZANIS: Absolutely. Dr. Loh can address the mechanistic explanation for the increase in heart rate.

DR. LOH: Turns out that it's actually pretty interesting for me as a cardiologist. During my post doc time, I actually worked at a muscarinic receptor lab, and that's really the etiology of what we see.

When you talk about chronotropia, it's not a

direct chronotropic effect in terms of being a beta agonist. It's actually related to the fact that omadacycline actually interacts with acetylcholine binding to a very specific subtype of muscarinic receptor, the M2, which actually controls vagal innervation of the heart. It doesn't interact with M1, M3, M4, or M5, and that's what you would see with a pan muscarinic receptor antagonist.

So what you actually have is it's kind of a vagolytic effect, releasing the normal break. So we actually observed those small changes in heart rate, anywhere between 10 to 15 beats per minute in normal healthy volunteers, generally younger patients with good vagal tone.

But when we actually investigated it in the phase 3 studies, we thought it was important to do extensive ECG monitoring. So we actually monitored electrocardiograms centrally with the data, specifically on day 1 as well as on day 2, within 30 to 90 minutes of the completion of the IV infusion of omadacycline, to actually notice whether it was actually Cmax related or not because

our data suggested it was Cmax.

We actually analyzed that in our phase 3 studies. If we could actually have slide 1 up, you can actually see the excursions in terms of overall heart rate from this study. And the first two sampling dots here are actually the day 1 and the day 2 sampling, looking at excursion and heart rate.

Actually, the attrition in heart rate was actually no more than about 5 beats per minute, and then over time -- it's a parasympathetic and sympathetic balance here, and over time, guess what? The sympathetic tone is actually going down because infections are getting better. You have less sympathetic drive. We actually saw that the heart rates are actually coalescing and coming together over time, and the delta is actually extremely small.

We had no associated clinical adverse events seen with those heart rate excursions. So we actually understand this very well.

We did also investigate, just for

completeness of the answer, beta receptor binding. We looked at hERG-channel binding and other receptors as well. We saw no affinity for those particular receptors.

So it seems to be a very specific interaction between acetylcholine and the M2 receptor antagonist, that omadacycline tends to actually get in the way of that particular interaction.

DR. BADEN: Thank you.

Dr. Calhoun, do you have a follow-on?

DR. CALHOUN: I do. I saw that explanation -- thank you -- of muscarinic antagonism in the briefing document. So this may be one of those things that's quite different in hearts and lungs, but in lungs, the M2 receptor serves to dampen the cholinergic response. When the M2 receptor is lost, it's a hypercholinergic state that occurs in lung.

I inferred from the briefing document that that's not true in heart, that the M2 is an accentuating receptor; that is, activation of the

M2 would be vagolytic?

DR. LOH: It doesn't actually bind to the M2 receptor. It has an interaction between acetylcholine binding to the M2. And so what it does, it actually -- and that's specifically where the vagus interacts with the SA node. So what you have is you have a reflex heart rate increase. And it actually is dependent upon the intensity of vagal tone and vagal innervation.

The literature tells us that, first of all, when you're sick and infected, you have a lot of sympathetic drive, and you have very little vagal tone. But also, when you look at older patients, vagal tone actually goes down. That's why, in the elderly population with hypertension, you tend to see higher resting heart rates, and beta blockers tend to be more effective in that elderly population.

DR. BADEN: Thank you. It is now 9:50. We'll take a 10-minute break.

Panel members, please remember that there should be no discussion of the meeting topic during

the break, amongst yourselves, or with any members of the audience. We will resume at 10:00. Thank you.

(Whereupon, at 9:51 a.m., a recess was taken.)

DR. BADEN: We will now resume, and we'll proceed with the agency's presentations, Dr. Toerner. And I apologize to Dr. Loh and Dr. Toerner earlier for being confused as to who was speaking previously.

Dr. Toerner, thank you for presenting the agency's evaluation.

**FDA Presentation - Joseph Toerner**

DR. TOERNER: Thank you, Dr. Baden.

Good morning. My name's Joe Toerner. I'm the deputy director for safety in the Division of Anti-Infective Products at FDA. And for this application, I'm the cross-discipline team leader. I'll go through this morning, the FDA review of safety and efficacy for the phase 3 development program that included the community-acquired bacterial pneumonia trial. And I'll just refer to

it as the pneumonia trial and discuss the efficacy results.

Then I'll move to the acute bacterial skin and skin structure infection trials. I'll just refer to them as the skin trials and their efficacy results, and then end by summarizing the safety of the phase 3 development program.

So first let's talk about the pneumonia trial. The applicant went through this in very nice detail, and I won't dwell on this except to emphasize that the trial was a double-dummy trial design such that patients randomized to omadacycline was giving a loading dose of omadacycline, but there was a corresponding placebo to account for the loading dose in the moxifloxacin treatment group.

The design principles were consistent with our current draft guidance for treatment of community-acquired bacterial pneumonia such that the inclusion and exclusion criteria were standard for any trial design that we would expect to see for this indication, and that it generally enriched

for a sicker population by not including patients with PORT risk class I.

The exclusion criteria were standard for this type of trial in pneumonia, including generally excluding patients who received effective anti-bacterial drug treatment with an exception -- and this is described well in our guidance document -- that we do allow up to 25 percent of study subjects to have received a single dose of a short-acting anti-bacterial drug treatment for the current episode of pneumonia, for which the patient is being evaluated for clinical trial entry.

In this trial, it was further enriched for a patient population that was more seriously ill by limiting the PORT risk class II subjects to not more than 15 percent, so that most patients were PORT III or PORT IV that were enrolled into this trial.

The primary efficacy endpoint is described in our guidance document as the early clinical response, which is symptom improvement in at least

2 cardinal symptoms at day 3 to 5 of therapy.

Before I go into our review of the results, I wanted to highlight some important differences in today's presentation that differs from even our briefing document and also differs from the applicant's presentation.

In terms of PORT scores, our presentation today is using the PORT scores that were originally ascertained by the investigator for purposes of randomization. In our briefing document, we had included the actual PORT scores, but we became concerned that some of the information that was used to recalculate an actual PORT score came from post-randomization information, and so we went with the originally ascertained PORT score.

We conducted analyses between the two, and there were very minor differences between the originally ascertained scores and the actual PORT scores.

In our briefing document, we described the subgroup of patients with CURB-65 scores, which is another pneumonia severity scoring system.

However, we will not be providing those results today. The applicant had informed us of some unit measurement concerns with the original PORT scoring, and we decided to exclude from our presentation today the CURB-65 scoring information and to emphasize that the PORT scores was prespecified in the protocol. The CURB-65 scores were not prespecified.

Finally, for our discussion on the all-cause mortality issue, we considered all-cause mortality up to study day 30, and we do acknowledge there was one additional moxifloxacin-treated patient who died at day 71 but was not included in our mortality analysis.

So the baseline demographics were well balanced between the treatment groups, and this patient population, nearly half, were greater than or equal to 65 years of age. They were well balanced. And, again, most patients were in the PORT risk class III or IV. And again, these are the originally ascertained. There was very little difference with the actual PORT scores as well.

We did have a discrepancy in our briefing document in the description of the region, and we neglected to include a couple of extra sites from Western Europe. But the main point that we wanted to make is that this was a trial largely conducted in countries located in the eastern part of Europe.

The baseline demographics were well balanced in terms of prior anti-bacterial drug therapy, and indeed not more than 25 percent had received a prior dose of an effective anti-bacterial drug. The trial was well balanced in terms of baseline disease severity and comorbidities in this patient population.

In the microbiologically confirmed intent-to-treat population, this did represent approximately half of the enrolled patients in the study. Not only did this subgroup represent culture from a respiratory pathogen or from blood, this also represented non-culture techniques of urinary antigen testing and serology for the atypical pathogens.

I wanted to point out that there were some

numerical differences with a somewhat higher number of omadacycline-treated patients having evidence at baseline of Streptococcus pneumoniae and Haemophilus influenza.

Now I'll move on to our review of the efficacy results. For the primary efficacy endpoint, we are in agreement with the applicant that 81 percent achieved a successful clinical response at the early clinical response in the omadacycline-treated patients and approximately 83 percent in the moxifloxacin-treated patients, for a difference of just under 2 percent. And the lower bound of the two-sided 95 percent confidence interval of 7.1 percent was well within the prespecified noninferiority margin of 10 percent.

A key secondary endpoint is to look at information after the patient has completed therapy and for a period of observation after completion of therapy. This assessment was prespecified and represents patients that are a success at the end of treatment as well as being a success at the post-therapy evaluation of 5 to 10 days following

the last dose. And the treatment effect was sustained at this later endpoint with similar proportion between treatment groups achieving a clinical success at the PTE evaluation.

I'll move on to our review of sensitivity and subgroup analyses. And I wanted to emphasize that all of our sensitivity and subgroup analyses focused only on the early clinical response endpoint.

We first became aware that some of the patients who died were ascertained as being a treatment success at the early clinical response endpoint and then subsequently died while being followed in the study. In a sensitivity analysis, we excluded those deaths from the treatment success. There were 4 such patients in the omadacycline treatment group and 2 patients in the moxifloxacin treatment group who were considered successes but who subsequently died.

In this analysis, there was no substantive difference in the success rates with a lower bound of the two-sided 95 percent confidence interval of

7.7 percent, which is again well within the noninferiority margin.

So we looked at several subgroup analyses of efficacy, again, at the early clinical response endpoint. An important subgroup are patients who did not receive any prior anti-bacterial drug therapy. This represents a treatment group that only received study drug. And here, 79 percent of omadacycline-treated patients were a clinical success and 83 percent of moxifloxacin-treated patients were a clinical success.

We then looked at PORT risk class at baseline, and we found, for the PORT risk class IV, there was a 76 percent success rate in the omadacycline-treated patients in this subgroup and an 80 percent success rate of moxifloxacin-treated patients in this subgroup.

In the subgroup of patients greater than or equal to 65 years of age, 76 percent of omadacycline-treated patients achieved clinical success and 79 percent of moxifloxacin-treated patients achieved clinical success.

We then looked at patients with chronic lung diseases at baseline, patients with diabetes, and in these two subgroups, there was a numerically lower response rate in the omadacycline-treated patients in comparison to the moxifloxacin-treated patients.

There were very few subjects with bacteremia in this study, and here we describe this very small subgroup with a 67 percent success rate in omadacycline-treated patients and an 89 percent success rate in moxifloxacin-treated patients. And the bacteremia was largely Streptococcus pneumoniae bacteremia.

In the subgroup of patients who fell within the microbiologically confirmed intent-to-treat population, there was an 80 percent clinical success rate in omadacycline-treated patients and an 86 percent success rate in moxifloxacin-treated patients.

Again, this subgroup included patients who not only had a positive culture result from sputum or from blood, but also included non-culture

methods, including the serology for the atypical bacterial pathogens.

In our briefing materials, we described the subgroup by baseline pathogen. And we came to realize that, in this subgroup analysis, there were multiple pathogens that could have been identified from the patient, not just a single pathogen.

In our briefing materials, we do describe, for example, the subgroup with Streptococcus pneumoniae in omadacycline-treated patients had a 79 percent success rate and an 88 percent success rate in the moxifloxacin-treated group. But looking at the mono pathogen where only Strep pneumo was identified, it didn't change the clinical success rates in these subgroup analyses.

For Haemophilus influenza, we noted that approximately 69 percent of omadacycline-treated patients had a treatment success at baseline and 87.5 percent of moxifloxacin-treated patients had clinical success at this baseline visit. But pulling out only those patients who had a monomicrobial infection, the treatment difference

didn't appear as large, with approximately 78 percent of omadacycline-treated patients having a treatment success, and the treatment success was similar in the moxifloxacin treatment group.

This table also showed -- this was a description of the positive culture at sputum or blood. This excluded patients with a serologic outcome measure. And here, we described the results for the very small subgroup that had Staphylococcus aureus identified on culture or Klebsiella pneumoniae identified on culture.

So our conclusions of efficacy for pneumonia, that omadacycline was noninferior to moxifloxacin at the early clinical response endpoint, and the response was sustained through later time points such as the post-therapy evaluation.

Our subgroup analyses of patients with baseline scoring of PORT IV at age greater than 65 years in patients with chronic diseases, such as diabetes or chronic lung disease, and in the patient population of microbiologically confirmed

intent-to-treat, showed numerically lower response rates at the early clinical response in omadacycline-treated patients. But looking at these subgroup analyses, there are limitations that prevent any strong conclusions.

These are all post hoc analyses. There are small sample sizes in the subgroups. And in terms of the microbiologic intent-to-treat data, there is confounding by polymicrobial mixed infections in this subgroup.

Now I'll move on to the mortality imbalance that was observed in the pneumonia trial. There were 8 deaths in the omadacycline-treated patients and 3 deaths in the moxifloxacin-treated patients. And again, we acknowledge the 1 death that occurred at day 71 in the moxifloxacin-treated patient that was due to metastatic pancreatic cancer.

This table is a summary of the mortality by different subgroups. I just wanted to point out a couple of things in this table. No deaths occurred in PORT risk class II, so all of the deaths occurred in patients who had greater disease

severity of PORT risk class III or IV.

There was 1 patient who was originally classified as PORT class II, but for this table, we reclassified this because baseline characteristics before randomization clearly showed that this was a PORT risk class III patient.

In terms of baseline bacteremia, there was 1 death in each treatment group. All of the deaths occurred in patients greater than 65 years of age; 6 out of the 8 deaths in the omadacycline group, these patients had chronic lung disease at baseline with chronic obstructive pulmonary disease, asthma, or chronic bronchitis; 4 of the 8 patients in the omadacycline group who died had diabetes at baseline; and 4 of the omadacycline treatment group deaths had a pathogen identified at baseline and was part of the microbiologic intent-to-treat population.

We also thought it was worth going through, in a little bit of detail, each of the deaths. And the applicant has gone through this, so I'll try to keep this as brief as possible.

Of the 8 omadacycline deaths that were observed, 3 of them occurred very early in the course of their treatment for community-acquired pneumonia. The first patient was admitted and received a single dose of omadacycline, and shortly thereafter experienced a decompensation and went to the intensive care unit, where the patient was intubated and ultimately died of multi-organ failure due to septic shock.

The second patient, who was a 76-year-old who was admitted with right lower-lobe pneumonia, had a relatively uneventful first 24 hours, and then was found dead in his hospital bed. The investigator suspected a pulmonary embolism, but an autopsy was not performed, so the cause of death was listed as a cardiorespiratory arrest.

The third patient was a 66-year-old with chronic obstructive pulmonary disease who had a myocardial infarction on his second hospital day and died of cardiogenic shock.

The fourth patient had a known thoracic aortic aneurysm and was judged to be a clinical

success at the early clinical response endpoint, but had a somewhat deterioration in his clinical course, but then on study day 9 died of a thoracic aortic aneurysm rupture. There was some evidence of worsening pneumonia, but the cause of death was thoracic aortic aneurysm rupture.

The fifth patient had an uneventful course for treatment of community-acquired pneumonia and was discharged on hospital day 7. This patient had a history of chronic obstructive pulmonary disease, congestive heart failure, and diabetes.

The patient was brought to the emergency department after discharge from the hospital approximately a week later in a semi-comatose state, was hypotensive, and was judged by the clinicians to have a cerebrovascular accident. But the patient was noted to be hypotensive, and sepsis or respiratory failure could not be ruled out in this patient.

The sixth patient also had an uneventful course and was a successful treatment for community-acquired pneumonia; was a 90-year-old

with chronic obstructive pulmonary disease, congestive heart failure, and diabetes. And this patient experienced a myocardial infarction and died of cardiogenic shock after being discharged from the hospital.

The seventh patient was a 74-year-old with a history of asthma and coronary artery disease who didn't do well in the first days after being admitted to the hospital and was intubated and sent to the intensive care unit on study day 2, where this patient experienced a stormy hospital course and ultimately died on study day 25 of acute respiratory failure.

The eighth patient was an 86-year-old who had a history of atherosclerosis and had an uneventful course for treatment of pneumonia and was discharged on hospital day 12. This patient came back approximately a week later with a new right lower-lobe pneumonia. A culture obtained upon the readmission showed Acinetobacter baumannii, so this patient clearly had hospital-acquired bacterial pneumonia and

subsequently developed adult respiratory distress syndrome and died on study day 30.

I put an asterisk by three of the patients that we feel study drug administration was highly unlikely to be causally related to the death.

Moving on to the 3 patients in the moxifloxacin group who died, there were no deaths that occurred early in study therapy in contrast to the omadacycline group. The first patient was an 85-year-old who had a history of atrial fibrillation and had a gradual downhill course for pneumonia, and was sent to the intensive care unit on day 5. The patient subsequently died of acute respiratory failure and worsening pneumonia on study day 9.

The second patient was an 83-year-old who was judged to be a success at the early clinical response endpoint, but then had a gradual decline in his clinical condition. And as part of a workup had an electrocardiogram obtained that showed evidence of a recent myocardial infarction likely to have occurred during the hospitalization. And

this patient died of cardiac failure on study day 9.

The third patient was an 82-year-old with a history of chronic obstructive pulmonary disease and coronary artery disease who, at the end of treatment, had a repeat chest x-ray and, his low-bar pneumonia had cleared sufficiently enough to show a lung mass on chest x-ray.

He remained hospitalized, receiving a workup for the lung mass when he was found dead in his hospital bed on study day 20. An autopsy was performed because the death was relatively unexpected, but an autopsy was found to have widely metastatic cancer as the cause of death.

So this summarizes our review of the efficacy results from the community-acquired bacterial pneumonia trial. Omadacycline was noninferior to moxifloxacin for the primary endpoint of early clinical response, and the response was sustained at the post-treatment evaluation visit.

Our subgroup analyses of patients with

baseline PORT scoring of IV, age greater than or equal to 65 years, and the subgroup with diabetes, and the subgroup with chronic lung disease, and the subgroup with microbiologically confirmed infections in the ITT populations showed a numerically lower response rate in the early clinical response endpoint in omadacycline-treated patients.

However, as I mentioned previously, there are limitations to these analyses that are all post hoc. The sample sizes are very small, and in terms of the microbiologic ITT population that we described, it's with mixed polymicrobial infections that it's hard to draw any strong conclusions.

So all the mortality cases occurred in patients who had greater disease severity at baseline with PORT risk class III or IV, and age greater than 65 years, and most if not all had evidence of having chronic comorbid diseases at baseline.

I'll move on to talk about the skin trials and the efficacy results. The applicant had gone

through these in great detail, so I won't dwell on this except to emphasize, again, it was a double-dummy design to account for the loading dose in omadacycline-treated patients, as well to emphasize that the second study of oral therapy was conducted in the United States.

The entry criteria is, again, standard and well described in our guidance document for acute bacterial skin and skin structure infections, where we ask that patients have a somewhat large evidence of a skin infection with cellulitis, major abscesses, or wound infection to help ascertain, then, the evaluation at early clinical response, which is an endpoint, a primary efficacy endpoint, early that the lesion size should be reduced by at least 20 percent.

Similar to the pneumonia trial, patients were followed to the end of treatment and a period of observation after completion of treatment for a post-therapy evaluation.

Here again, we're in agreement with the applicant's efficacy results in which, for both

trials, a finding of noninferiority to linezolid was established with a lower bound of the two-sided 95 percent confidence intervals of negative 6.3 percent and negative 0.2 percent. They're both well with the prespecified noninferiority margin of 10 percent.

The key secondary endpoint was the investigator's assessment of clinical response to the post-treatment evaluation. And here, too, we're in agreement with the applicant's analysis. There were high rates of success in both studies in both treatment groups, and there were no substantive differences between the treatment groups.

There was one death observed in omadacycline-treated patients as a 30-day all-cause mortality assessment. And the death that occurred in the omadacycline group was a drug overdose.

We concluded for acute bacterial skin and skin structure infections, the two phase 3 trials provided evidence that omadacycline has efficacy for the treatment of acute bacterial skin and skin

structure infection. The results showed noninferiority to linezolid.

We also looked at a number of subgroup analyses, but we couldn't find any concerns with regards to efficacy and evaluation of any of these subgroup analyses.

Now I'll summarize safety in the phase 3 development program. I wanted to remind you that the dose was the same for both the pneumonia trial and the skin trial. We have just over a thousand patients with the same dose and duration of treatment that comprised the phase 3 safety population.

A large proportion of patients completed study treatment. In fact, a somewhat higher proportion in omadacycline treatment groups completed study treatment. And conversely, a somewhat lower proportion had prematurely discontinued from study treatment in the omadacycline treatment arms.

Here, I have listed the reasons for premature discontinuation from study treatment, and

no patterns emerged here with the exception of deaths during study treatment in the pneumonia trial that we had already talked about.

We focused on serious adverse events that were observed in the skin trials. Serious adverse events were infrequent in these trials with infections and infestations being the most common category of serious adverse events. However, when we looked at each of these, all of these events were assessed as treatment failures in the efficacy analysis.

Taking a closer look here, no patterns emerged in very small numbers in each of these groups of serious adverse events. Wound infection, or a new subcutaneous abscess, or development of sepsis, those were regarded as treatment failures in the primary efficacy analysis and were recorded as serious adverse events in the safety database.

Similarly, in the pneumonia trial, there were relatively few serious adverse events and no patterns emerged in the review of serious adverse events with the exception of respiratory, thoracic,

and mediastinal, as well as infections and infestations. And similar to the skin trial, most of the serious adverse events were assessed as treatment failures in the primary efficacy analysis.

So taking a closer look at these two disease categories, again, no patterns emerged, and there were relatively small numbers of characterization of these serious adverse events. Most of them were in the respiratory framework. For example, development of septic shock, worsening pneumonia, development of pleural effusion, these were all characterized as failures in the primary efficacy analysis and were considered serious adverse events in the safety database.

So this is again a summary of all treatment-emergent adverse events. This table, I believe, is very similar to what the applicant had presented with a somewhat higher proportion of subjects randomized to omadacycline in the skin trials having any treatment-emergent adverse event, a somewhat fewer proportion of omadacycline-treated

patients having any treatment-emergent adverse event in omadacycline-treated patients for the pneumonia trial.

We just went through the serious adverse events and relatively few serious adverse events and similar in proportion between treatment groups. We again show the difference in serious adverse events leading to death, the difference in the pneumonia trial, and very few patients discontinued due to a serious adverse event.

So for the pooled skin trials, nausea and vomiting emerged as being more commonly associated with omadacycline, and this was primarily driven by the oral trial in which an oral loading dose was given for patients randomized to omadacycline.

Infection site extravasation was also seen somewhat more commonly in the omadacycline treatment group. However, the rest of the treatment-emergent adverse events occurred with similar proportions between the treatment groups, and no patterns emerged other than nausea and vomiting and infusion site extravasation.

Treatment-emergent adverse events in the pneumonia trial were similar between treatment groups, and no patterns emerged here in the safety database. A somewhat higher proportion of moxifloxacin-treated patients experienced nausea in this safety database.

Our conclusions are that omadacycline overall in safety appeared to be similar to control groups in the phase 3 development trials. There were no significant differences in serious adverse events or adverse events leading to treatment discontinuations that were observed between the treatment groups.

Nausea and vomiting is associated with oral omadacycline, and this is largely due to the oral loading dose for the first day of therapy. Infusion site reactions, which were mainly extravasations, were associated with intravenous omadacycline.

In the skin trial of IV to oral switch, curiously, in the pneumonia trial, it was not observed as an adverse event. So we're left with

the imbalance in mortality at 30 days in the CABP pneumonia trial, 8 deaths in omadacycline versus 3 deaths in moxifloxacin.

But we do note that all deaths in the pneumonia trial occurred in patients with higher disease severity, higher PORT scores at baseline, and occurred in an older patient population greater than 65 years of age. Most if not all the patients who died had comorbid diseases such as chronic obstructive pulmonary disease or asthma, heart disease, and/or diabetes.

I just wanted to acknowledge and thank the review team for this application.

**Clarifying Questions**

DR. BADEN: Thank you, Dr. Toerner.

We will now move to the clarifying questions part for the agency and we get our attention. I'll start with the first question. If we can bring up slide 22, I found this very helpful.

Dr. Toerner, can you help me understand, what do we expect of background and mortality in PORT III and IV? Is it that the omadacycline is

higher or the moxi is lower?

DR. TOERNER: That's a good question. We've been struggling with that question, too. You know, it appears that the mortality rates in PORT risk class III and IV for moxifloxacin-treated patients seems to be quite a low mortality rate, considering the disease severity for these patients. The corresponding mortality in the omadacycline-treated patients, PORT risk class III and IV, particularly looking at PORT risk class IV and that subgroup, mortality rate was just over 5 percent.

In an all-comer population with PORT IV, I might expect to see a higher mortality rate. But as you know, when patients get enrolled in clinical trials, they're generally different than an all-cause population, and we generally see somewhat lower mortality rates in patients who are entering a clinical trial and being randomized.

DR. BADEN: But typically PORT IV risk is higher for mortality.

DR. TOERNER: That's true, for higher risk for mortality. That's true.

DR. BADEN: Thank you.

A follow-on, Dr. Daskalakis?

DR. DASKALAKIS: Just a quick follow-up, which is, do you have a Venn diagram, in effect, of how many of the 8 who were greater than 65 also happened to be the higher risk category, either PORT III or IV? That may be a question for the company, but do you have a set?

DR. TOERNER: Certainly, age is a risk factor. Greater than or equal to 65 years of age portends a poor outcome in pneumonia. We don't have a Venn diagram to describe. Again, all the deaths occurred in patients with greater disease severity at baseline.

DR. BADEN: Are these follow-ons?

Dr. Proschan?

DR. PROSCHAN: Yes. Regarding whether moxi might have a lower mortality rate, I think also the sponsor's slide CC-71 is helpful because here you see, in the comparator, there are 5 moxi arms that are comparators, and those represent the 5 lowest comparator event rates. If you look at the moxis,

those are the 5 lowest event rates. So it's possible that moxi has a lower mortality rate than some of the other drugs.

DR. BADEN: I agree. I thought of this slide as well. What's missing on this slide for me is the PORT score because I'm not sure the studies are equal. So looking at the high-risk group trying to understand what the mortality background rate should be for PORT 4, not for all studies.

DR. PROSCHAN: Right.

DR. BADEN: And that was missing in this for me.

DR. PROSCHAN: Right. It is interesting, though, looking at this, you might say this is troubling because even though the event rate is in the middle of the pack for -- the treatment arm is in the middle of the pack, when you look at the control, you say, well, wait a second, the control rate is way over on the left compared to all the other trials. But then, when you look at the other moxi trials, you realize that moxi does seem to have lower mortality rate.

DR. BADEN: Other follow-ons? Dr. Weina?

DR. WEINA: Yes. I understand what Demetre was getting to, and I was kind of bothered by it as well when I was looking at slide 22 from the agency. You've got these things that are really independent variables. There are 8 deaths and 5 of them are PORT class IV, but then 4 of them are diabetic and 6 of them are COPD.

Could all of those have occurred in the same individual in which you just had somebody with bad protoplasm and just bad randomization, and you ended up with the increased deaths.

So it'd be nice to see how much of that kind of converged together because, obviously, it had to have converged together because just for COPD and diabetes, you have 10 people. So obviously it wasn't --

DR. M. GREEN: This is just a quick follow-on with that. All they would have to do is adjust slide 23 to put the PORT score in.

DR. TOERNER: Hi. This is Joe Toerner. We can certainly look and pull together that

information. It's part of the reason why we included a case summary of all of the deaths in the briefing information. But we can pull that together out of the briefing information, the case summary of the deaths.

DR. BADEN: Noting slide 22 and 23, we really appreciate the detailed information.

Dr. Ofotokun?

DR. OFOTOKUN: It's just a quick follow-on. I was just wondering. These studies were conducted in different parts of the world. Were these deaths coming from a particular region of the world or were they uniform across the regions where this study was conducted?

DR. TOERNER: Eighty percent or more of patients were from countries that were located in the eastern part of Europe. We didn't look at any specific location, but we can pull that information for you as well.

DR. BADEN: Another follow-on? Dr. Proschan? No. Dr. Floyd?

DR. FLOYD: Related to geographic

distribution, I'm curious. Is this distribution typical of other pneumonia trials or is this unusual with very few research sites in the United States but a majority in Eastern Europe?

DR. NAMBIAR: Yes. In general, for anti-infective trials, this is very consistent, not just for pneumonia. We've seen this across most indications, that we're able to get very few for many reasons. And I'm sure the applicant can add to it, but it's not for lack of trying. I think they have tried to have some sites in the U.S., but I think they've had difficulties.

So across the board for multiple indications, this is a pattern we've seen where most of the sites are from Eastern Europe and you get a handful of patients from the U.S.

DR. BADEN: Just one comment to the applicant. As you hear our discussion, if you have clarifying information, please track it, and then when we come back to further discussion, you'll be able to provide that information, because the goal here is to get the best information to the

committee.

Dr. Proschan, you had a follow-on?

DR. PROSCHAN: Yes. I was just wondering, Dr. Toerner, you mentioned that they were from Eastern Europe. And I wonder does that concern you? And the reason I bring that up is because I do remember situations where data in at least one trial did look suspicious at an Eastern European site.

Is that the reason you mentioned this?

DR. TOERNER: Yes. This is Joe Toerner. The data are what we have. In our review of this phase 3 development program and our review of the pneumonia trial in particular, the fact that there was a large proportion in countries located in Eastern Europe didn't alarm us or didn't give us any reason to pause.

DR. BADEN: Dr. Nambiar?

DR. NAMBIAR: And as part of our evaluation of any new drug application, we do conduct study site audits. And there isn't anything that raised a concern for us with these applications as well.

DR. BADEN: Dr. Farley, did you have a comment? Dr. Schaenman has a follow-on.

DR. SCHAENMAN: While we're talking about the countries where the study was conducted, I was wondering if FDA or the sponsor had information about the racial and ethnic breakdown of study participants.

DR. TOERNER: I think, as expected, most of the patients were white that participated in this trial. We have a breakdown, and I'll have that for you in just a moment.

DR. BADEN: The glasses. They're coming for all of us.

(Laughter.)

DR. TOERNER: Overall, just over 80 percent of study participants were white. There were very few Asian patients enrolled, very few black patients that were enrolled, less than 2 dozen. So the vast majority of the study were patients who were white.

DR. BADEN: A follow-on?

DR. OFOTOKUN: No.

DR. BADEN: Okay. You're on the list, and we're checking it twice.

Dr. Swenson, you have been very patient.

DR. SWENSON: Thank you. Erik Swenson. Could we go to slide 18 of the agency's presentation? It was the discussion of some subgroup analysis, those patients with just monoculture infections as opposed to polymicrobial.

You've given us the data for just the ECR, and you've intimated a sort of worrisome trend that maybe omadacycline is not as good as moxifloxacin in that polymicrobial group. But did that extend also to your PTE time point, or by that point, did we see equivalence?

DR. TOERNER: In our analysis, we really only focused on the early clinical response for the sensitivity analyses. We did not look at the PTE from these.

DR. SWENSON: Do you think that might be important? Simply because, obviously, some antibiotics may work just a little bit better early on, but ultimately they're going to be equal. And

I think we saw some of that, that PTE numbers rose, and in some cases, there was a slight change in position vis a vis superiority.

Could you look into that data for us?

DR. TOERNER: Yes, sure. We'll have that data for you.

DR. BADEN: A follow-on. These data struck me as well with the H. flu data being a little less responsive earlier as you noted. Any microbiology data, the MICs, to omadacycline or tetracycline? Were there any corollary data that could inform us as to why this finding may have occurred?

DR. TOERNER: I'll start from the beginning. We really started to look at this application from the point of view of mortality imbalance, and is there anything in these data that could help us explain why 8 deaths were observed in omadacycline-treated patients and 3 deaths observed in moxifloxacin-treated patients.

So this was sort of the get-go. That's what we started from when we conducted our analysis, and that's why we paid so much attention to these

subgroups and looked into -- for example, the microbiologic intent-to-treat population, we were concerned about that because in the 8 deaths, 3 of them had evidence of having Haemophilus influenza at baseline.

So it actually started our concern. And then when we looked at the subgroup and saw 69 percent response rate at ECR in omadacycline-treated patients and 87 percent success rate in moxifloxacin-treated patients. So that sparked our interest in looking in greater detail in the microbiologic and intent-to-treat population.

We also looked at minimum inhibitory concentrations for the patients. Those data are not available for all patients who had culture positivity at baseline, but we do have them for most patients.

Our review of the MIC data showed there was no correlation with clinical success. There was no correlation in the 3 of the 8 deaths who had evidence of Haemophilus influenza infection. There was no indication that a lack of efficacy played a

role in helping to understand the mortality imbalance between these studies and helping to understand the lower point estimate of treatment effect in omadacycline patients in these subgroups. We could not explain that by the MIC data.

DR. BADEN: Thank you. And I'll ask the applicant, when we get to it later, to respond to this question as well and be able to show us the MIC data, including any baseline tetracycline resistance, so we can be reassured that the proposed mechanism is playing out as suggested.

Dr. Brittain has a follow-on?

DR. BRITTAIN: Right. I do want to go to slide 17, which was the whole micro-ITT. This one did jump out at me. I wonder, first of all, if you did a confidence interval for this. And also, just from my understanding, the patients who don't fall into the micro ITT, is there any question about whether they have bacterial infections that obviously say that they were susceptible to antibiotics?

It seems like this might be the group that

if there is a difference in efficacy, it might be the group that you'd see it in?

DR. TOERNER: Yes. Thanks for the question. We do provide a confidence interval in our briefing materials, table 15. So the difference between omadacycline-treated patients and moxifloxacin-treated patients in this subgroup is minus 5.8 percent, and the bounds of the 95 percent confidence interval are minus 13.3 and plus 1.8. So the 95 percent confidence intervals crossed zero for the difference.

DR. BADEN: But it looks like about 50 percent of the time they identified a pathogen, 50 percent of the time they didn't. Is that unusual in these kinds of studies for community-acquired bacterial pneumonia?

DR. TOERNER: Yes. Joe Toerner again. Just to add that the opposite was true in the patients who did not have a pathogen identified. You have the numerically higher response rate in omadacycline-treated patients, and it's a concern in these trials.

We do ask the patients -- these types of investigations make every attempt possible to try to identify a pathogen. In clinical practice, anywhere between even less than 10 percent up to 20, 25 percent, you're able to identify a pathogen. It struck us as quite interesting that almost 50 percent of patients in this study were able to identify a pathogen, but that included patients who had a serology for the atypical pathogens.

It's really hard to know what that would mean, but it's not unusual at all to have a 25, 28, 30 percent identification of bacterial pathogen in the context of a clinical trial be conducted for an indication of a new antibiotic. We've generally seen it on 25 to 30 percent, so 50 percent here was quite unusual.

DR. BADEN: Thank you.

Dr. Brittain, did you have another line of questioning? You're on the list.

DR. BRITTAIN: It just happened to work out.

DR. BADEN: Great. We like to build on themes. Dr. Proschan?

DR. PROSCHAN: So regarding the 8-3 versus 8-4, is it typical for the agency to look within 30 days as opposed to all deaths? To me, it makes a pretty big difference in my mind, thinking 8-3 versus 8-4, even though the numbers are still small either way.

That's question number 1. And I wonder if you could just comment on the noninferiority margin of 10 percent and how that came about. It seems like it's fairly large.

DR. TOERNER: Joe Toerner. So your first question pertained to the 8 versus 3 and 8 versus 4. We did focus on 30-day mortality. If you look at our guidance document for hospital-acquired and ventilator-associated pneumonia, we found a strong treatment effect on a mortality outcome measure, an all-cause mortality outcome measure; similar disease process; obviously a different set of pathogens and different development trial for that indication.

But there is a very strong treatment effect on mortality for pneumonia. In the draft guidance

document for hospital-acquired and ventilator-associated pneumonia, we do recommend the 30-day all-cause mortality endpoint. So in part, that's why we focused on 30-day mortality here for this community-acquired pneumonia. But again, you bring up a good point. We do acknowledge there was a fourth death in the moxifloxacin treatment group.

Dr. Anita Das in her presentation had mentioned the work of the Biomarkers Consortium, the Foundation for the National Institutes of Health. And part of that work was to help identify an endpoint that could support the noninferiority trial design for studies in skin and studies in pneumonia.

Part of the work that was done was presented in an advisory committee meeting, actually, I think in 2010 or 2011, where we identified data from evaluations that were conducted in the pre-antibiotic era, with observational cohorts of patients that were followed for their pneumonia. Then similarly, we looked at data just after the introduction of anti-bacterial drug therapy.

These were observational studies that were done largely in the same sites, the same centers, and initially observed improvement in mortality. But moving to a contemporary study, we knew that mortality rates were much lower than the 30, 40, 60, 80 percent mortality that was observed back before antibiotic therapy was introduced.

So we looked at symptoms that were recorded in these studies and found evidence of a very large treatment effect early in therapy. As you go later in therapy, the symptom improvement looks similar between placebo and antibacterial -- not even placebo; between the natural course of pneumonia and patients treated with an antibiotic in that middle of the 20th century time period.

So what the Biomarkers Consortium did was look at recently conducted trials and trials that had looked at daily evaluation of patient symptoms and were actually able to correlate then in recently conducted trials that you can observe an improvement in at least 2 symptoms of the 4 cardinal symptoms of pneumonia.

The working group looked at a number of different improvement in one symptom, improvement in 3 symptoms, absence of symptoms, looked at all kinds of ways of approaching this, and found that improvement in 2 symptoms at least improved by 1 point seemed to be at a good place. Around 60, 70, 80 percent of patients would achieve that in clinical trials.

So that helped us to inform, then, the primary endpoint and the noninferiority margin. The treatment effect between day 3 to 5 is about 30, 40 percent. And so we felt confident then discounting some of that treatment effect. Actually, our guidance documents describes an appropriate noninferiority margin of minus 12.5 percent. So the applicant chose the 10 percent NI margin.

DR. BADEN: Thank you. Is that a follow-on? Dr. Floyd?

DR. FLOYD: This is related to Dr. Brittain's question, too, about the micro-ITT population. I believe the historical evidence for

establishing the treatment effect of antibiotics primarily comes from low-bar pneumonia, principally pneumococcal. But the micro ITT in contemporary trials includes chlamydia, mycoplasma, and things like that.

I wonder, could you generate the sensitivity results for typical bacterial pathogens, things like Strep pneumo, H. flu, Klebsiella? Is it possible to generate the results amongst the typical pathogens?

DR. TOERNER: Yes. We have those in our briefing document. We have here a breakdown of the subgroup of patients who had an early clinical response rate in the subcategory of Streptococcus pneumoniae who that isolated at baseline. There were 43 patients in the omadacycline treatment group; 34 of them had a success for a 79 percent success rate.

In moxifloxacin, there were 34 patients who had Streptococcus pneumoniae identified at baseline and 30 out of the 34 were judged to be a success at early clinical response for an 88 percent response

rate. So here, there was a point estimate of approximately 9 percent difference between the treatment groups and a 95 percent confidence interval of minus 25 and positive 8.6 percent, so a wide confidence interval.

For Haemophilus influenza, there were 32 patients in omadacycline treatment group who had Haemophilus influenza identified at baseline; 22 of those 32 patients had evidence of clinical success at the early clinical response endpoint for a 69 percent rate of response.

There were actually much fewer patients randomized to moxifloxacin who had Haemophilus influenza. Only 16 identified at baseline; 14 of those 16 were judged to be a success for a success rate of 87.5 percent.

So the difference is 18.8 percent as a point estimate difference, but it's a small subgroup and the confidence intervals are very wide minus 39.8 percent and plus 8.7 percent.

You're also interested in the atypical pathogens?

DR. FLOYD: No. I was interested in the typical pathogens specifically because those form the basis for estimating a treatment effect. That's the basis for the noninferiority trial, so just what you read, thank you.

DR. BADEN: Thank you. There are more questions for the agency, but we need to move to the open public hearing part of the meeting, and then we will come back to the further clarifying questions.

**Open Public Hearing**

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you

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

If you choose not to address 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 in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore,

please speak only when recognized by the chairperson. Thank you for your cooperation.

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

DR. CHOPRA: Good morning. I'm Dr. Teena Chopra. I'm an infectious disease physician at Detroit Medical Center, Wayne State University. I also practice infection control and antibiotic stewardship. And I'm a researcher in hospital-acquired infections, including gram negatives and C. diffs.

My disclosures, my travel was supported by Paratek, but I have no financial interest in the outcome of this meeting. I wanted to state the same unmet need that has been previously stated around antibiotic resistance.

We all know that antibiotic resistance is fast growing and killing millions worldwide. We are in critical need of more broad spectrum antibiotics, particularly MRSA and gram-negative

infections.

As I previously stated, I practice infectious diseases in Detroit, and this is a place we see very high-risk patients, including IV drug users, homeless patients, dialysis patients, patients coming from nursing homes. And very often, they'll present with severe infections, including MRSA, community-acquired pneumonia, skin to skin structure infections that are very hard to treat, and we have no antibiotics available to treat these patients.

Above all, many times, we treat them inpatient, but we don't have oral choices for these patients because we many times cannot send them on IV drugs because we cannot give them IV lines at that point.

Additionally, I'm also the director for a fecal transplant program at my hospital and I see a lot of C. diff patients that are coming from the community with severe C. diff infections. So I think that we need not only more effective antibiotics, but also more safe antibiotics that

don't alter the microbiome and are well tolerated by patients.

We want more antibiotics that don't have high risk for C. diff. Thank you.

DR. BADEN: Thank you. Will speaker number 2 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. BATTLES: Yes. My name is Scott Battles. I represent the C. Difficile Foundation. I just want to preface with, Paratek paid for my travel, but I have no financial interest in this meeting.

I would just like to say good afternoon. As I said, my name is Scott Battles, vice president of the C. difficile Foundation, educator of renewable energy technology. Speaking as a patient advocate who recognizes the detrimental impact of some antibiotics, the C. diff Foundation is not only to share our experiences, but to raise awareness of the lack of therapeutic options for healthcare providers to treat patients safely and effectively

without causing harm.

New antibiotics are needed and ones that will not promote or be associated with CDI. Over a decade ago, I suffered a long and drawn-out upper respiratory infection. I was given amoxicillin 3 times over two months. It was ineffectual.

I gave up and hoped that I would slowly get better. Six months later of the illness, I was gaunt and looked like walking death. Needless to say, I felt the same way. I decided to revisit my primary physician and requested that chest x-rays be ordered. Despite three previous courses of antibiotics, the doctor told me it was simply allergies.

I strongly disagreed and was very persistent that he take a chest x-ray. He came back with an x-ray in his hand and his head down. He sheepishly announced I had walking pneumonia. And most likely, I had it for 6 months. Tetracycline was then ordered and resolved the illness in a few days.

Subsequently, I developed chronic mild

pneumonia. It would be treated with broad-spectrum antibiotics. The symptoms were often unresolved and lingered for 3 months or more. Persistent coughing for months left my lungs inflamed and my chest sore.

I then started to develop severe allergies. The environmental allergies and subsequent frequent respiratory infections reached the point of almost shutting my respiratory system down. Breathing became a chore and exhausting. Being treated with repetitive broad-spectrum antibiotics had minimal therapeutic effect. It was exhausting and it was frustrating. After a decade, I'm somewhat better. And what I know is we need new, safe antibiotics to combat infections and reoccurrences that occur.

In terms of safety of antibiotics, as I said, I'm vice president of the C. Diff Foundation, and in my lifetime, I've encountered numerous friends and families that have been diagnosed with major infections, including C. difficile.

One of my coworkers' 7-year-old acquired a C. difficile infection during an inpatient stay at

the hospital. Another coworker caring for her elderly grandfather was diagnosed with CDI. She was a mother, wife, and full-time administrator at my work. She suffered immensely.

The symptoms associated with this infection mandated that she take frequent bathroom breaks. It eventually caused her to resign and shifted her home chores and duties to her husband. The loss of wages placed a severe impact on her family, and it affects her adversely today. It took 5 rounds of antibiotics to treat this GI infection, which left her with many unresolved side effects.

Nancy Caralla, the founder of the foundation, a nurse, two-time survivor of C. difficile, survivor who witnessed the death of her father from unresolved major infections, including CDI and the pain and suffering caused by two years of infections for herself, envisioned this organization to help others from enduring this life-altering journey and loss of lives. One infection and one lost life is too many.

The C. Diff Foundation was brought to

fruition on November 1, 2012. The foundation is a nonprofit dedicated to educating, advocating for C. difficile treatment, clinical trials, environmental safety, and support worldwide.

The dedicated members around the globe also educate and advocate for antibiotic awareness and a need for new antibiotics for tools physicians can utilize and ones that have a therapeutic value without adding CDI.

CDI is developed from antibiotics prescribed to treat symptoms and the most common medications are known to cause this infection are broad-spectrum antibiotic, including clindamycin, quinolones, ampicillin, and other broad-spectrum antibiotics.

The majority of calls received by the foundation on the nationwide hotline are patients explaining the symptoms and how CDI was acquired from being prescribed clindamycin by their dentist for oral infections prior to undergoing oral surgery.

From our experience, it seems that

tetracyclines are among the lower-risk antibiotics associated with CDI. According to an article recently published in the Clinical Infectious Diseases, tetracycline antibiotics, specifically doxycycline, were shown to be associated with lower risk of Clostridium difficile infection compared with other antibiotics.

My full-time vocation, teaching wind energy and industrial maintenance, causes me to constantly preach to my students, but one thing I tell them frequently is don't use a big hammer when a small tap will suffice. In my opinion, I've seen the damage caused by these broad-spectrum antibiotics. They're a big hammer when a small tap will suffice. Today, I ask the panel to consider the greater good of the general public in supporting the right tool for the job for physicians. Thank you today for this opportunity to speak.

DR. BADEN: Thank you. Will speaker number 3 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. VAN HISE: Hello, everyone. My name is Nick Van Hise. I am here also on behalf of the C. Diff Foundation, where I am the committee chair for the antimicrobial stewardship and C. diff prevention committee. I am also an infectious disease pharmacist at Metro Infectious Disease Consultants, and I run the research portion for Clostridium difficile and antimicrobial resistance.

I would like to disclose that Paratek did pay for my travel today, but I have no financial interest in this meeting. And then I am also on the speaker bureau for Melinta Therapeutics and Merck.

I have spent countless hours in infectious disease, primarily Clostridium difficile and antimicrobial resistance. I have done antimicrobial stewardship now for the last eight years, and the problems that I see in everyday world are countless.

There is multiple times that I am not able to discharge a patient a week in combination with the physicians that I work with because of

antimicrobial resistance and the lack of options available. I would like to give a patient case just as an example of the issues that we interact with.

This was a patient who was a 60-year-old male, who did have typical insurance. He had a diabetic skin soft tissue infection, which would have met the ABSSSI requirements, and he had an abscess that was trained. It grew in EBSL and a vancomycin intermediate Staph aureus.

He was placed on telavancin and ceftolozane/tazobactam for 7 days. After the abscess was drained, it continued to get better, although he was not able to be discharged due to insurance and the lack of availability in the outpatient setting.

He ended up developing recurrent hospital-acquired C. diff due to being in the hospital for multiple days along with being on broad-spectrum antibiotics. His morbidity was dramatically affected due to all of these different factors.

The importance of having oral antibiotics

and multiple options for antimicrobial resistance is extremely important, and I strongly advocate for companies like Paratek and any other pharmaceutical company out there to develop new antibiotics, especially IV and oral, in order to make options dramatically available for our patients.

I thank you for being here today and thank you.

DR. BADEN: Thank you. Will speaker number 4 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GIORDANO: My name is Philip Giordano. I have practiced emergency medicine at the Orlando Regional Medical Center for the last 25 years, where I'm currently vice chairman. I received travel expenditures from Paratek today, and I've done consulting work for them in the past.

Having said that, what I wanted to talk about today is just a very general need for more antibiotics that treat pneumonia. Many of the things that I was going to say have already been

said, and Dr. Kaye and Dr. Mortensen said it quite a bit better than I could have. So what I'm going to do is focus more specifically and very briefly on the challenges we face in the E.D. with respect to that.

So you might think that emergency physicians, with the fast pace and chaos of the E.D., are not really into scoring systems. If you think that, you'd probably be correct. However, one exception to that is the PORT score.

Ever since the work for the Pneumonia Outcomes Research Trial came out, emergency physicians have embraced that. We every day have to risk-stratify patients and decide who can go home, who has to stay in the hospital. If this person goes home, who's going to second-guess me after the fact? And having such a great scoring system that really stratifies risk so well for a particular disease has been very useful for us. So we definitely use the PORT score.

If I'm going to try to speak to what happens in emergency departments, I have to speak to where

there's some consistency. If you look at PORT Is and IIs in any emergency department in the country, those patients tend to go home. They tend to go home on oral antibiotics, and the most common antibiotics used are doxycycline and azithromycin. Because mortality in PORT Is and IIs is low enough, we don't see a lot of bad outcomes even though those drugs are probably ineffective in some of those patients.

If you look at the IVs and Vs in any E.D. in the country, they obviously get admitted on multiple IV antibiotics, sometimes to the ICU. So it's the PORT IIIs where you have variability in treatment, and obviously that's the largest group.

The more cavalier and those with very high intestinal fortitude may try to send a PORT III home on oral antibiotics, clearly looking at the mortality risk, it's something that was considered. IIIs can be outpatients if they can be treated correctly. But what we have available now makes it very difficult to do that. So if you send them home on doxycycline or azithromycin, you really are

risking a resistant bug or a bad outcome.

That's actually not a very common practice right now. What's more common is for patients to get a dose of ceftriaxone and either doxycycline or azithromycin and then possibly get sent home on pills, where really only their first 24 hours is guaranteed or be admitted to the hospital after that.

But what happens most commonly to those patients is they get ceftriaxone and azithromycin and get admitted to the hospital. And you may be asking about observation and things like that, but to be honest, at most hospitals, observation is a status. They end up going to the same inpatient bed and they just are under observation status.

So under the current crisis that we have with overcrowding in the EDs and trying to increase our throughput, as a public health crisis right now, we are looking for appropriate and equal care options that don't put the patient up in that bed.

So I think honestly a pneumonia drug that's both potent and available in both IV and oral form

could be a game changer for us. How do I know that? Because it was in the past. In the late '90s and early 2000s, when the respiratory fluoroquinolones came out, we used levofloxacin and moxifloxacin to actually send many more people home than we ever did before. There was definitely a change in behavior. People would get sent out on P.O. or they'd get an IV dose and get sent out on oral.

Even the behavior of the community physicians changed. If the family medicine or internal medicine doc by physical exam thought they had a patient with pneumonia, currently they send that patient to the ED with the thought that if their chest x-ray shows pneumonia, I already think they need to be admitted.

During the time where they were using a lot of fluoroquinolones, they actually would just treat those patients in their office and not send them to the ED. But what happened there is we obviously probably used fluoroquinolones a little too much. We started to see the collateral damage, decreased

sensitivities with pseudomonas, and then on top of that, the C. diff risk.

So with large academic medical centers like where I work, where antimicrobial stewardship is very strong, we've severely restricted fluoroquinolone use. So I don't really have that available to me, appropriately so, so we've gone back to admitting most of the patients.

So I really think that if we could get new agents again that are available in IV and oral form, and are potent, and could give us the confidence to treat people as outpatients, then we'll start doing that again.

So I really appreciated the chance to speak to the committee. Thank you very much.

DR. BADEN: Thank you. Will speaker number 5 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. THERIAULT: Hello. My name is Nicolette Theriault, and I'm here as a patient advocate and MRSA survivor. For my disclosures, Paratek paid

for my travel, but I have no financial interest in the outcome of this meeting.

As opposed to all of the other people who have spoken to you before, I don't have a lot of medical experience per se, but what I would like to share with you is my experience with recurrent MRSA infections. Resistance to antibiotics and prevalence of MRSA is widespread, and research and data tell one portion of the story, but the part of the story that is often lost is that of the patient and how a recurrent MRSA infection can be debilitating and really affect your life.

The beginning of my spring semester as a student at a university, I was brought to the ER. I don't remember getting there. I was diagnosed with MRSA. I had a large infection and very, very, very large cellulitis spot on my upper left buttock, which is a very fun place to have that infection.

The infection was cleared out and stuffed, and I was sent home with antibiotics and instructions on, "In a couple of days, you take

that packing out." They don't tell you how much that will hurt.

Three days later, I was having a follow-up appointment with a surgeon, and he saw the infection. He saw the cellulitis was growing and said, "Okay. Let's take that out. Let's do some more of that." That was without anesthetic pretty much, so that was a good time.

So I basically had an incision that was about 7 inches wide and about 2 inches deep, and gauze was put on that, I was sent home, and I proceeded to spend the next few weeks cleaning that, putting new gauze on, tilting to the right a whole bunch.

I returned to college classes. I was also interning in New York City and having to travel on a 2-hour train ride both ways a couple times a week. So on top of making everyday life pretty uncomfortable, and painful, and irritating, I was tired. It was tremendously exhausting to be continuously fighting an infection.

Probably about 2 weeks after being in the

hospital, the hospital called and said, "We got your lab results. You in fact have MRSA and the antibiotics we gave you are not going to work." So they gave me a new course of antibiotics, which I believe may have been oxacillin. I'm not sure. It seemed to be healing up and clear out. And about 6 or 8 weeks later, the infection seemed to have returned, and I ended up having another surgery. They at least knocked me out for this one.

So I had to start the process all over again. So that was recurrent infections and surgical procedures over a course of about 4 months. I did manage to graduate on time, surprisingly. I probably should have taken a semester off, but I did not.

To follow up with that, about 7 years later, following shoulder surgery, I also then got a few suspicious infection sites and proceeded to spend about 18 months on and off being treated for additional MRSA infections. This was located more so on my torso and in my arm pit. And I actually had two infection sites combined that I could

barely put my arm down because it was so painful.

The last time I had one of the infection sites cleaned out was actually the night before my best friend's wedding, where I was supposed to be the matron of honor. I did attend the wedding as the matron of honor with a nice gauze pad under my arm, which I managed to hide while wearing a strapless dress.

But essentially, what I wanted to share was how challenging it can be for a patient to continue leading a normal life while having recurrent infections, and that if the doctors I had seen had better options for treatment, ideally it wouldn't have been a recurrent event to be going back to the doctor, having an infection site dealt with, and being on antibiotics again, being on a series of antibiotics.

Up to 5 times in 18 months is pretty unpleasant. So having antibiotics that are effective that could make patients' day-to-day lives better or if they could avoid hospital stays would really make a difference in the lives of

patients who have skin infections and have to deal with MRSA. Thank you very much for your time.

DR. BADEN: Thank you. Will speaker number 6 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. MEHTA: Hi. My name is Seema Mehta. I'm from Johns Hopkins Hospital. I'm a transplant and oncology infectious disease physician there. I must disclose that Paratek paid for my travel, but I otherwise do not have any financial interest in the outcome of this meeting.

Today, I would like to impress upon you the dire need for new antibiotic agents in the era of rising multi-drug-resistant organisms. As an infectious disease physician, I repeatedly encounter patient cases where the organism at play is one that is highly resistant to our available drugs.

These cases often require the use of highly toxic agents, which may only partially be effective against the etiologic organism. For example, I had

a patient who received a bone marrow transplant. She subsequently developed vancomycin-resistant enterococcus bloodstream infection and pneumonia.

Unfortunately, the only drug that was available based upon microbiologic sensitivities to treat both of these entities is also highly bone marrow suppressive when given at prolonged durations.

She had not yet engrafted her bone marrow transplant. In other words, we were waiting for count recovery. In these scenarios, we often continue antibiotics until count recovery or engraftment.

As mentioned, the drug available to treat these infections, her bacteremia and pneumonia, is marrow suppressive. As a result, she ultimately did not engraft and she lost her transplant. Her only life-saving therapy, a bone marrow transplant, failed at the hands of an agent that is toxic to the bone marrow. She eventually passed away from her underlying malignancy because of her failed bone marrow transplant.

If we had an agent to treat her that did not suppress the bone marrow, she may have survived and she may be still living with her now 7-year-old son, enjoying his birthdays, his company, and watching him grow into someone she could be proud of.

Another example I have is one where I had a patient who had undergone a liver transplantation. Several months after transplantation, he presented with acute rejection of his liver. He was admitted to the hospital and was being treated for such.

Several days into his hospitalization, he developed fever and a new oxygen requirement. He was found to have a pneumonia with an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae.

He began therapy with the antibiotic of choice for this infection. However, he subsequently developed seizures thought to be due to the lowering of the seizure threshold from the antibiotic he was receiving. Unfortunately, we had to change his antibiotics to a different agent.

However, with this new agent, he subsequently developed acute kidney injury and ultimately required dialysis.

He fortunately survived, but has ongoing dialysis needs. His quality of life is greatly diminished because of this. If we had a better agent that was not toxic to the kidneys and did not lower the seizure threshold, he likely would have recovered without incident, and his quality of life thereafter would have been preserved.

This illustrates two cases of desperate need for new, better agents to treat common infections. Although I only describe two cases, I have witnessed many deaths due to the lack of antibiotic therapies to cure multi-drug-resistant infections.

In the cases where life is sustained, the adverse effects of the antibiotic agents used often portend a greater mortality on top of the mortality and morbidity of the infection alone. As a result, the quality of life of the patient suffers and their remaining days are often spent connected to dialysis machines, ventilators, and other life-

sustaining measures.

This is just at the patient level, which in my opinion is a microcosm of the greater problem at hand. We are seeing these highly resistant infections due to a variety of environmental and societal exposures to antibiotics.

Although this public health aspect of the fight is a separate campaign, the battle I fight on a daily basis entails one where we are in desperate need for newer, better, stronger weapons in our armamentarium. I believe that we as a scientific community are faced with the moral obligation to better serve our patients and our community as a whole. It is my opinion that the bacteria cannot win this fight. We must maintain an upper hand by aggressively devising and approving of new drugs that can be used for common infections caused by resistant bugs.

On many occasions, I have told patients we are using our big-gun antibiotics to treat your infection. In cases where they have multi-drug-resistant organisms causing their infection, I

frankly feel like a fraud naming these antibiotics as big guns, as our big guns are no longer that. They are now in many cases like bringing a knife to a gun fight.

The need for newer drugs cannot be stressed enough. I loathe the days where I have to tell the patients that the drugs we have may not be sufficient for treating their infection or the drugs we have can cure their infection, but not without adverse effects on the quality of their life. The response I get from the patient is often that of despair. It mirrors the situation at hand, a helpless situation with drugs that have outlived their glory days.

In conclusion, I would like to implore the committee to take the necessary steps to approve of new agents that can be used to save lives and simultaneously not have a negative impact on the quality of the life of these patients.

I urge the committee to keep in mind these two patients as they proceed in reviewing in making their decision. I have faith that, one day, we

will win this fight and that, when we use our big guns, we are indeed doing exactly that. Thank you for your time.

DR. BADEN: Thank you. Will speaker number 7 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. BRUNTON: Good morning. My name is Stephen Brunton. I'm a board-certified family physician and geriatrician. My travel expenses have been paid by Paratek, but I have no other financial interests in this meeting and no other conflicts of interest.

I wear many hats. Actually, when you have this little hair, you have to have as many hats as you can. And one of those is I practice family medicine in the Los Angeles area. I have two practice areas. One is a general suburban practice. The other is more of an inner city Hispanic elderly population.

There, we really feel we're on the front lines. We were managing patients that have a

multitude of illnesses, particularly in the Hispanic practice, where we see a lot of diabetes. And these patients present with other comorbidities and so are much more susceptible to the infections we're talking about today, particularly skin infections and community-acquired pneumonia.

I also have the role of executive director of the primary care respiratory group. We are a database of about 4,000 different clinicians, and we're the U.S. affiliate of something called the International Primary Care Respiratory Group, which is an international group of primary care associations and about 14 different European and Asian countries.

One of the things that we have dealt with as an organization is really looking at the importance of antibiotic stewardship and also the concern about the lack of very effective antibiotics. We sponsor an annual meeting of physician assistants and nurse practitioners. As part of our needs assessment, we ask them what are some of the greatest challenges that they have, and one of

those that consistently gets identified is the lack of new antibiotics and the concern about antibiotic resistance.

I think, as in primary care, we're seeing this firsthand. And as we heard from our patient representatives today, we are concerned and increasingly concerned that we're not going to have the antibiotics that we need.

I've been managing primary care patients for a long time, and I've seen an evolution of antibiotics. Actually initially when I started my practice, all we had was sulfonamides and leaches. And we've certainly come a long way since there, but now I think we're seeing, as mentioned, the antibiotics that were providing answers are now no longer providing answers and we need new and more effective antimicrobials. I think part of the situation is the frustration of managing these patients, being on the front line, and not having alternatives.

So I thank you for having me here today, and I encourage support for you to look at how we might

effectively provide these antibiotics, both the oral as well as intravenous for management of these patients. Thank you.

DR. BADEN: Thank you. Will speaker number 8 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. On behalf of the National Center for Health Research, I am Dr. Stephanie Fox-Rawlings. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from the drug or medical device companies, so I have no conflicts of interest.

We greatly support the efforts to develop new anti-bacterial drugs that will be effective against resistant pathogens. However, the data reviewed by the FDA indicates that omadacycline may not be as safe and effective as the drug currently on the market for some specific groups of patients.

In the clinical trial, comparing the effects of the new drug to moxifloxacin to treat pneumonia, moxifloxacin potentially did not work as well or perhaps as quickly for older or sicker patients and patients with conditions like lung disease, bacteremia, and diabetes.

The study used a population with varying underlying conditions, but because of this there were small numbers of patients in these important groups. But these are patients who tend to have more fragile health, so they especially need safe and effective treatments.

Also in this study, there were more patients who took the new drug compared to the old one and, again, these patients with more serious infections, older patients, and patients with chronic conditions, were among those that died.

As you know, other antibiotics have been found to have severe systemic effects, including harming cardiac health, but those serious adverse effects were not determined until years after they were widely prescribed. Many patients were

seriously harmed as a result.

For this reason, the number of deaths needs to be carefully analyzed and any increased risk would need to be included in the label if this product is approved. This is especially true since this drug is not shown to be superior to its comparator for patients on average.

Two final points that may affect the generalizability here in the U.S. and were brought up by the panel, first, analysis of racial diversity and clinical trials is important because limited diversity can raise questions about the generalizability. And finally, there were very few patients from North America, and differences in medical practice could affect the safety and efficacy of use here in the U.S.

In summary, this drug is no better than some other drugs on the market, and it may be less safe or effective for some patients. It is important to conduct further studies to know whether these particular patients should be excluded from the indication. Thank you.

DR. BADEN: Thank you. Will speaker number 9 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

**Clarifying Questions (continued)**

DR. BADEN: Speaker number 9 is not here. Then this will conclude the open public hearing portion of the meeting, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, and we will continue with the clarifying questions that we were pursuing before.

We have two more questions for the agency, and then we'll turn back to the applicant for further clarifications. I think Dr. Ofotokun had a question for the agency.

DR. OFOTOKUN: Thank you. Probably my question can also go to the sponsor of this product. I'm really intrigued by the fact that this product, you can start with IV and deescalate to oral just like you do for the comparators,

moxifloxacin or linezolid.

When you look at the pharmacokinetic data that was presented, the oral bioavailability of this product is about 34, 35 percent as provided by the sponsor, as compared to what we traditionally know about the quinolones and linezolid, which is in the 60 percent to 100 percent level of oral bioavailability.

I was wondering if we have additional PK data for both the IV and the oral formulation. In particular, I would be interested in seeing the trough concentration of this product for both the IV as well as the oral formulation.

The other question I have are two additional questions, the disposition of the product itself. What is the route? How is it metabolized in the body, and how is it cleared? I'm really interested in that.

Then lastly, how much fluid is required to administer 100 milligrams of this product? Does it require high fluid overload? So those are some of the clarifications that I wanted particularly the

sponsor to provide. And if the agency has information, that would be also helpful.

DR. TOERNER: Hi. It's Joe Toerner. We would prefer that the applicant respond, and we can follow up with any additional information.

DR. BADEN: Then if the applicant can add that to the list. We have one more question for the agency, and then we'll turn back and go through this systematically. Dr. Calhoun?

DR. CALHOUN: I hope this is a quick question for the agency. I looked through both briefing documents, and I didn't note it in either of the presentations. And that's a question that has to do with duration of therapy, so the experimental design was to give a loading dose and then give at least 7 days total, but that dose could be continued for up to 14 days.

So the question is, were there differences in the duration of antibiotic treatment between the comparators and the product at hand? And the reason this is of some concern to me is that, presumably, this was a clinical judgment that was

made, when antibiotic treatment had been sufficient to cure the infection or to resolve the pneumonia.

So was there a difference in the duration of treatment between the comparators?

DR. TOERNER: Joe Toerner. The protocol had prespecified criteria by which a patient could be transitioned from intravenous to oral therapy. So we were interested in this issue to look at any potential differences between the treatment groups because this was a prespecified list of criteria that each investigator should have followed in the protocol. It's essentially criteria for clinical stability.

So we did not find any differences between the treatment groups in terms of the timing of transitioning from oral to IV therapy. Approximately 50 percent of the patient population in both of the treatment groups by study day 3 had transitioned to oral therapy.

In terms of the mean number of days for IV treatment overall, it was 5 days for omadacycline-treated patients and 4.4 days for linezolid-treated

patients in the skin studies and 5 days in the pneumonia studies of IV omadacycline and 5.7 days of IV therapy for moxifloxacin.

The mean number of days was 6.4 days for omadacycline-treated patients, and 6.8 days for linezolid-treated patients in the skin studies, and 6.4 days for omadacycline-treated patients, and 5.2 days for moxifloxacin-treated patients in the pneumonia studies.

DR. CALHOUN: So the total duration of treatment was overall no different, not really the transition point between IV and oral, but the total duration of treatment was no different.

DR. TOERNER: There was no difference in the total duration of treatment, which was prespecified to be between 7 to 14 days. And the mean total duration of exposure in the phase 3 trials was 9 days for omadacycline -- and this was overall in the phase 3 development, was 9 days for omadacycline, 8.5 days for linezolid, and 9.6 days for moxifloxacin.

DR. CALHOUN: Thank you.

DR. BADEN: Thank you.

We will now turn back to the applicant, and if you can, from the questions that arose already -- I'm sorry. Dr. Toerner?

DR. TOERNER: Yes, Dr. Baden. There were three outstanding questions that we could provide some responses to.

DR. BADEN: Please.

DR. TOERNER: Dr. Daskalakis asked about a Venn diagram, and we don't have that. But if we can go back to slide number 23 of our presentation, I can walk through some of the issues that were brought up.

So patient number 1, patient number 2, and patient number 4 were characterized at baseline as PORT risk class III. The rest of the patients were PORT risk class IV at baseline. And 7 of the 8 patients had evidence of baseline cardiovascular disease as a comorbid condition.

Then 6 of the 8 patients had evidence of chronic lung disease, but all 6 of those had concurrent evidence of cardiovascular disease at

baseline. And then diabetes accompanied the chronic lung disease in 3 patients.

So if that helps to answer your question.

Then Dr. Swenson had a question about the post-treatment evaluation. The reason we focus on the early clinical response is that this was a noninferiority study, and we feel we only have evidence to support a finding of noninferiority at the early clinical response endpoint. We have no evidence to support efficacy at the PTE evaluation endpoint. So that's the reason why we focused on the ECR endpoint.

As the applicant had presented our findings, too, as you look at the proposed treatment evaluation endpoint in each of the subgroups, there was a much larger proportion of patients who achieved a clinical success at the PTE endpoint, and the treatment differences between the groups became smaller as you look out to that PTE evaluation. But again, because we can't support a finding of noninferiority at that endpoint, we didn't focus on that.

Then Dr. Floyd had a question about the differences between, in particular, bacteremia. The differences had to do with -- we looked at the ITT patient population, and the applicant's analysis looked at the microbiologically evaluable population. So that may explain some of the differences between the two.

DR. BADEN: Thank you.

Now we can turn to the applicant. And if you can, systematically respond to the issues raised.

MR. TZANIS: Absolutely.

DR. BADEN: And as you respond to each issue, if there are follow-on questions, it's probably best to address things thematically.

MR. TZANIS: First question I have is a question around bacteremia and the confidence interval. Dr. Das can review the confidence interval with you.

DR. DAS: Yes. So at ECR, the confidence interval for the bacteremia -- and let me remind you there were 15 patients in the omadacycline and

18 patients in the moxifloxacin group. The confidence interval at ECR was minus 50 percent to 7 percent. And at the post-therapy evaluation, the confidence interval was minus 39 percent to 19 percent; so very wide, given the small numbers of patients in both treatment groups with bacteremia.

MR. TZANIS: Great. Thank you. Next is a review of the bacteremia cases specifically, and Dr. McGovern will review that. We'll start with the skin, and then we'll switch to the pneumonia study. Dr. McGovern?

DR. McGOVERN: Thank you. First, can I have slide number 3 up, please? So we went back and we looked. And unfortunately, there's not enough post-baseline blood cultures to actually calculate a duration of bacteremia.

However, the success of patients with bacteremia can be inferred from the overall clinical success at PTE. And in the OASIS-1 and OASIS-2 trial, you can see there were 3 patients that had bacteremia who were failures; 2 were staff

aureus and one was a Streptococcus viridans group organism.

All three of those patients were failures. In 2 of the 3 cases of the failure, the duration of treatment exposure was only 2 to 3 days. Sorry. In all three, they were either 2 or 3 days.

If we switch over to the OPTIC study for a second, slide number 3 up, please. There were 4 bacteremia clinical failures. Going from top to bottom, there was a Klebsiella pneumonia. The duration of therapy was 2 days. The patient had amikacin given to the patient as of day 1 and through the total duration of therapy for that patient, day 13, so the patient never really had a real evaluation of the Klebsiella bacteremia.

The second patient was a Staphylococcus aureus, which had 14 days of therapy. The patient had documented clearance of the MSSA on day 6 and day 13 and was a clinical success at ECR and EOT. However, the patient traveled back to their home city and missed their PTE appointment, so they were counted as an indeterminate and therefore a

failure.

The third patient was a Streptococcus pneumonia that had a duration of therapy of 1 day. That was the Streptococcal pneumoniae case that Dr. Loh presented that had 1 dose of omadacycline and then quickly went into septic shock.

The final failure is the patient next to bottom on the screen had 2 days of omadacycline. The patient was clinically stable on day 2 and switched to ceftriaxone therapy on day 3.

MR. TZANIS: So staying along the theme with microbiology and specifically MITs associated with the cases that resulted in mortality, Dr. McGovern will review those cases with you, showing you the microbiology in those patient responses and the MICs.

DR. McGOVERN: Can I have slide 2 up? Of the 8 cases who died in the OPTIC study, only 4 of those patients actually had microbiology. The first case was the septic shock patient who had Strep pneumonia in the sputum and the blood, had Haemophilus in the sputum, but the patient most

likely died from overwhelming pneumococcal sepsis.

OMC3 had an acute myocardial infarction on day 2, had a Klebsiella and pseudomonas at baseline. Although the patient did die of the MI per the description of the investigator, it is of note that the Pseudomonas aeruginosa that was also identified at baseline is intrinsically resistant to omadacycline.

OMC4 was the aortic aneurysm rupture that had a Haemophilus influenza with an MIC of 1. It was the only one that had a monomicrobial infection. And as Dr. Loh presented, the symptoms on day 9 were actually more consistent with an aneurysm rupture than progression of the pneumonia.

Finally, OMC7 had an E. coli as well as Haemophilus influenza, post-baseline had multiple organisms identified from blood BAL and respiratory specimens, including a Proteus mirabilis on day 5 and day 6, which was intrinsically resistant to omadacycline, but was susceptible to the meropenem that was given for 10 days as rescue therapy.

MR. TZANIS: Next, we'll switch to mono-

versus polymicrobial response rates at PTE. So I'll ask that the data come up, and then we'll go to the geography response rates.

Slide 1 up, please. Here, you'll see the monomicrobial versus the polymicrobial response rates for both omadacycline and moxifloxacin. The top part of the slide actually shows you overall response rates, which you've seen previously. And as you can see, between monomicrobial and polymicrobial, response rates are high and similar between the treatment groups.

In terms of geography response rates, slide 1 up, please. As you can see, response rates are similar between omadacycline and moxifloxacin across the geography, noting that there are some differences by geography, mainly driven by sample size within the rest of the world and Western Europe, and North America was pulled together with Western Europe. But generally, these data are similar between the treatment groups.

Finally, I'll show you the resistant pathogen data. Slide 1 up, please. This is

specifically from the OPTIC trial, showing you the overall response rate at the very top of the slide, the baseline pathogen identified, and the response rates by the resistant pathogen.

As you can see, the tetracycline response rates are high for both omadacycline and moxifloxacin. And across the board, you see high response rates for resistant pathogens.

Finally, I think there were some questions around oral bioavailability and the IV. And first of all, I'll start with metabolism. So omadacycline is actually not metabolized. It's eliminated primarily through biliary elimination with about 35 percent of it eliminated renally, so no metabolism whatsoever of omadacycline.

In terms of the oral versus the IV, you're correct. As we presented 35 percent oral bioavailability of omadacycline, we've demonstrated exposure equivalence between the IV and the oral, therefore the dose adjustment between those.

To review the PK data around trial concentration, Dr. Lakota will come up and review

that data with you.

DR. LAKOTA: Elizabeth Lakota from the Institute for Clinical Pharmacodynamics, consultant for Paratek. We developed a very robust population pharmacokinetic model using over 11,000 omadacycline pharmacokinetic concentrations collected from over 600 subjects, of which 180 were from the phase 3 studies.

If I could have slide 1 up, please? Here, we have simulated concentration time profiles, over 5 days, for the IV loading regimen on day 1, so these subjects received 100 milligrams IVQ12 on day 1 followed by 100 milligrams IVQ24 on day 2.

Then they switched to the 300-milligram oral regimen on day 3. The medium profile is shown with a solid black line in the lower fifth, and 95th prediction percentiles are shown with the dotted line.

Now, as you can see, the concentrations are similar following IV administration and oral administration following the IV to oral switch.

MR. TZANIS: Finally, I think there was a

question around food effect. At least that's what my note indicated. Is that correct?

DR. BADEN: Is there a follow-on question from Dr. Daskalakis?

MR. TZANIS: I'm sorry. It's 100 mL infusion with omadacycline.

DR. DASKALAKIS: Just a quick question since we are on pharmacokinetics and dynamics. Any data on non-white populations? If you do have that, we'd love to see it?

MR. TZANIS: Yes. Obviously, as you saw from the demography, there's very little diversity in the clinical trial by virtue of where the trial was conducted. We have extensively evaluated omadacycline in phase 1 studies, looking at age, gender, race, and see no difference from a PK perspective.

DR. BADEN: Any other questions on your list?

MR. TZANIS: I think that completes the list we have, Dr. Baden.

DR. BADEN: Thank you. Then is there a

follow-on? We have more questions on the list.

DR. CALHOUN: A follow-on.

DR. BADEN: Please.

DR. CALHOUN: Calhoun. I was pretty interested in your pharmacokinetic accumulation data in the briefing document regarding the accumulation epithelial lining fluid and in macrophages; so a quick technical question of how you measured epithelial lining fluid concentrations.

MR. TZANIS: We conducted a bronchoalveolar lavage study specifically, where we sampled the cells and the actual EOF. So we spin them out and actually look at concentrations intracellularly as well.

DR. CALHOUN: So that works for alveolar macrophages. It's not so good for epithelial lining fluid. You didn't put pledgets in and pick up fluid from the airway lining itself then? You calculated the epithelial lining fluid on the basis of your BAL concentration? Is that right?

MR. TZANIS: That's correct. That's

correct.

DR. CALHOUN: Do you have evidence that the drug accumulates in other cells like, for instance, monocytes or neutrophils? Do you have any PK data on that?

MR. TZANIS: I don't believe we have any PK data specifically. Obviously, there is some accumulation within plasma.

DR. CALHOUN: Versus plasma.

MR. TZANIS: Versus plasma.

DR. CALHOUN: Thanks.

DR. BADEN: Thank you.

Earlier this morning, members of the committee suggested they had questions. We'll continue to go down the list. If your question's been answered, just let us know and we'll move forward.

Dr. Brittain?

DR. BRITTAIN: I think my question was answered.

DR. BADEN: Thank you. Dr. Honegger?

DR. HONEGGER: Just a follow-up on slide 71

in the sponsor's presentation, where they compare the rates of mortality to other clinical trials. I assume the regimens where there were IV treatments, those were similarly ill patients. But I just wondered if you could comment on which of these studies had PORT III predominant with some PORT IV in them. Would you know?

MR. TZANIS: Yes. Generally, these studies that have IV and oral or IV only had very similar patient profiles relative to PORT risk class classification. Where there is some differences in the oral-only arms, there was predominantly almost more than 50 percent in most of the studies for PORT risk class IIs in the oral-only studies.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: I have a question for the sponsor regarding their slide 54. I was curious to just observe. I know it didn't quite reach statistical significance, but for the ATS criteria greater than or equal to 3 patients, especially for ECR, it really seemed like there was a trend towards decreased efficacy. And we see something

similar in the high PORT scores, although it's really more marked with the ATS criteria. We also saw that perhaps signaled towards decreased efficacy against Haemophilus influenza.

I was just wondering if the sponsor had a theory as to the potential mechanism for this observation. Certainly, it could be a chance association, but if it's real, could there be something about the pharmacokinetics or antimicrobial effects that might explain something such as related to patient characteristics, septic patients, protein binding, or maybe time to a therapeutic level, et cetera, that might explain this difference?

MR. TZANIS: From a protein binding perspective, omadacycline has very low protein binding, allowing more free drug to get to tissue, which we actually see as an advantage from that perspective, allowing more active drug.

So we don't think there's a link there at all. We've done extensive evaluation in trying to come up with some analysis to determine if there is

anything, but I think most importantly, we see high and similar response rates both in ECR and PTE.

Specifically, we talk about the ATS response rate at greater than or equal to 3. I would ask Dr. Das to come back up and review that again and give you a perspective from the sample size.

DR. DAS: Yes. So we think that the data support that omadacycline is efficacious at this early time point. What we're seeing is, again, in these subgroups are very small subgroups, so there's expected to be wide variability.

Can you bring up the core slide, please, I believe, with the stabilization of vital signs and anti-bacterials?

In the core presentation, while we're waiting for that slide, what we also presented for those subgroups was other efficacy measures at that early time point, so the stabilization of vital signs and the receipt of anti-bacterials. In both of those analyses, we're seeing very high rates of stabilization of vital signs as well as very low rates of anti-bacterial use.

Can we show slide 1 up, please? With respect to the ATS, 1 patient in both treatment groups received a rescue anti-bacterial. So at that time point, the investigator believed that the only 1 patient in each group was not improving. And then if you look at stabilization of vital signs, almost 90 percent of patients had stable vital signs.

Finally, if you look at change of cardinal symptoms, CABP symptoms by day, slide 2 up, this isn't in the ATS subgroup specifically, but again, what it shows for each of the cardinal CABP symptoms is that the patients are improving by symptom with respect to those 4 symptoms.

Then finally, what we see at PTE, again, once the patient has completed therapy and has been gone out to the follow-up period, we're seeing very high and similar outcome rates.

Slide 1 up, please. So this is the slide again from the core. And you'll see for ATS specifically that we have high outcome rates at PTE. So omadacycline is efficacious in these

subgroups when you look at the totality of the data.

DR. SCHAENMAN: The H. flu signal; any theories about that?

MR. TZANIS: So H. flu; we can go to the core by pathogen response slide. Slide 1 up, please.

As you can see here, from an H. influenza perspective, omadacycline is effective with greater than 81 percent response rate at the PTE for H. flu. And most notably here, you see that's with twice as many isolates identified for omadacycline versus moxifloxacin.

We achieved sufficient exposures to cover MICs of H. flu, which also supports the efficacy of omadacycline against H. flu infections.

DR. SCHAENMAN: But just as a follow-up question, the FDA had encouraged us to look at the ECR rather than PTE, and it was in their analysis that it really seemed more striking. So again, any in vitro data or other speculation about --

MR. TZANIS: No. In vitro microbiology

assessments don't show any delayed response. Again, those are models, but we believe the PTE is actually most relevant as it relates to the pathogen data.

DR. BADEN: Thank you. We have about 10 more of us who have questions. We have limited time, but I've also been advised that we shouldn't vote under pressure. So we need to take a 5-minute bio break, and I will encourage committee members to move quickly so we can stay efficient. So we'll take a 5-minute break.

(Whereupon, at 12:08 p.m., a recess was taken.)

DR. BADEN: We shall resume. I thank everybody for moving quickly during that unscheduled break. We'll resume with questions for the applicant and I think, Dr. Daskalakis, if you still have a question.

DR. DASKALAKIS: My question has been answered.

DR. BADEN: Okay. Then, Dr. Baden.

(Laughter.)

DR. BADEN: The patient that died at day 1, Dr. Loh, you said that it was not related. Now I just want to understand why -- how was the determination made that it couldn't be related to failure of therapy?

MR. TZANIS: I'll actually ask Dr. McGovern to discuss that. That's specifically the Strep pneumo septic patient on day 1.

DR. BADEN: Yes, who died after 1 dose, and the comment was made, "Nothing would have saved this patient." The assertion is that it was unrelated, so I just want to understand the basis for that determination.

MR. TZANIS: Yes. Dr. McGovern can review that with you.

DR. McGOVERN: So OMC number 1, who had septic shock, starting on day 1, the patient actually came in with a PORT score of II or III depending on how you actually calculate it. One of the limitations of the PORT score is that sometimes patients actually can miss some of the threshold criteria by just a point or two.

For example, the pH criteria is less than 7.35. This patient had a pH of 7.36, so missed the number of threshold criteria and actually had -- if they measured it probably a few minutes later, they probably would have been not qualified for the study.

With those things in mind, the patient was likely more of a IV or V, actually. And after the first dose of omadacycline, the patient progressed very rapidly into septic shock. The patient also had a dose of moxifloxacin during that period of time when he was deteriorating.

So it's our belief or the data suggests actually that earlier antibiotics might have altered the outcome, but not necessarily which antibiotic they received.

DR. BADEN: So just on the mortality issue, because that's been a focus of our discussion, in my re-looking at the PORT scoring system, PORT IIIs and IVs, PORT IIIs have a mortality in the 1 to 3 percent range and PORT IV is in the 8 to 12 percent range. Is that correct in the

literature?

DR. McGOVERN: The PORT IIIs generally range between about 1 and 3 percent, and the PORT IVs are generally between 8 and 9 percent roughly.

DR. BADEN: Then if I understand your data, your mortality, just all-comer, without parsing the way we have, was about 1 percent and 5 percent?

DR. McGOVERN: Correct.

DR. BADEN: So the mortality seen with omadacycline was comparable with what would be expected with those PORT scores, and the mortality with moxifloxacin appears to be lower than what would be expected, if I'm reading the data correctly.

DR. McGOVERN: That's correct.

DR. BADEN: Thank you for clarifying.

Dr. Calhoun?

DR. CALHOUN: My question's been answered. Thank you.

DR. BADEN: Dr. Swenson?

DR. SWENSON: This may be for both the agency and the applicant. But to the applicant

first, the data presented on page 36 of your briefing document, it's the early clinical response versus lesion size.

You've told us that you didn't think that there were any important differences with respect to lesion size, but as I look at this, it appears to suggest a very small dose response, possibly in favor of linezolid rather than omadacycline.

Could you comment on that? And maybe the agency does have it, because it does also address some concern that's been raised about those with community-acquired pneumonia that are much sicker, that seem possibly not to do as well.

MR. TZANIS: Absolutely. And Dr. Das can review that data with you. That was table 11 from the briefing book.

DR. DAS: Yes. So you're referring to our table 11 in the briefing book, which is OASIS-1 and OASIS-2. And if I could actually have the slide for OASIS-1, please, if you look at the two studies separately, there does appear to be a trend in OASIS-1 with increasing lesion size. Again, the

subgroups are very small with respect to the 600 to greater than 1,000 as well as the greater than 1,000 groups.

Slide 3, please, up. So this shows the data for just OASIS-1. And again, as you mentioned, there does appear to be an increase in failures with increase in lesion size.

We did similar types of analyses as we did in the OPTIC study, and one of those was to look at, again, receipt of anti-bacterial therapy, or when the physician would feel that the patient was a true failure at that time point.

If we could have slide 2, please. What that showed is very few patients received a rescue anti-bacterial; no patients in either treatment group in the highest area, which is the greater than 1,000 and 3 versus 1 in the 600 to 1,000.

Can we also have slide 2 up? Overall, the lesion size is decreasing by day as shown in this slide. And finally, at PTE, the differences between those treatment groups go away. Slide 1 up, please. So we have high and similar efficacy

rates at PTE by lesion size in OASIS-1.

In OASIS-2, can we have slide 1 up, please? The trend that was seen at early clinical response is not seen in OASIS-2 for ECR. And then slide 2 up, please. And similarly for PTE, we have high and similar outcome rates by lesion size in OASIS-2.

DR. BADEN: Thank you. Dr. Ofotokun?

DR. OFOTOKUN: My questions have been addressed.

DR. BADEN: Dr. Proschan?

DR. PROSCHAN: I don't remember having a question.

(Laughter.)

DR. BADEN: I appreciate the ability to move expeditiously. Ms. D'Agostino?

MS. D'AGOSTINO: I have just a quick question about the nausea and vomiting, just thinking about compliance. Can you just clarify, did that resolve by day 2 after the loading dose? And also, you may not have information on this, but was there any effort made to control that effect?

MR. TZANIS: So in fact, the loading dose completed on day 2 and nausea and vomiting rates resolved subsequent to that. In terms of patients tolerating it, patients were able to tolerate without discontinuation, which I think is most notably important.

Then your question was whether there was an attempt to mitigate the nausea and vomiting. In some patients, there was an attempt to use antiemetic therapy, which didn't seem to have an impact.

DR. BADEN: Dr. Gripshover, you have a follow-on?

DR. GRIPSHOVER: Yes. I just wondered, if they threw up their loading dose, did you have them take it again? Because I think it's hard for us to know what --

MR. TZANIS: Absolutely, yes. So the instruction was, if it was obvious that they had actually vomited up their loading dose, they were to administer immediately. Otherwise, if it was indeterminate, they had to wait 8 hours before the

next dose.

DR. GRIPSHOVER: So you said the antiemetics didn't help and they can't take it with food, either, so there's --

DR. BADEN: Microphone.

DR. GRIPSHOVER: Sorry.

DR. BADEN: No. It was on. Talk in towards it.

DR. GRIPSHOVER: Sorry. Yes. I know they can't take it with food, and you also said antiemetics didn't help. Is that right?

MR. TZANIS: That's correct.

DR. GRIPSHOVER: You don't have any suggestions then for -

MR. TZANIS: No. It appears to be a local tolerability issue.

DR. BADEN: Thank you. Dr. Hennessy?

DR. HENNESSY: Thanks. The sponsor is hypothesizing that the mortality imbalance in the pneumonia indication is due to chance. I'm wondering if it would be a good idea to confirm or refute that hypothesis using observational studies

post-approval and, if so, what the plans are to do that.

MR. TZANIS: Yes. We are fully committed to a post-approval surveillance effort that can appropriately evaluate patient safety. So we would absolutely consider that. And these are discussions that we are just now entering in with the agency.

DR. HENNESSY: There may be members of the committee who would vote differently depending on what those plans looked like if you wanted to share any with us now.

MR. TZANIS: Yes. The discussions are early. They range from a clinical trial potentially to real-world evidence, observation, or potential registries; again, very early. We're just initiating this discussion now.

DR. BADEN: But you're committed to doing follow-on studies --

MR. TZANIS: Absolutely.

DR. BADEN: -- in conjunction with the agency.

MR. TZANIS: Absolutely.

DR. BADEN: We have exhausted the list. Are there any other clarifying questions from the committee? Dr. Swenson?

DR. SWENSON: I think it was introduced very, very early that there was a trial to be done in urinary tract infections. And I wonder if you could comment on why we didn't see that. Obviously, you possibly decided to focus down on two other important areas as well.

Then just a point; it was rather disappointing not to see any methicillin-resistant Staph aureus data in the community-acquired pneumonia group. I know it's not the prevalent pathogen, but I was disappointed we didn't see anything really.

Can you comment on that?

MR. TZANIS: Yes. I'll start with the MRSA. Dr. McGovern can discuss the MRSA rates with you. It typically is very low. Dr. McGovern?

DR. McGOVERN: So while we're waiting for the slide to come up. Whether it's MRSA or

MSSA -- slide 1 up, please -- Staph aureus is still an uncommon cause of community-acquired pneumonia. And in the OPTIC trial, we saw 8 of 11 patients that were cured at PTE for Staph aureus. In the omadacycline arm, that was all MSSA, and there was only 1 subject in the moxifloxacin arm who had an MRSA pathogen. Thank you.

MR. TZANIS: As it relates to UTI, the dossier that we submitted to the FDA was only for ABSSSI and pneumonia. We are currently conducting a phase 2 study in simple cystitis, and we have plans to initiate an acute pyelonephritis phase 2 study later this year. So those are ongoing programs not completed or part of the dossier.

DR. BADEN: Dr. Brittain, you had a follow-on? Turn on your microphone and please ask.

DR. BRITTAIN: From one question before.

Back on the commitment to do a follow-up study or investigation, I guess I was a little unclear about the nature of the study. Obviously, there can't be any randomized comparison, so what kind of analyses could you -- or what can you do?

MR. TZANIS: In fact, there could be a randomized component to it, prospective post-approval study. Again, we could absolutely do that, and that's the types of discussions we'll have with FDA.

DR. BADEN: Yes, and I would encourage randomized with appropriate comparators where possible, in addition to registry since there will be failures in the community that will have to be understood.

Other questions from committee members? Dr. Floyd?

DR. FLOYD: This is a question for you, actually. I'm wondering if there will be opportunity for comment and discussion amongst the panel members before we vote or if you want us to save our comments for at the end when we vote on the questions?

**Questions to the Committee and Discussion**

DR. BADEN: So if there are no more questions for the agency or applicant, we can then move to that phase. And I see no more questions.

So we will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that, while this meeting is open for the public observation, public attendees may not participate except at the specific request of the panel.

So what we can do now before we go to the two questions is, with a discussion amongst panel members, we should not indicate how we're going to vote. It's more to understand aspects of the presentation, leveraging each other's expertise.

After we vote, we all can express our considerations around our votes to help inform the agency about our thinking and issues for them to pay attention to going forward.

I don't know, Dr. Floyd, if there are issues for us to discuss as a committee, not indicating how we intend to vote.

DR. FLOYD: It's kind of a follow-up to points brought up by Dr. Hennessy and Dr. Brittain about there is this safety signal here, and we're wondering how do we get more information about it.

One suggestion has been raised in terms of post-approval studies. And the comments I have are about the study design and kind of interpreting the safety signals.

I think the important context is this is not robust evidence of efficacy from a superiority trial. If it were, I would interpret the safety signals very differently. The evidence of efficacy is from a noninferiority trial. The evidence and the causal inference is indirect. It's based on information external to the trial. It's based on a number of assumptions that are not testable.

Even though the sponsor designed and conducted the trial well and according to FDA guidance, there is residual uncertainty. And at best, we can exclude that this drug is unacceptably worse than the comparator. And I think that context is important for discussing what we see in the safety signals.

So the data are sparse. These trials are not powered to look at mortality differences. I did some back-of-the-envelope calculations, and

maybe the biostatisticians can correct me. But a trial this size can only show a statistically significant difference with a background mortality rate of 1 percent if the experimental drug had a five- to sixfold increase in mortality.

We just simply don't see drugs with that kind of mortality signal. So the fact that we're not doing hypothesis testing and there is not a statistically significant difference, to me doesn't erase that there is a concern.

I think that there are plausible mechanisms. One is through cardiac toxicity, through increased heart rate. I think with an average treatment effect of 5 beats per minute, you have a lot of heterogeneity. And it is very plausible that you have some patients, especially with coronary heart disease, where that's enough to cause off-target effects. We've seen some results in the bacteremia subpopulations, people with larger lesion sizes, where possibly the effect size and the ECR endpoint may be less.

So I think that there are a lot of potential

mechanisms by which there could be a safety signal here. And in my mind, post-approval studies are not the right way to study it. I think that, in this case, it may require a second study. And I wanted to raise that before we all vote because I think that's one option for how to get more information about is there a mortality effect versus doing post-approval studies, trials, or observational studies.

DR. BADEN: So I guess a question to the agency is any advice on how to balance the level of evidence, given the study design, and the difficulty of evaluating rare signals; just by the fundamental nature of the design, any guidance on how to weigh that.

Dr. Proschan?

DR. PROSCHAN: And just to follow up, it would be helpful for me to hear from the MDs about the trade-off of how important is it to have another drug available versus potential safety. We hear about the armamentarium. It's important to maintain an armamentarium. And I'd just like to

hear a little bit about that, how important that is versus off-setting with a safety signal.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: I guess I'd also make the comment that unless there was a really large mortality difference, it would be very hard to design a study to detect what that effect is, unfortunately.

DR. FLOYD: So related to that, I did some additional calculations. The baseline mortality rate was quite low in this trial. The sponsor provided data comparing to contemporary trials in CABP.

If you had a baseline mortality rate of 2 or 3 percent, you could conduct a trial of the same size and find a threefold difference. I'm not talking about a 30- or 50-percent, but to exclude large differences in mortality. If that's a goal of a second trial, it can be designed to do that, and I think we could advise the FDA on how to do that.

DR. BADEN: So I guess, in struggling with

this, as we all are, trying to figure out the ruler, is the ruler the comparison between the two arms? Is the ruler what we know goes on with this kind of condition? And that's where trying to understand the PORT score, at least for me, is figuring out, is it that there's an increase in the new treatment or decrease in the old treatment?

How do we weigh that? Because, as Dr. Toerner said, when you're in a study, you're different. Everything about being in a study is different, but yet, I'm struck by how reduced the mortality rate was for the PORT score. And I'd be interested in your thoughts on how do you weigh internal/external data on such a key parameter. But they tried to with the PORT score by stratifying.

DR. FLOYD: I agree. And I think the internal comparison that preserves the power of randomization is the most critical comparison. I think similar discussions were had over a decade ago with naproxen and Vioxx, where one explanation for low rates of MI were, oh, naproxen is just

cardioprotective. And I think that we have to focus on the randomized comparison.

There are lots of reasons why people in the comparator group may have had low mortality rates. It could have to do with geography, the clinical trial recruiting sites, the types of patients. But in my mind, the most important comparison is the randomized one. And I think there are things you can do to target patients who are at high risk.

I think the sponsor carefully pointed out, or the FDA, that 7 out of the 8 deaths in the experimental arm all had existing cardiovascular disease. If we're worried about both off-target potential cardiovascular effects, potential on-target effects in terms of reduced efficacy for severe infection, you can enrich a trial with higher PORT score patients or people with comorbidities. And I think those are the types of discussions that might be informative. If you were to require another trial, how could you get the most information out of it? And I think there are ways to do it without exorbitant sample sizes.

I think on the order of what was done with the current phase 3 trial we're seeing.

DR. BADEN: Dr. Proschan?

DR. PROSCHAN: This is part of the reason that I asked the question I did about the trade-off of how important it is to have another antibiotic because you may believe that this drug, omadacycline, has a higher mortality than moxifloxacin, but you may also believe that -- I'll call it moxi so I can pronounce it correctly. But you may also believe that moxi tends to have lower mortality than compared to other drugs that are being used.

So if it's really important to have an additional antibiotic out there, then you might say, even though I think the evidence is suggestive that there could be increased mortality compared to this one drug, I think there could be benefit. That's part of the rationale for why I asked my question.

DR. BADEN: Yes. And I think we need to have the discussion as how do we clarify issues and

not how we may vote. From my perspective as an infectious disease practitioner, having antimicrobial active agents for emerging -- for increasing spectrum of bugs and resistant organisms that are relatively easy to administer is not a trivial issue. It's actually quite important, as some of the speakers raised.

On the other hand, we don't want to accept excessive risk, and how do we balance that? And I'm sure that's why we're here. But the emerging antimicrobial resistance, at least in my view, is not a trivial issue, but I'm interested in others' thoughts on that. Dr. Calhoun?

DR. CALHOUN: So death is a hard outcome and we, as you rightly pointed out, don't want to have an agent that might be associated with an increased frequency of death.

But I think, in looking at safety, it's maybe too narrow to look solely at the death signal. I think the comparator drugs have a considerably higher risk of C. difficile, which is a big deal. I don't see death very much in my

patients, but on occasion, we do see CDI as a consequence of antibiotic treatment.

So I think it's an important thing to make sure that we're not prescribing a drug that would be associated with an increased risk of death. It looks as though those risks are, as the FDA I think rightly pointed out, small and hard to make definitive conclusions on the basis of the data that we've got. But I think the safety issue is a broader issue than just the relatively few number of deaths.

DR. BADEN: Don't know if other panel members wanted to comment.

(No response.)

DR. BADEN: Then we shall move to the voting. I'm sorry. Dr. Brittain?

DR. BRITTAIN: I don't know -- I guess this is an FDA question -- if it's possible to approve and then do the type of study where you would be looking into mortality, and then the drug only stays on the market as long as that looks good. Are there mechanisms for doing that?

DR. NAMBIAR: We have the authority to require studies if we have concerns about safety. So if you're concerned about a safety signal, we can require. And these are called postmarketing requirements, and we do have discussions with the applicant. And it's a requirement. There are timelines around it.

Your question is more if we continue to see a safety signal and we're worried about a mortality imbalance and that pans out in subsequent trials, does the product stay on the market, does it come off the market?

Is that what you were trying to get to? It's hard to answer that right now. Certainly, depending on safety data that accrues postmarketing, there are things that we can do. But again, depending on the signal, whether you strengthen the label further, you typically do things in a step-wise manner, and it also depends on the intensity of the signal.

But I just want to make one point before the committee votes. I think the kinds of discussions

you're having is exactly what we're seeking your input on. Whether risks can be communicated adequately in labeling, how might one communicate that, or is there a need for additional study, I think that's what we are seeking your input on. So I just wanted to make that point.

DR. BADEN: Thank you. And I think in prior conversations, we could suggest to the agency to require a follow-on study. That obviously has other factors that have to be dealt with, but that could be one of the suggestions, is to require a follow-on study. And they would then work with the applicant to help investigate the signal.

Dr. Schaenman?

DR. SCHAENMAN: I have a question, I guess, either to my co-panel members or to FDA, and that's regarding the structure of these two questions that we're posed with. I think it's pretty straightforward to separate the two in terms of efficacy. One of the questions is on the skin and the other is on pneumonia. But when it comes to safety, it seems like that concern is going to

bleed between both studies. And I guess I wanted to get some guidance from fellow committee members or the FDA in terms of applying safety data or concerns between questions 1 and 2.

In other words, should we really look at these two questions completely insular? Is there an air-tight separation between them? Or is safety something that can move between questions?

DR. BADEN: Dr. Farley?

DR. FARLEY: John Farley. I can give that a try. I think I would invite you to think the way we think. So the statutory standards are substantial evidence of efficacy and safe for its intended use. That implies kind of a risk-benefit consideration for the use that's proposed. That's why we've separated the questions by indication. And we would invite you to give us your thoughts regarding the overall benefit-risk as you're considering both safety and effectiveness.

DR. BADEN: Fair enough. And just to work with your question, Dr. Schaenman, in thinking about safety, I share your sense that a drug is a

drug is a drug. You have a blood level; you have side effects.

However, safety might be different depending on the underlying illness. And the signal that we debated is really in the community-acquired bacterial pneumonia. It looked like the skin soft tissue. It wasn't as clear. And maybe that's to do -- we can speculate. The signal itself has opacity and complexity because of the small number.

I look at safety as in toto, but then also might there be modifying factors that might influence it? Dr. Brittain?

DR. BRITTAIN: So I just have a question, which is, would the populations of the skin trials generally be less likely to have pre-existing cardiovascular conditions, et cetera? Are they likely to be different types of populations?

DR. BADEN: I guess how will use be in relation to what was studied, and I think that's an intrinsic question to any study. Has it been de-generalized? So share the uncertainty.

Dr. Weina, you had a comment?

DR. WEINA: I was just going to say, with safety, though, if the signal is there for pneumonia because of the fact that they've got underlying cardiac disease or they have diabetes, I can tell you serious soft tissue, I see that every day in clinic in which I've got an 85-year-old diabetic being sent to me because they've been put on an antibiotic by somebody, and it maybe isn't working as fast as they would like it, and they say, "Fix them." And this is the same population that may be coming in with pneumonia.

So the safety signal, if it's there and if it's really a true safety signal, is going to ding I think that individual as well the pneumonia person.

DR. BADEN: Other discussion points? Dr. Brittain?

DR. BRITTAIN: But at the same time, we're not seeing a signal in the skin trial. Right?

DR. BADEN: We have the data we have.

DR. BRITTAIN: Right.

DR. BADEN: Then how it gets generalized is

always tricky, but that goes for any data set. Dr. Swenson?

DR. SWENSON: I think the point is that in that skin and soft tissue infection trial, the patients were much younger, and I wouldn't carry the same cardiovascular burden of the CABP population.

DR. FLOYD: I think we have a real issue of effect modification here if there is a genuine signal, not just by disease, but by prior cardiovascular disease, age. And these are the types of things that need to be teased out with further study, I think.

DR. BADEN: I think we should proceed to the questions. So we will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will begin flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the

corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO will read the vote on the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to.

We will continue in this same manner until all questions have been answered.

Question number 1. Has the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of acute bacterial skin and skin structure infections? If yes, please provide any recommendations concerning labeling. If no, what additional studies, analyses are needed?

Are there any questions about the question?

(No response.)

DR. BADEN: Then we shall proceed to voting.

(Voting.)

DR. TESH: For the record, the voting is 17 yes; 1 no; zero abstentions; zero no voting.

DR. BADEN: Then we shall start on the left with Dr. Hennessy. State your vote and any comments to the agency about your vote.

DR. HENNESSY: Sean Hennessy. I voted yes. I don't have any comment.

DR. SWENSON: Erik Swenson. I voted yes, and I think the data are solid. You could almost say that, in this case, the linezolid was noninferior to the test drug.

DR. EVANS: Scott Evans. I voted yes. Obviously, there will have to be postmarketing surveillance in terms of the GI effects, the fasting requirements, and ultimately a survival signal, but I really have very few concerns.

DR. BRITTAIN: Erica Brittain. I voted yes. It was a little bit of an uncomfortable yes with the mortality, the possible signal that we're seeing in the other population. But because, at least within this population that was studied, we didn't see any issue with mortality. And the

efficacy results were quite strong. Especially in one study, it's almost significantly better for the drug.

DR. SCHAENMAN: Joanna Schaenman. I voted no. As the one outlier here, I should say I voted no with some regret and taking to heart the comments of the FDA in terms of trying to balance risk and benefit.

I voted no for concerns of safety. I do firmly believe that the sponsor has demonstrated noninferiority to linezolid, has shown effectiveness over a range of skin flora, including MRSA, including relatively large areas of skin involvement in patients with abscess. So that part was excellent. However, the length of treatment was relatively short, 7 to 10 days. It was a relatively young population that was generally Caucasian.

Therefore, although no significant safety signals were shown, as Dr. Weina was suggesting, if this product is used for its intended use, which would be all patients with skin and soft tissue

infections, I think it's likely or possible that with use in older patients and patients with comorbidities, because of the findings in the OPTIC study, we might have a safety signal emerge, and we really lack data in a wide range of racial and ethnic groups.

Were this drug to go to market, I do think that the labeling should indicate that this may not be ideal therapy for patients with bacteremia given the limited data and, again, that it's not tested in older patients or patients who are immunocompromised.

DR. BADEN: Thank you.

DR. DASKALAKIS: Demetre Daskalakis. I voted yes. I think that the sponsors did demonstrate very good efficacy and noninferiority against linezolid. From the future study perspective, I do think that we should consider studies that do look at specific populations, so looking at not just modeling pharmacokinetics, pharmacodynamics in response in African-Americans and others that actually enrolls people of color in

the study. I think that's going to be really important.

Additionally, I think that having vigilance toward any adverse effect signal in folks using this for soft tissue infections is important, and I think postmarketing studies will be important to follow up.

DR. HONEGGER: Jonathan Honegger. I voted yes. I believe the phase 3 trials showed noninferiority to linezolid clearly and had an acceptable and predictable adverse effect profile. I welcome a new option for skin infections, including MRSA, that have an IV to PO option.

Dr. Green might share the same concern. In children, we also have this need and encourage PK safety and tolerability studies in children. And it's noted recently that doxycycline is actually safe at any age in terms of tooth staining. So it may be interesting to look at the likelihood of enamel staining in the younger populations, too, and whether this would be an option for younger children as well.

DR. BADEN: Dr. Baden. I voted yes. I think the data were, as already stated, solid. They demonstrated noninferiority. And there was no evident safety signal in this population. As others have mentioned, I'll come back to the safety concerns next go-around. Dr. Weina?

DR. WEINA: Peter Weina. I voted yes. I'm thrilled about the possibility of having yet another IV to PO option, and I will reserve comments about safety for the next question.

DR. M. GREEN: Michael Green. I voted yes. I think that, as stated, both analyses by the sponsor and the agency demonstrated no issues with effectiveness as demonstrated by noninferiority. The safety signal for this indication looked to be nausea, vomiting associated with the oral loading dose.

The ability to use an oral therapy or transition to oral from IV is a real plus, and the apparent lower risk for CDI is not insignificant. I don't have any specific suggestions for labeling for this indication beyond awareness of the issues

with nausea and vomiting and the need to restrict oral intake around the dose.

I'm not certain if concerns identified with the CABP population should be translated to the label for this indication.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. I'm Barbara Gripshover, and I voted yes. Like others have said, I think that the studies showed that there was clear efficacy in meeting the noninferiority to linezolid in an area where I also am very glad to have new therapies. And there were no safety signals other than the nausea and vomiting with the oral load.

Regarding the label, I do think there's not enough data to support including the words, "Including cases with concurrent bacteremia for Staph aureus." We know that people with Staph aureus bacteremia usually require at least 14 days of treatment and often more in an evaluation for disseminated disease. And I don't think that we had enough data to show that this

drug worked for bacteremia.

DR. BADEN: Dr. Lo Re?

DR. LO RE: I voted yes. I thought the data from the OASIS-1 and 2 trials sufficiently demonstrated that omadacycline was noninferior to linezolid. I thought the subgroup analyses did not reveal really any concerns regarding efficacy and certainly there were very few serious adverse events for this indication.

I think we have an enormous need for additional antibiotics like this, given emerging community-acquired resistance.

DR. OFOTOKUN: Igho Ofotokun. I voted yes for the same reason that has been expressed by other committee members, and I am very convinced about the noninferiority of this drug to linezolid. And I also think there is a need for an alternative agent in this space.

I would also add the caution that we really don't have enough data to recommend this in a certain way. There is soft tissue infection in addition to bacteremia, especially Staph aureus

bacteremia.

I think whatever label is approved, there should be a clear indication that we really don't have enough data to support the use of this drug in cases where the soft tissue infection is complicated by bacteremia.

MS. D'AGOSTINO: Emma D'Agostino. I voted yes for the reasons already stated for this application. I thought that the safety and efficacy were convincing.

DR. BADEN: Thank you. Ms. Nelkin?

MS. NELKIN: My name is Tina Nelkin. I'm a patient representative. Due to the fact of the emergence and rising of antibiotic resistant bacteria, I think it's so important to have more options open to physicians. And I know patients are very concerned about the quinolone concerns, and this would of course address that. Thank you.

DR. BADEN: Thank you. Dr. Calhoun?

DR. CALHOUN: Bill Calhoun. I voted yes for reasons already stated.

DR. BADEN: Dr. Floyd?

DR. FLOYD: I voted yes. I thought that the phase 3 trials showed that the potential benefits outweigh the potential risks, but I do share concerns expressed about use in patients with bacteremia and also the concerns of the potential mortality signal from the CABP trial with sicker and comorbid patients. So I think that information should be communicated in the label somehow.

DR. BADEN: Dr. Proschan?

DR. PROSCHAN: Yes. I'm Michael Proschan. I voted yes for, I think, all the reasons stated so far. GREEN

DR. BADEN: So the summation from question 1 is 17 yes, 1 no. The yeses, the key themes were the two RCTs, data are solid, they met the noninferiority margin. However, much data are needed for many groups beyond what was studied, bacteremic groups, the young, the comorbid. So that will all need to be taken into consideration.

The safety signal for the total portfolio will need to be in the label and clear if this were to go forward, and there was some echoing of just

the importance of having more agents to treat resistant organisms and to have both IV and oral options.

The no concurred with the efficacy signal, but the limitations of the data and the safety concern were significant.

We should now move to question 2. We'll have the same voting mechanism. Has the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of community-acquired bacterial pneumonia? If yes, please provide any recommendations concerning labeling. If no, what additional studies, analyses are needed?

Any questions about the question?

(No response.)

DR. BADEN: If not, then let's proceed to the vote.

(Voting.)

(Pause.)

DR. BADEN: I hope everyone's voted.

Somebody has not voted, so please, everyone,

press your buttons again in case you happen to be that one.

(Voting.)

DR. BADEN: We now have completed voting early and often.

DR. TESH: For the record, the voting result is 14 yes; 4 nos; zero abstentions; zero no voting.

DR. BADEN: So we shall now start from the right with Dr. Proschan. State your vote and any key reasons or guidance to the agency.

DR. PROSCHAN: I'm Michael Proschan. I voted no. This wasn't easy for me, actually, because, again, I have to try and figure out what the benefit of having an additional antibiotic versus the safety signal.

I am concerned about the safety signal. 8 to 3, I don't see how you could feel confident that there's not a problem here. And the fact that 3 of the deaths were very early also bothers me. So I have enough concern that it caused me to vote no, although as I've said, I had a hard time figuring out whether the benefits offset the disadvantages.

DR. BADEN: Thank you. Dr. Floyd?

DR. FLOYD: I voted no, not because I thought there was absolutely convincing evidence from the one trial that the drug is ineffective or unsafe, but because I don't think there's enough information to conclude that it is both effective and safe for the reasons that I've already raised.

I think that there is a way forward. I think that we need more information from a well-designed, adequately powered second phase 3 trial with clear objectives. And in particular, we're concerned about patients with comorbidities who are older, who are at higher risk of bad outcomes. And I think that you can enrich that population to do the trial efficiently.

DR. BADEN: Dr. Calhoun?

DR. CALHOUN: Bill Calhoun, and I voted yes. And let me separate my comments into the efficacy and the safety piece. In terms of the efficacy, I think the data were convincing that omadacycline is noninferior to moxi.

I think there are important advantages to

the omadacycline versus some of the comparators with respect to the non-fatal adverse events. So I think, although this was only one study, it was the pre-determined pathway that the agency outlined for the sponsor, that one study was going to be sufficient so long as there was a study in a different indication, as I understood the briefing document.

So they met the regulatory requirement that the agency had laid out for them. So from the efficacy standpoint, that was a solid yes.

From the safety side, people with community-acquired pneumonia die, and it is of concern that 8 of them died in the omadacycline group and only 3 of them died in the moxi group.

Having said that, it is not impossible that that's a statistical variance. And I think the data that we've got don't exclude the possibility that that's a statistical fluke; that's something that just happened.

I share the concerns that have been expressed that this needs careful monitoring and

follow-up and would encourage the agency to work well with the sponsor to sort out appropriate postmarketing follow-up, whether that's a randomized trial or exactly what that is, that's your expertise. But I do think that the question of increased death in people who have got diabetes, who have got high PORT scores, and are more aged is something that needs to be followed.

So the safety appears acceptable to me in this population, but I think there are some concerns that will require longer-term follow-up.

DR. BADEN: Ms. Nelkin?

MS. NELKIN: My name is Tina Nelkin. And again, I'm the patient representative. It's a little more personal for me. I am a pneumonia survivor, and I was rushed to the emergency room in respiratory failure. I feel that having another drug that's available is so important and the fact that, again, as I stated before, it addresses the quinolone issue. I do think there's always room for follow-up study, so I certainly voted yes.

MS. D'AGOSTINO: Emma D'Agostino. I voted

yes. I'm going to echo what others have said and probably will say. And in postmarketing, I would like to see those higher-risk populations carefully studied. But for me, seeing that mortality rates were in line both with other CABP trials as well as the expected rates by PORT risk class really alleviated the concern a lot.

I agree with Dr. Calhoun that a statistical anomaly is definitely possible with these really low numbers. And I would also echo that I fully recognize that having other antibiotic options is absolutely critical.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted yes for the same reason that has been expressed. I am quite convinced that this drug is noninferior to moxifloxacin. The efficacy data is quite convincing to me.

I also have the same reservation concern about the safety of the product, and I'm reassured by the fact that the applicant has indicated interest in doing an additional postmarketing

study. I would strongly recommend that that should be done, especially in the special population with multiple comorbidities, particularly cardiovascular comorbidities.

I think there is also a need to study this product in a diverse population amongst blacks. I did not see a breakdown of the analysis by sex or gender. It would be really interesting to look at whether there are differences in the way men and women respond to this product.

So these are some of the things that I would like to see, but otherwise, I think there's a need for an additional agent, and I think efficacy has been demonstrated. I think some of the limitations regarding the safety of this product, in especially the elderly and comorbid patients, should be clearly outlined in the package should this product be approved by the FDA.

DR. BADEN: Dr. Lo Re?

DR. LO RE: I thought that the data from the community-acquired pneumonia OPTIC trial clearly suggested that omadacycline was noninferior to

moxifloxacin for both the primary endpoint of early clinical response and that the result was sustained at the post-treatment evaluation.

Recognizing that the mortality difference between omadacycline and the moxifloxacin groups was really the key reason for convening this committee, I thought it was reassuring that the incidences of mortality for omadacycline users with PORT III or IV scores were within the typical ranges for these scores.

I do have concerns regarding the results of some of the subgroup analyses, particularly among patients with bacteremia, diabetes, the more advanced PORT IV scores, and by the etiologic organisms. But I think, as was noted, these were limited really by the post hoc nature of the analyses, the small sample sizes, and the fact that the polymicrobial mixed infections.

Really, none of these analyses shed light on the reasons for the mortality difference. So consequently, I think it might be prudent to warrant additional studies in the postmarketing

setting, preferably both randomized and observational components, to examine these results in larger samples of the subgroups of interest as well as in racial ethnic groups that were underrepresented in these studies.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. I'm Barb Gripshover, and I voted yes. As others have said, I think that this study did clearly meet noninferiority to moxifloxacin. And regarding non-fatal adverse events, it did appear safe as well.

I think the deaths are concerning, although I think it's unclear if it's due to the drug being less efficacious in sick patients with many comorbidities or if it's due to randomization chance, given the very small numbers.

How to reflect this in the label is challenging. and it's not clear that it is worse in sick patients. I suggest a statement acknowledging that there were a few deaths in total, but more in the omadacycline arm, and that these patients were older, had higher PORT scores, and more

comorbidities, including COPD and diabetes.

Like others have said, I think a post-approval randomized study in sicker pneumonia patients would be valuable to answer this question and also to then make prescribers feel more comfortable using in this population; so an incentive for both sides. Thank you.

DR. BADEN: Dr. Green?

DR. M. GREEN: Michael Green. I voted yes. I think both the sponsor and the agency's efficacy analysis show noninferiority, though for proven typical bacterial pathogens, there may be some concerns, but the numbers were small.

At least for H. flu, this could potentially be explained by the association of H. flu with something like chronic obstructive pulmonary disease. But the challenging aspect of this submission is clearly the death signal. And this clearly appears to be occurring in a very high-risk subset with more severe disease at onset, who are older and had one or more additional comorbidities.

The review of the prior comparative trials

for CABP was somewhat reassuring for the death rate seen in the current study and that it was within the expected range, especially given the severity, age, and comorbidities.

We do need additional options for treatment of patients with resistant organisms. Coupling this with the IV to PO option and the apparent decrease in CDI warranted my support.

However, I do think the label should raise attention regarding the use of omadacycline, or however one pronounces it, in patients greater than 65 with severe disease and the presence of key comorbid conditions seen in this study. The label might also raise a bit of concern with bacteremia, though the data to support this are not strong.

Finally, I would strongly support the agency requiring follow-on studies to clarify the mortality signal.

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. I voted yes. Efficacy, as in how things work in clinical trials versus effectiveness, how they work in the real

world, is critically important, and the pharmacology and trial data is comforting to me as to the potential for effectiveness and frankly for both indications.

As far as safety, the only way to be sure that we as a committee can recommend approval of a drug that in the future won't potentially come back to bite the FDA in the backside is to deny all drugs brought to our attention, not really a realistic option.

While no one has yet created the clinical trial equivalent of a crystal ball, I think that the mortality data available has been pretty much flawed both by the agency and by us here today. The reality is we're going to see deaths with really sick people, especially in those with comorbid conditions.

It's comforting to me that this drug is safe and effective within the parameters that we look at normally for infectious disease products and especially given the size of the trial that was done.

Postmarketing surveillance is always prudent and will occur whether mandated or not. There are a lot of watchdog groups out there to keep clinicians, the FDA, and the pharmaceutical industry honest eventually. Additional studies in those with cardiac conditions, COPD, and diabetes would be helpful, though.

DR. BADEN: Thank you. Dr. Baden. I voted yes. I won't restate the comments already made. But I think the challenge is not that medications have side effects. They do. There's nothing we'll approve or use, even penicillin, that has lethal side effects. The question is how to minimize overuse, which is antibiotic stewardship, and how to understand those side effects so they are kept proportionate for the disease they are treating.

Community-acquired pneumonia with high PORT scores is not a trivial disease with significant morbidity. I think that the safety signal that has been dwelled on by all, as Dr. Calhoun said, it's unclear what it means; small numbers, lot of comorbidity, and complicating features that demands

further follow-up. And I think requiring follow-on studies will make sense and be important.

I think that one needs to bear in mind that there are other risks to antibiotics from C. diff to the requiring an IV in a PICC line, and other kinds of side effects that also have to be weighed as one thinks about what options are available to those of us who are taking care of patients.

I think key subgroups that can be looked at with the data available and will need to be understood in the future are different aspects of the host and different aspects of the pathogen in relationship to the syndrome. But I think that will be evident in the need for the future studies.

I commend to the applicant just the story with Trovan and trovafloxacin to be careful about overuse with side effects can have an untoward effect. And one needs to be careful that the pushing of the use is proportionate to the disease, so if side effects emerge, they can be proportionate to the benefit. And I think that is important for all to pay attention to, so that we

can maintain having more options to treat our patients.

Dr. Honegger?

DR. HONEGGER: Jonathan Honegger. I also voted yes for the reasons that have been mentioned. I was convinced of the adequate efficacy and safety overall, which showed the concerns that others have mentioned in the high-risk subgroups, those with bacteremia.

The mortality excess is obviously a concern. I was reassured by what the norms are in other community-acquired pneumonia studies, people with a similar degree of illness, and also for the lack of unifying mechanisms of death in the 8 patients who died.

So I felt that, overall, the benefits outweighed the risks. And I agree with the labeling and the follow-up recommendations that have already been mentioned.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis. I voted yes, that the omadacycline did demonstrate

effectiveness, noninferiority to moxifloxacin, and the data is pretty clear that it is a welcome addition to the armamentarium for treating pneumonia, and that the risk and benefit needs to be something that clinicians who are using the drug have to weigh.

That reflects the need, I think, for the commentary we've already had around labeling and the need to be transparent about what we do know and what we don't know from the perspective of a signal related to mortality as well as the limits that the drug may have in certain subpopulations that we've heard about from everyone else who spoke, so I won't repeat them.

Ultimately, I think labeling, as well as, again, mandatory, postmarketing studies that include specific focus on those subpopulations, including bacteremic pneumonias as well as individuals with higher PORT scores and cardiovascular disease, will be critical.

Again, I want to comment, it is important to also include a diverse range of people from the

perspective of racial and ethnic background. Thank you.

DR. BADEN: Thank you. Dr. Schaenman?

DR. SCHAENMAN: I'm Joanna Schaenman. I voted no due to concern for safety in the single phase 3 trial data that was presented. Certainly, a new antibiotic in what is a relatively novel drug class, at least for 2018, is very welcomed, especially one that has such convenient dosing and an option for oral dosing, especially in the growing environment of growing antibiotic resistance in C. diff. I think all of us as ID providers are acutely aware of that situation.

My concern is that because these features are so attractive, I feel that once approved, this drug would probably be used widely regardless of the labeling. And to me, that makes it more important for us to be more assured with additional data before approval is granted.

Ironically, a more toxic or an IV-only drug would be easier to restrict compared to one that is once-a-day dosing with an oral pill.

I certainly would vote yes for effectiveness. I think the sponsor's clearly demonstrated noninferiority to moxifloxacin by the prespecified endpoints, although some concerns were raised previously regarding efficacy in older patients and in more severe episodes of pneumonia.

In terms of additional studies, given the safety concerns, as was mentioned by Dr. Floyd, it would seem prudent to conduct additional studies to ensure that the safety signal observed is not a real issue. I'm specifically talking about the death signal, again, because of the large number of patients who would likely receive this drug, including older patients, who might be at increased risk for adverse events and who might currently have other antimicrobial options, although those might require hospital admission.

I think it was very notable that the safety signal was, again, seen in older patients who had comorbidities, including lung disease, cardiovascular disease, and diabetes, and that the events, although not clearly causally related to

the drug, were nonetheless respiratory and cardiac, which is, again, intriguing given that heart rate increase noted in day 1 and 2. I just think it's interesting.

Certainly, it's very possible that, as the sponsor suggested, this was due to chance. And I am aware that for these ill patients, there is a certain mortality rate that would be expected. Nonetheless, it'd be very reassuring for me and others to see a repeat randomized controlled study to confirm that the safety signal does not exist. I certainly hope that it does not, as again this would be a wonderful drug to add to the medications that we have.

As was mentioned by several people, I think it would also be reassuring to see that it could be used safely in racial and ethnic groups that are more representative of the U.S. population.

I think the labeling should mention the limitations in terms of antimicrobial spectrum of coverage, lack of efficacy against pseudomonas and the other SPICE organisms, that it should not be

used for empiric therapy for hospital-acquired pneumonia, nor for polymicrobial infections, nor MRSA pneumonia unless additional data is presented and certain utility in immunocompromised patients; also perhaps not a first-line choice for a critically ill septic patient or patient with bacteremia.

However, as indicated by the sponsor, this would really be an effective option for community-acquired pneumonia, and I believe that this drug does hold real promise for this indication.

I also wanted to mention that, despite the microbial spectrum considerations, I do really think that with increased use of molecular methods for diagnosis, it's going to become increasingly common for hospitalized patients, for us to have a causative pathogen at or near the time of admission. This would allow for informed antibiotic choice and allow the use of a narrow or moderate spectrum drug such as omadacycline and avoid unnecessarily broad antibiotics when appropriate.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: Erica Brittain. I voted no, which is pretty much a 50/50 vote for me. I could have voted either way. It was very hard to vote. And I had the same -- shared Dr. Proschan's feeling about it's really hard as not a clinician to juggle the possible mortality imbalance risk with the obviously importance of getting new antibiotics to the market.

Even though the efficacy is not the reason I voted no, and certainly the overall results are fine, I did want to mention, it is true that there are some -- I had a minor concern about the numerically lower results in the micro-ITT and, again, in the sicker patients, which kind of echoes the issue about the sicker patients in the mortality imbalance. So I did kind of wonder about that, but that's certainly not why I voted no.

Again, the question said substantial evidence of safety, and I felt just barely that there's obviously still an open question about if the mortality imbalance represents the true problem

in the older, sicker patients. So clearly, there needs to be a randomized trial in the older, sicker patients. I do not feel strongly about whether that's premarketing or postmarketing, but there does need to be a trial.

As a final comment, just not about this study, I just wanted to give my appreciation to the FDA about this challenging noninferiority design seems to be a rigorous process to the endpoint definition and the setting of the margins that I very much appreciate.

DR. BADEN: Dr. Evans?

DR. EVANS: Scott Evans. I voted yes. I think I did so with less anguish than some of my colleagues. I think the noninferiority has been well established. I do have some concern about the safety signal, but as Dr. Calhoun said earlier, those of us that care for patients with pneumonia know that sick patients with pneumonia die.

When I look at this list, there's no unifying mechanism, as was stated earlier, and I have to wonder about the possibility of

randomization effects there. Relative to what we would expect based on the CURB-65 or the PSI, these patients did very well. I think it's appropriate to have a randomized evaluation prospectively collected going forward, but I think this is going to be an important drug. Thanks.

DR. BADEN: Dr. Swenson?

DR. SWENSON: Erik Swenson. I voted yes as well. I think in terms of the noninferiority margins, it passes and I have no concerns there within the group that we saw data for. I don't know that we should absolutely discount the vagolytic effect in these older people even though they have less vagal tone in general.

Many of them are probably being given beta agonists and possibly even inhale anticholinergics during their treatment of pneumonia if they have any degree of bronchospasm.

So it could be piling on in a very sensitive group here, and I'd like to see that issue explored a bit further. And I think that could be done possibly in that group enriched for PORT IV, more

ill patients, and that that study I think would be very, very important to also include some of the other weaknesses in patient recruitment that were mentioned as well.

DR. BADEN: Thank you. Dr. Hennessy?

DR. HENNESSY: Thanks. Sean Hennessy. I voted yes. I think that the mortality imbalance should feature prominently in the label until such time as that's been more thoroughly evaluated and disproven.

I think that a pragmatic trial would be useful and complimentary to the explanatory trials that have been done to date in addition to non-randomized studies using real-world data.

DR. BADEN: Thank you.

Question 2, the summation is 14 yes, 4 no. Those in favor, the efficacy was convincing, and that was largely expressed by all 18 of us. There are advantages to omadacycline, met the regulatory requirements. Community-acquired bacterial pneumonia has a high mortality, so the signal seen, it's difficult to understand what it means,

although we all share the concern.

There is a need for more antibiotics for resistant pathogens. There needs to be more data generated on all the different subgroups mentioned with comorbidity, different organisms, bacteremia. And with those data, then we can have greater confidence for use in those circumstances.

The nos agreed with the efficacy, but the safety signal is a concern and wanted more data on the safety signal before this is used more widely, particularly since it is so easily used, the potential for overuse is high, and therefore the risk in that setting is high.

I think that you heard all the other comments, but I think a theme that emerged was that we would recommend for you to require a follow-on study of high quality in a population that is somewhat analogous to where the risk signal was seen.

Whether it's community-acquired pneumonia PORT IIIs/IVs, the specifics of it take more than we can discuss here, but I think the sense that I

get from the committee was that there is a strong sense that we would want to require such data to be generated to help the community understand how to use this safely, studying it in those who are at a higher risk for the events of concern. And that is of course for your consideration.

This concludes the business of the committee, but before I conclude the business, I just want to thank the agency for the amount of energy in the presentations that you presented -- that was a tremendous amount of data -- as well as to the applicant.

I don't know how many backup slides you have, but it's clear to me it's in the 1 [000] to 2,000 range easily --

(Laughter.)

-- with a BU-1038 being the highest one that I saw, but there's the XX series and the double CC series, and the CU series. And the ability to jump between the data quickly and share it with us was incredibly important for us to be able to come to the assessments that we were able to come to, as

you heard.

So I want to thank both parties for presenting a tremendous amount of data efficiently and to rework the data based on the committee's concerns.

I don't know if Dr. Nambiar would like to have any final comments.

DR. NAMBIAR: I do. Thank you, Dr. Baden. I know we are running a little late, but if it's okay with you, can I have a couple of minutes?

I would like to take a few minutes to recognize some of the committee members who will be rotating off the committee later this year. On behalf of the Office of Antimicrobial Products and the Division of Anti-Infective Products, I would like to extend my sincere thanks to the following committee members, Dr. Daskalakis, who is acting deputy commissioner, New York City Department of Health and Mental Hygiene; Dr. Honegger, assistant professor of pediatrics, Ohio State University College of Medicine; and Dr. Lo Re, who is associate professor of medicine at the University

of Pennsylvania; and Dr. Corbett, who is a clinical associate professor at the University of North Carolina. She is not able to join us with the two-day meetings.

We do recognize that your participation at these meetings is a major time commitment that adds to your busy work schedules and also takes you away from your primary work responsibilities. Your participation at the meetings and the advice you provide plays a very important role in our decision-making process and in making safe and effective therapies available for patients.

We thank you for your dedicated service to public health and for your contributions to the field of anti-infective drug development.

Before you're too happy, I just want to let you know we might certainly tap on your expertise at future meetings, depending on the topics at hand, and we do hope that you will be willing and able to participate in these meetings.

Dr. Cox, who's the director of the Office of Antimicrobial Products, could not join us for

today's meeting as he's attending another meeting downtown. He sends you his best wishes and appreciates all your contributions and efforts as well.

Next, I would like to thank all the committee members for very useful advice and robust discussion during today's meeting. I have to admit that we have kept you very busy over the last three weeks, with this being the fourth advisory committee within a three-week span.

Some of you have been kind enough to participate in all of our meetings, so special thanks to those of you who could do that, particularly noteworthy given that they occurred over the summer. So please accept our sincere appreciation for your commitment to this process.

Our thanks also to the Paratek team for their work on these new drug applications; thanks to the speakers at the open public hearing; and many thanks to the FDA review team for all their hard work as well.

Safe travels, and we hope we can give you a

bit of a break in the ensuing few months.

**Adjournment**

DR. BADEN: Thank you. And I would like to echo Dr. Nambiar's appreciation to Dr. Honegger, Lo Re, Daskalakis, and Corbett. Your contributions have been tremendous and tremendously valued.

Some of the committee members have suggested that we take a photo, so for those who have a couple of minutes, if we can come up front, we'll figure out how to take a quick photo. But I do not want to delay anyone else's travel plans. Thank you all for your participation.

(Whereupon, at 1:31 p.m., the meeting was adjourned.)