

Capital Reporting Company
Anti-Infective Drugs Advisory Committee (AIDAC) Meeting 11-29-2012

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (AIDAC) MEETING

8:00 a.m.

Thursday, November 29, 2012

DoubleTree by Hilton Hotel

Washington, D.C. - Silver Spring

8727 Colesville Road

Silver Spring, Maryland

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2

1 MEETING ROSTER

2 DESIGNATED FEDERAL OFFICER (Non-Voting)

3 Diane P. Goyette, RPh, JD

4 Division of Advisory Committee and Consultant Management

5 Office of Executive Programs, CDER, FDA

6

7 ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

8 Diane M. Cappelletty, PharmD

9 Associate Professor of Pharmacy Practice

10 The University of Toledo College of Pharmacy

11 Toledo, Ohio

12

13 Archana Chatterjee, MD, PhD

14 Professor of Pediatrics

15 Chief, Pediatric Infectious Diseases Division

16 Creighton University School of Medicine

17 Omaha, NE

18

19

20

21

22

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1 TEMPORARY MEMBERS (Voting)

2 Wallace Kemper Alston, MD, MPH

3 Professor of Medicine, Infectious Diseases Unit

4 Fletcher Allen Health Care

5 University of Vermont College of Medicine

6 Burlington, VT

7

8 William Calhoun, MD

9 Vice Chair for Research

10 Department of Internal Medicine

11 University of Texas Medical Branch

12 Galveston, TX

13

14 Dean Follman, PhD

15 Chief Division of Clinical Research

16 Biostatistics Research Branch

17 National Institute of Allergy and Infectious Disease

18 (NIAID), National Institutes of Health (NIH)

19 Bethesda, MD

20

21

22

6

TEMPORARY MEMBERS (Voting)
(Continued)

1

2

3 Matthew Goetz, MD

4 Chief, Infectious Diseases

5 Veterans Affairs Greater Los Angeles Healthcare System

6 Los Angeles, CA

7

8 Peter Katona, MD FACP, FIDSA

9 Clinical Professor of Medicine

10 David Geffen School of Medicine at UCLA

11 Los Angeles, CA

12

13 J. Stephen Mikita, JD (Patient Representative)

14 Assistant Attorney General

15 Office of the Utah State Attorney

16 Salt Lake City, UT

17

18 Rodney Mullins (Acting Consumer Representative)

19 Public Health Consultants and Advocates

20 Duluth, GA

21

22

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18 Rodney Mullins (Acting Consumer Representative)

19 Public Health Consultants and Advocates

20 Duluth, GA

21

22

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1 TEMPORARY MEMBERS (Voting)
(Continued)

Judith Voynow, MD

Professor of Pediatrics

Division of PULmonary Medicine

Duke University Medical Center

Durham, NC

9 FDA PARTICIPANTS (Non-Voting)

10 John Jenkins, MD

11 Director

12 Office of New Drugs (OND)

13 CDER, FDA

14

15 Edward Cox, MD, MPH

16 Director, Office of Antimicrobial Products (OAP)

17 OND, CDER, FDA

18

19 Lisa LaVange, PhD

20 Director, Office of Biostatistics (OB)

21 Office of Translational Sciences (OTS)

22 CDER, FDA

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1 FDA PARTICIPANTS (Non-Voting)

2

3 Katherine Laessig, MD

4 Deputy Director

5 Division of Anti-Infective Products (DAIP)

6 OAP, OND, CDER, FDA

7

8 Benjamin Lorenz, MD

9 Medical Officer

10 DAIP, OAP, OND, CDER, FDA

11

12 Scott Komo, Dr.PH

13 Statistical Reviewer

14 Division of Biometrics IV

15 OB, OTS, CDER, FDA

16

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1 P R O C E E D I N G S

2 (8:01 a.m.)

3 Call to Order and Introduction of Committee

4 DIANE GOYETTE: Good morning. First, I would
5 like to remind everyone to silence your cell phones,
6 your Smartphones, any other devices that make noises,
7 if you've not already done so.

8 I'd also like to identify our press contact,
9 Stephanie Yao. She is on her way, not here yet, but
10 she'll be sitting in the front row. If you have any
11 press inquiries, you should direct them to her, and
12 we'll see her later.

13 Right now, I'll turn it over to our Chair Dr.
14 Tom Moore.

15 DR. MOORE: Okay. So I guess I'll call the
16 meeting to order.

17 Welcome, everybody. What we'll do first is,
18 as our first order of business, is to go around the
19 table, have everybody introduce themselves.

20 Dr. Robinson, why don't we start with you?

21 DR. ROBINSON: Patrick Robinson from
22 Boehringer- Ingelheim. I'm the Non-Voting Industry

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1 Representative.

2 MS. CAPPELLETY: Diane Cappelletty,
3 Infectious Disease Pharmacist from the University of
4 Toledo.

5 DR. VOYNOW: Judy Voynow, Pediatric Pulmonary
6 and Director of the CF Center at Duke University.

7 MR. MULLINS: Rodney Mullins, National
8 Director, Public Health Advocates.

9 DR. GOETZ: Matthew Goetz, Infectious
10 Diseases Specialist, UCLA, and VA Medical Center, Los
11 Angeles.

12 DR. KATONA: Peter Katona, Infectious
13 Disease, UCLA.

14 DR. SHYR: Yu Shyr, Professor of
15 Biostatistics, Vanderbilt, University.

16 CAPT PARISE: Monica Parise, Infectious
17 Disease, Centers for Disease Control.

18 DR. ALSTON: My name is Kemper Alston. I'm
19 an Adult Infectious Disease Specialist at the
20 University of Vermont.

21 DR. CALHOUN: Good morning. I'm Bill
22 Calhoun, Professor of Medicine, Pulmonary, and Allergy

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1 Critical Care at the University of Texas Medical Branch
2 in Galveston.

3 DR. CHATTERJEE: Good morning. Archana
4 Chatterjee. I'm a Professor of Pediatrics and
5 Pediatric Infectious Diseases at Creighton University
6 School of Medicine.

7 MS. GOYETTE: I'm Diane Goyette, the
8 Designated Federal Officer for the Anti-Infective Drugs
9 Advisory Committee.

10 DR. MOORE: I'm Tom Moore, Infectious Disease
11 at the University of Kansas in Wichita.

12 DR. KAPLAN: Sheldon Kaplan, Pediatric
13 Infectious Diseases, Baylor College of Medicine in
14 Houston.

15 MR. MIKITA: Steve Mikita, Assistant Attorney
16 General, State of Utah. I'm the Patient
17 Representative.

18 DR. STEVENSON: Kurt Stevenson, Adult
19 Infectious Diseases at Ohio State University.

20 DR. FOLLMAN: I'm Dean Follman, Head of
21 Biostatistics at the National Institutes of Allergy and
22 Infectious Diseases.

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1 DR. KOMO: Good morning. I'm Scott Komo in
2 the Division of Biometrics IV in the Office of
3 Biostatistics at the FDA.

4 DR. LORENZ: Good morning. I'm Ben Lorenz,
5 Medical Officer in the Division of Anti-Infective
6 Products at the FDA.

7 DR. LAESSIG: Katie Laessig,
8 Deputy Director, Division of Anti-Infective Products,
9 FDA.

10 DR. COX: Ed Cox, Director of the Office of
11 Antimicrobial Products, FDA.

12 DR. LaVANGE: Lisa LaVange,
13 Director of the Office of Biostatistics at FDA.

14 DR. JENKINS: John Jenkins. I'm the Director
15 of the Office of New Drugs at FDA.

16 DR. MOORE: Thank you. So for topics, such
17 as those being discussed at today's meeting, there are
18 often a variety of opinions, some of which are quite
19 strongly held. Our goal is that today's meeting will
20 be a fair and open forum for discussion of these issues
21 and that individuals can express their views without
22 interruption.

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1 Thus, as a gentle reminder, individuals will
2 be allowed to speak into the record only if recognized
3 by the chair. We look forward to a productive meeting.

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

9 We are aware that members of the media are
10 anxious to speak with the FDA about these proceedings.
11 However, the FDA will refrain from discussing the
12 details of this meeting with the media until its
13 conclusion.

14 Also, the committee is reminded to please
15 refrain from discussing the meeting topic during breaks
16 or lunch. Thanks.

17 I'll now pass it to Diane Goyette, who will
18 read the Conflict of Interest Statement. Conflict of
19 Interest Statement

20 MS. GOYETTE: The Food and Drug
21 Administration is convening today's meeting of the
22 Anti-Infective Drugs Advisory Committee under the

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1 authority of the Federal Advisory Committee Act of
2 1972.

3 With the exception of the Industry
4 Representative, all members and temporary voting
5 members of the committee are special government
6 employees or regular federal employees from other
7 agencies and are subject to federal conflict of
8 interest laws and regulations.

9 The following information on the status of
10 this committee's compliance with federal ethics and
11 conflict of interest laws, covered by but not limited
12 to those found at 18 USC Section 208, is being provided
13 to participants in today's meeting and to the public.

14 FDA has determined that members and temporary
15 voting members of this committee are in compliance with
16 federal ethics and conflict of interest laws.

17 Under 18 USC Section 208, Congress has
18 authorized FDA to grant waivers to special government
19 employees and regular federal employees who have
20 potential financial conflicts when it is determined
21 that the agency's need for a particular individual's
22 services outweighs his or her potential financial

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1 conflict of interest.

2 Related to the discussion of today's meeting,
3 members and temporary voting members of this committee
4 have been screened for potential financial conflicts of
5 interest of their own, as well as those imputed to
6 them, including those of their spouses or minor
7 children, and, for purposes of 18 USC Section 208,
8 their employers.

9 These interests may include investments,
10 consulting, expert witness testimony, contracts,
11 grants, CRATAs, teaching, speaking, writing, patents,
12 and royalties, and primary employment.

13 Today's agenda involves the discussion of a
14 new drug application, NDA-22407, Vibativ, a Telavancin
15 hydrochloride sterile powder for injections, submitted
16 by Theravance, Incorporated, for the requested
17 indication of nosocomial pneumonia, including
18 ventilator-associated pneumonia caused by susceptible
19 isolates of the following

20 Gram-positive bacteria: Staphylococcus
21 aureus, including methicillin-susceptible and resistant
22 isolates, or Streptococcus pneumonia, penicillin-

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1 susceptible strains.

2 This is a particular matters meeting during
3 which specific matters related to Vibativ will be
4 discussed.

5 Based on the agenda for today's meeting and
6 all financial interests reported by the committee
7 members and temporary voting members, no conflict of
8 interest waivers have been issued in connection with
9 this session.

10 To ensure transparency, we encourage all
11 standing committee members and temporary voting members
12 to disclose any public statements that they have made
13 concerning the product at issue.

14 With respect to FDA's invited Industry
15 Representative, we would like to disclose that Dr.
16 Patrick Robinson is participating in this meeting as a
17 Non-Voting Industry Representative, acting on behalf of
18 regulated industry.

19 Dr. Robinson's role at this meeting is to
20 represent industry in general and not any particular
21 company. Dr. Robinson is employed by Boehringer-
22 Ingelheim.

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

8 FDA encourages all other participants to
9 advise the committee of any financial relationships
10 that they may have with the firm at issue.

11 Thank you.

12 DR. MOORE: Thank you. And with that,
13 we'll proceed to Dr. Laessig's remarks. Welcome and
14 Introductory Remarks

15 DR. LAESSIG: Good morning and welcome to the
16 second day of this Anti-Infective Drugs Advisory
17 Committee Meeting.

18 Today, we have a different topic which is to
19 discuss NDA-22407, Telavancin for Injection, Trade Name
20 Vibativ. The Applicant, as you've heard, is
21 Theravance, Incorporated. Formulation is 250 or 750mg
22 vials for reconstitution, and the dose is 10mgs per kg

1 by intravenous infusion every 24 hours.

2 The proposed indication is treatment of
3 patients with nosocomial pneumonia, including
4 ventilator- associated pneumonia caused by susceptible
5 isolates of the following Gram-positive microorganisms:
6 *Staphylococcus aureus*, including methicillin-
7 susceptible and resistant isolates, or *Streptococcus*
8 pneumonia, penicillin-susceptible strains.

9 So the data contained in this package include
10 two trials, Studies 15 and 19. They were both
11 randomized, double-blind, active-controlled parallel
12 group, multi-center, multinational trials of identical
13 design.

14 The objective of these studies was to
15 establish the non-inferiority of Telavancin to
16 Vancomycin for a clinical response endpoint at the test
17 of cure visit. The pre-specified non-inferiority margin
18 of 20 percent for clinical response was included in the
19 protocol and statistical analysis plan.

20 Note that mortality in the protocols as
21 originally designed was collected as a safety outcome.

22 Together, these studies enrolled

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1 approximately 1,500 subjects with nosocomial pneumonia.

2 So now I'm going to try to walk you through
3 some complicated regulatory history of this application
4 against the backdrop of the evolving thinking and
5 ongoing dialogue for development of products for this
6 indication and hopefully I will not confuse you and
7 myself in the process.

8 So Telavancin was originally approved for the
9 treatment of adult patients with complicated skin and
10 skin structure infections on September 11th, 2009. At
11 that time, it was also under development for nosocomial
12 pneumonia caused by Gram-positive bacteria.

13 In place at the time was a guidance for
14 industry dating from 1998 entitled Nosocomial

15 Pneumonia: Developing Antimicrobial Drugs for
16 Treatment. That guidance did recommend a clinical
17 response endpoint as assessed by the investigator.

18 And as I've said, the pivotal trials, Studies
19 15 and 19, used the NI design, a clinical response
20 endpoint, and they were conducted from 2005 through
21 2007.

22 In July 2008, this committee met to discuss

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1 an Application for Doripenem for Nosocomial Pneumonia
2 and, despite exhaustive efforts by the FDA Review Team,
3 the historical evidence was found to be insufficient to
4 justify a non-inferiority margin for a clinical
5 response endpoint. However, there were data available
6 to justify an all-cause mortality endpoint.

7 Subsequently, in January of 2009, NDA-22407
8 was submitted. Then in April of that year, the agency
9 co- sponsored a workshop with multiple medical
10 professional societies, including the Infectious
11 Disease Society of America, the American Thoracic
12 Society, the American College of Chest Physicians, to
13 discuss all aspects of clinical trial designs for this
14 indication.

15 Importantly, a variety of endpoints were
16 discussed, including clinical response, change in CPIS
17 or other scores, all-cause mortality, PAO2 over FIO2
18 ratio, and some others. But the difficulty remained in
19 justifying an NI margin for endpoints other than
20 mortality.

21 A complete response for NDA-22407 was issued
22 in November of 2009 for the following deficiencies:

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1 the mortality data were incomplete and were
2 missing for 29 to 35 percent of subjects. However,
3 recall that this was not the pre-specified primary
4 endpoint that was being collected as a safety outcome.
5 There was also concern that subjects did not have the
6 disease of interest and the agency recommended that
7 Theravance determine if the study subjects met the
8 criteria for nosocomial pneumonia as based on the
9 American Thoracic Society IDSA Guidelines of chest x-
10 ray findings, plus two clinical features.

11 The applicant resubmitted in June of 2010.
12 They had made a Herculean effort and recovered
13 substantial amount of missing mortality data, so that
14 the amount that was missing was now less than six
15 percent.

16 Unfortunately, about 86 percent of the study
17 population met the ATS IDSA criteria which alleviated
18 some of the concerns that the subjects did not have the
19 disease of interest.

20 In November of 2010, the agency issued a
21 Draft Guidance titled The Hospital-Acquired
22 Pneumonia and Ventilator-Associated Bacterial

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1 Pneumonia: Developing Drugs for Treatment. You can see
2 the link on the slide there is still up.

3 In this guidance, we recommended a 28-day
4 all- cause mortality endpoint. We recommended two
5 randomized controlled studies and an anti-margin of 10
6 percent for the all-cause mortality endpoint in the
7 microbiological intent to treat population, if using an
8 NI design, and the microbiological intent to treat
9 population is the IT population from whom bacterial
10 organism is isolated that is likely to cause nosocomial
11 pneumonia.

12 However, a complete response was issued for
13 the application in December 2010 for the following
14 deficiency: Study 10 did not meet the 10-percent NI
15 margin for mortality based on the MITT populations
16 among subjects with the Gram-positive isolate, and it
17 could either be a Gram-positive isolate alone or Gram-
18 positive with other organisms.

19 Study 19 did meet the NI positive of 10
20 percent. However, it was felt to not be sufficient to
21 stand on its own as evidence of the treatment effect.

22 The applicant submitted a Request for Formal

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1 Dispute Resolution in August of 2011 to Dr. Cox and
2 that was denied. An appeal was submitted to Dr.
3 Jenkins in October of 2011 which was also denied.
4 However, in his response, he recommended a resubmission
5 of the application, convening of this committee, and a
6 consideration by everyone of all the available data,
7 and as he aptly put in his response, "The evolution in
8 the agency's approach to NI trials has been driven by a
9 more complete understanding of the scientific issues
10 that underlie the design, analysis, and interpretation
11 of these trials."

12 Many of you may recall last November we
13 convened this committee to discuss clinical trial
14 designs for this indication. We were interested in
15 seeking the committee's advice regarding comments to
16 the Docket about the Draft Guidance which included
17 concerns about trial feasibility, low rates of
18 mortality, making the mortality endpoint not practical,
19 and trial populations needed to meet the guidance would
20 be too large.

21 This committee recommended that the 28-day
22 all- cause mortality endpoint for an NI trial use a

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1 margin of 1.7 for an odds ratio metric or a 10-percent
2 margin for risk difference, if the mortality rate was
3 20 percent or more.

4 The committee also suggested that a single
5 trial in HAPB or VABP using the MITT as a primary
6 analysis population with adequate support of evidence
7 may be acceptable. To this day, there is still
8 dialogue ongoing about the best way to study this
9 indication, particularly about everyone's willingness
10 to accept more uncertainty and the estimate of
11 treatment effects, such as using a larger NI margin, to
12 make these trials more feasible and to make new drugs
13 available for therapy.

14 Some of the parties involved in these
15 dialogues includes CDER's Antibacterial Task Force,
16 Brookings, and Duke's Clinical Trials Transformation
17 Initiative.

18 Then in July of this year, Theravance
19 resubmitted NDA-22407. So that brings us to today. So
20 the agenda for today is first you will hear several
21 presentations from Theravance, followed by two
22 presentations from the FDA Review Team.

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1 Dr. Ben Lorenz, the Medical Officer, will
2 reiterate some of the salient points of the regulatory
3 history, as well as go over the safety findings, and
4 Dr. Scott Komo, Statistical Reviewer, will discuss the
5 efficacy findings.

6 Then we will have lunch followed by an Open
7 Public Hearing and then the Questions for the
8 Committee.

9 So we have three questions, as you've seen,
10 the first of which is considering the totality of data
11 presented, including analyses of clinical cure and 28-
12 day all-cause mortality, do the results provide
13 substantial evidence of the safety and efficacy of
14 Telavancin for the treatment of nosocomial pneumonia?
15 This is a voting question. We ask that in your
16 discussion of your vote, if you answer yes, please
17 provide any recommendations concerning labeling, and if
18 you vote no, what additional studies and analyses do
19 you believe are needed?

20 We added a second question. Should the
21 committee vote no for the first one, whereby there may
22 be adequate evidence to support a more limited

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1 indication. Therefore, the question is considering the
2 totality of data presented, including the analyses of
3 clinical cure and 28-day all-cause mortality, do the
4 results provide substantial evidence of the safety and
5 efficacy of Telavancin for the treatment of nosocomial
6 pneumonia when other alternatives are not suitable?

7 As with Question 1, if you vote yes, please
8 provide any recommendations concerning labeling, and if
9 you vote no, please describe what additional studies
10 and analyses are needed.

11 The third question discusses or requests that
12 you discuss the nephrotoxicity of this product, which
13 has been established based on the experience with the
14 treatment of complicated skin and skin structure
15 infections, and is labeled in the current package
16 insert.

17 For the treatment of nosocomial pneumonia,
18 are there any additional concerns or further
19 recommendations from the committee, particularly
20 concerning the use in patients with baseline renal
21 dysfunction, and, if so, what are they?

22 Thank you for your attention, and I will turn

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1 it back to Dr. Moore.

2 DR. MOORE: Thanks, Dr. Laessig, for that
3 excellent summary of the complex history.

4 We'll now proceed with the presentations of
5 Theravance.

6 Before we do, I need to read this. Both the
7 FDA and the public believe in a transparent process for
8 information-gathering and decision-making. To ensure
9 such transparency at the advisory committee meeting,
10 the FDA believes that it is important to understand the
11 context of an individual's presentation.

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

20 Likewise, the FDA encourages you at the
21 beginning of your presentation to advise the committee
22 if you do not have any such financial relationships. If

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1 you choose not to address this issue of financial
2 relationships at the beginning of your presentation, it
3 will not preclude you from speaking.

4 Let's proceed now with the presentation
5 from Theravance. Sponsor Presentations Introduction

6 MS. COLEMAN: Good morning. My name is
7 Rebecca Coleman. I am the Vice President of Regulatory
8 Affairs and Quality at Theravance.

9 My colleagues and I are pleased to have the
10 opportunity to present the results of studies
11 evaluating the use of Telavancin for the treatment of
12 nosocomial pneumonia.

13 This morning, you will hear from Dr. Marin
14 Kollef of Washington University, St. Louis, who will
15 share his view on the medical need for additional
16 treatment options in this infection.

17 Dr. Steven Barriere and Mathai Mammen from
18 Theravance will describe the clinical studies conducted
19 to characterize the efficacy and safety of Telavancin
20 in the treatment of nosocomial pneumonia.

21 Finally, Dr. Louis Saravolatz of St. John
22 Hospital, Detroit, will provide his benefit-risk

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1 assessment on the use of Telavancin for nosocomial
2 pneumonia.

3 Telavancin was approved in the U.S. and
4 Canada for the treatment of complicated skin and skin
5 structure infection in September 2009. In November
6 2011, the product was approved in the European Union
7 for the treatment of nosocomial pneumonia, including
8 ventilator- associated pneumonia, known or suspected to
9 be caused by MRSA.

10 Based on sales figures, we estimate that
11 approximately a 125,000 patients have been treated with
12 Telavancin in the U.S. to date.

13 Theravance first met with FDA in mid 2004 to
14 discuss the planned Phase III nosocomial studies.
15 Agreement on the design of the studies was reached and
16 two identical global studies were conducted between
17 early 2005 and mid 2007. The NDA for nosocomial
18 pneumonia was filed in January 2009 and reported the
19 results of the analyses of the pre-defined clinical
20 response endpoint.

21 Later in 2009, recognizing an increasing
22 interest in evaluating mortality as an outcome in this

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1 indication, Theravance made the decision to return to
2 the clinical sites and collect additional vital status
3 data for each participant in the studies.

4 Theravance received a complete response
5 letter at the conclusion of the initial review of the
6 NDA. In the intervening years, Theravance has filed
7 multiple resubmissions and a Request for Formal Dispute
8 Resolution, the appeal that Dr. Laessig described,
9 which resulted in a third resubmission and the
10 scheduling of this advisory committee today.

11 The initial resubmission included additional
12 mortality data collected from the clinical sites. The
13 remaining resubmissions included additional analyses of
14 the mortality data from Studies 15 and 19 and responses
15 to questions about the diagnostic precision of the
16 inclusion criteria.

17 All of this brings us here today to review
18 the data supporting an indication for the treatment of
19 nosocomial pneumonia, including ventilator-associated
20 pneumonia caused by susceptible isolates of Staph
21 aureus and Strep pneumonia.

22 Now I would like to invite Dr. Kollef to the

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1 podium. Medical Need

2 DR. KOLLEF: Good morning. My name is Marin
3 Kollef, and I'm from Washington University in St.
4 Louis, where I am intensivist, and I have research
5 interests in the area of nosocomial pneumonia for about
6 the last 20 to 21 years.

7 I am here as a consultant for Theravance. I
8 am going to discuss the medical need in nosocomial
9 pneumonia due to Gram-positive pathogens.

10 Nosocomial pneumonia is an infection that
11 occurs in the hospital setting with onset greater than
12 48 hours after patients are admitted. It does not
13 appear to be incubating at the time of hospital
14 admission.

15 Ventilator-associated pneumonia is a subtype
16 of nosocomial pneumonia, as illustrated on the Venn
17 diagram, again with onset typically greater than 48
18 hours from the time that patients receive endotracheal
19 intubation.

20 I think it's important to recognize that VAP
21 tends to be a more virulent infection because of the
22 type of patient population in which it occurs,

1 typically meaning the ICU population.

2 The criteria for establishing the diagnosis
3 of nosocomial pneumonia were looked at in 2005 when the
4 ATS IDSA Nosocomial Pneumonia Committee met
5 and the clinical criteria are shown here, requiring the
6 presence of a new or progressive infiltrate on the
7 chest radiograph and at least two of three clinical
8 criteria: fever greater than 38 degrees, leukocytosis
9 or leucopenia, and purulent secretions.

10 The impact of nosocomial pneumonia has been
11 well described. A number of references are shown on
12 this slide. It's the second most common nosocomial
13 infection in the U.S. About five to 10 cases per 1,000
14 admissions to the hospital. Nosocomial pneumonia
15 accounts for up to 27 percent of all ICU infections and
16 VAP develops in approximately nine to 27 percent of
17 intubated patients in the ICU setting.

18 Nosocomial pneumonia is also associated with
19 one of the highest mortality rates among hospital-
20 acquired infections. The all-cause mortality rates are
21 reported to be between 20 and 50 percent. The majority
22 of patients die from their underlying conditions.

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1 However, attributable mortality in VAP has been
2 estimated to be between five and 10 percent and very
3 clearly the development of nosocomial pneumonia
4 increases hospital stays and the costs of medical care.

5 When nosocomial pneumonia is caused by MRSA,
6 one of the issues is the increase in Vancomycin MICs
7 that have been described and they're associated with
8 increased mortality in the setting of treatment with
9 Vancomycin.

10 This is a study by Hack and colleagues that
11 was published in Chest a couple of years ago examining
12 158 ICU patients with nosocomial pneumonia due to MRSA
13 from four U.S. academic centers between 2006 and 2007,
14 and you can see from the graph that mortality increases
15 as the MIC to Vancomycin increases from less than or
16 equal to one to 1.5 to greater than or equal to two.

17 So the use of Vancomycin should be considered
18 with caution when MICs are between one and two and
19 certainly if the MIC is two or higher, alternatives
20 should be considered for therapy in those
21 circumstances.

22 Now we know that nosocomial pneumonia due to

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1 Staph aureus is relatively common in the U.S. This is
2 a slide from Dr. Jones and colleagues published about
3 two years ago from the Century Program outlining the
4 etiology of nosocomial pneumonia between 2004 and 2008,
5 approximately 31,400 cases.

6 You can see that when we group all regions
7 together, Staph aureus is the leading cause of
8 nosocomial pneumonia when you look at it from an
9 individual organism perspective, although Gram-
10 negatives make up the majority when they're grouped.

11 In the U.S., compared to Europe and Latin
12 America, Staph aureus is even more common as the cause
13 of nosocomial pneumonia and this is also true for
14 ventilator-associated pneumonia.

15 When we look at what's happened with Staph
16 aureus in U.S. hospitals, specifically looking at MRSA,
17 we see that the rates of methicillin resistance
18 steadily increased to about the late 1990s, after
19 which, there seems to be a leveling off of rates in the
20 range of 55 to 60 percent.

21 While the NIST has not published this data
22 since after 2004, other more recent studies suggest the

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1 rate of MRSA is stable or perhaps declining slightly.

2 So again in the hospital setting and
3 particularly in the ICU setting, when we're talking
4 about Staph aureus, the majority of these pathogens are
5 going to be MRSA.

6 This data is from a study that we carried out
7 a number of years ago and this has been replicated and
8 confirmed a number of times. We demonstrated that when
9 we look at patients in the ICU setting who develop
10 nosocomial pneumonia, if there is a delay in delivering
11 appropriate antibiotic therapy, meaning an antibiotic
12 regimen that's active against the organism based on in
13 vitro susceptibility testing, those patients have a
14 statistically higher risk of death, almost a twofold
15 increase overall, as well as the attributable
16 mortality.

17 This study and others like it really
18 emphasize the importance of getting early appropriate
19 antibiotic therapy to these patients who are critically
20 ill.

21 Moreover, in this study that was done by the
22 group in Barcelona, by Vidaur and colleagues, you can

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1 see that not all pathogens are alike. Here, we're
2 looking at time to effervescence of fever. The more
3 antibiotic- susceptible pathogens, such as MSSA,
4 Haemophilus influenza, and pan-susceptible Pseudomonas,
5 have a response to antibiotic therapy which is rapid.

6 On the other hand, Pseudomonas that is
7 inappropriately treated initially and MRSA receiving
8 appropriate therapy typically with Vancomycin, these
9 pathogens have a delayed response. This delay is
10 probably related to issues with the antibiotic therapy
11 available for these particular pathogens.

12 The MRSA patients also required significantly
13 longer respiratory support, even though they were being
14 treated adequately at the time.

15 When we look at the guidelines that are
16 available to us, the ATS IDSA Nosocomial Pneumonia
17 Guidelines make the recommendation that for patients at
18 risk for MDR pathogens, combination therapy should be
19 used, including Linezolid or Vancomycin, to cover MRSA.

20 The IDSA Guidelines for Hospital-Acquired
21 MRSA or Community-Acquired MRSA Pneumonia also
22 recommend Vancomycin or Linezolid but note that

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1 Clindomycin may also be an option if the strain is
2 susceptible, although there are limited data to support
3 that.

4 There are some limitations with the available
5 therapies that we have. For Vancomycin, there is
6 uncertainty about the dose that we should be using to
7 ensure efficacy and clearly there's nephrotoxicity
8 associated with increasing doses of Vancomycin,
9 particularly in the ICU setting.

10 There are also infusion-associated reactions
11 and, most importantly, decreasing susceptibility. For
12 Linezolid, it's a bacteriostatic drug. There is a
13 warning about use in catheter-related infections due to
14 mortality imbalances seen in an open label study. There
15 are drug interactions, including monoamine oxidase
16 inhibitors, adrenergic and seroternergic agents, again
17 particularly in the ICU setting, and there are
18 metabolic and hematologic toxicities, and again there's
19 emerging resistance that has developed.

20 Vancomycin is losing its effectiveness. True
21 Vancomycin resistance or VRSA is relatively rare. On
22 the other hand, hetero-resistant VISA is becoming more

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1 common certainly in hospitals, like the one where I
2 practice. Worldwide, estimates are that between five
3 and 15 percent of MRSA are hetero-resistant.

4 Clinical failures with hetero-resistant VISA
5 strains causing sustained bacteremia have been well
6 described and the lack of diagnostic tools precludes
7 rapid detection of hVISA.

8 Additionally, there's a well-documented MIC
9 crepitus occurred with Vancomycin. MICs of 1.5 to two
10 mcgs per ml predict poor response to Vancomycin, both
11 for pneumonia as well as for bacteremia, and 11 percent
12 of MRSA clinical isolates had MICs greater than or
13 equal to two in 2009.

14 Importantly, prior exposure to Vancomycin has
15 been shown to be a predictor for higher MICs to
16 Vancomycin.

17 These are the data from Hauser published
18 about a year ago demonstrating increased proportions of
19 MRSA with Vancomycin, MICs greater than or equal to two
20 mcgs per ml. Almost 20,000 clinical isolates were
21 collected between 2004 and 2009 for both MRSA and MSSA
22 in the Tigacycline Surveillance Program, and one can

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1 see from the results that this MIC creep has also
2 occurred for MSSA.

3 One response to the MIC creep has been to
4 consider increasing the dose for Vancomycin. However,
5 from Tom Lodise's study shown on this slide, we know
6 that increasing Vancomycin dosing can be associated
7 with increased nephrotoxicity.

8 When we look at the rates of nephrotoxicity,
9 they're related to the trough levels. As one goes from
10 trough levels of less than 10 to 10 to 15, 15 to 20 and
11 higher, one can see that the incidence of
12 nephrotoxicity increases and there have been a number
13 of other studies, including one from our own center,
14 that have corroborated this finding.

15 Linezolid also has limitations. It's
16 associated with myelosuppression, including anemia,
17 anleukopenia, pan-cytopenia, as well as thrombo-
18 cytopenia.

19 The drug interactions, such as the serotonin
20 syndrome, I've already mentioned and with long-term
21 use, one can see peripheral and optic neuropathy.

22 There are also new resistance mechanisms that

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1 have been described via the CFR gene on a transmissible
2 plasmid. Cross-resistance to other antibiotic classes
3 with fitness costs has been described for these
4 strains.

5 The first outbreak occurred in the ICU
6 setting in Madrid in 2008, though now this has become
7 more of a global problem with outbreaks described in
8 the U.S., including in Ohio.

9 So, in conclusion, there is an increased
10 challenge in treating nosocomial pneumonia,
11 particularly in the ICU setting, due to MRSA. There's
12 significant impact on morbidity and mortality and cost
13 of care from these infections. MRSA is the most common
14 Gram-positive pathogen that we deal with when we're
15 talking about nosocomial pneumonia, including
16 ventilator-associated pneumonia, and the outcomes are
17 worse, even with effective therapy.

18 Early appropriate therapy is critical but
19 there are only two approved therapies for nosocomial
20 pneumonia due to MRSA currently available in the U.S.
21 Both Vancomycin and Linezolid have limitations. Most
22 importantly, we're seeing increased rates of resistance

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1 or reduced susceptibility for both of these agents.

2 For these reasons, we urgently need new
3 additional effective antibiotic therapies for
4 nosocomial pneumonia due to MRSA in the ICU setting for
5 the benefit of our patients.

6 With that, the next speaker will be Dr.
7 Barriere. Efficacy

8 MR. BARRIERE: Good morning, ladies and
9 gentlemen. It's a pleasure to be here today.

10 My name is Steven Barriere. I'm the Head of
11 Anti-Infective Clinical and Medical Affairs at
12 Theravance.

13 This morning, I'm going to provide an
14 overview of Telavancin and give details of the pre-
15 specified analyses of clinical response and the post-
16 hoc analysis of all-cause 28-day mortality.

17 I'll begin with an overview of the pre-
18 clinical and clinical data for Telavancin, including
19 the rationale for its use in nosocomial pneumonia.
20 Next, I'll provide an overview of the two nosocomial
21 pneumonia studies, followed by a brief discussion of
22 some analysis considerations that are quite important

1 as they pertain to our endpoints.

2 Then I'll turn to a discussion of the pre-
3 specified efficacy endpoint of clinical cure and the
4 post-hoc analysis of all-cause mortality determined 28
5 days post randomization.

6 Telavancin is a lipoglycopeptide antibiotic
7 with a unique dual mechanism of action that inhibits
8 not only cell wall biosynthesis but also disruption of
9 the bacterial membrane function leading to bactericidal
10 effects.

11 It has a broad and potent Gram-positive
12 spectrum and is active against nearly all strains of
13 clinically- important Gram-positive bacteria. This
14 includes hetero- VISA and VISA strains which are less
15 susceptible to Vancomycin, Staphylococci, which are not
16 susceptible to Linezolid.

17 Single step and serial pathogen studies have
18 shown a low potential for resistance and our post-
19 marketing surveillance has not revealed any organisms
20 with newly-acquired resistance.

21 Efficacy has been demonstrated in numerous
22 animal and in vitro models of infection, including

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1 pneumonia, endocarditis, and sepsis. The
2 pharmacokinetics of Telavancin are linear and
3 predictable with good penetration into sites of
4 infection, such as the lung.

5 Finally, as a post-marketing commitment
6 following the approval of Telavancin for the
7 complicated skin and skin structure infection studies,
8 we performed a Phase I study recently that was
9 examining the serum bactericidal activity of a single
10 dose of Telavancin administered to subjects with severe
11 renal impairment, including those on hemodialysis.
12 Serum bactericidal titers were found to be high and
13 prolonged following the single dose, suggesting no
14 decrease in biologic activity of Telavancin in patients
15 with severe renal impairment.

16 Here are the results of a recent worldwide
17 assessment of Telavancin against more than 10,000 Gram-
18 positive respiratory pathogens. The left column shows
19 the type of pathogen, the center column is the compound
20 tested, and the columns to the right show the levels of
21 potency expressed as the MIC and then the 50-percent
22 and 90-percent susceptible.

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1 Telavancin was found to be the most potent of
2 these four agents with MIC-90 of 0.25mcg per ml against
3 the strains of Staphylococcus aureus, both MRSA and
4 MSSA, and 0.03mcg per ml versus Pneumococci and this
5 included penicillin non-susceptible strains.

6 Note that the upper range of MICs for MRSA
7 for Daptomycin and Linezolid exceeds their
8 susceptibility cutoffs indicating emerging resistance,
9 as Dr. Kollef mentioned. These strains remain fully
10 susceptible to Telavancin.

11 Dr. Saravolatz and colleagues recently
12 published this study comparing the activity of several
13 agents against clinical isolates of VISA from their
14 institution. The strains were fully susceptible to
15 Telavancin and Linezolid, although Telavancin was four-
16 to five-fold more potent compared with Linezolid.
17 Notably, 15 percent of strains were resistant to
18 Sephteraline and fully 70 percent of these strains were
19 resistant to Daptomycin.

20 I'll now discuss the design and conduct of
21 our nosocomial pneumonia studies.

22 The ATTAIN Studies of Telavancin versus

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1 Vancomycin in nosocomial pneumonia were identical
2 protocols, 0015 and 0019. Each was a randomized
3 double- blind, multi-center, multinational, Phase III
4 trial to evaluate the efficacy and safety of Telavancin
5 versus Vancomycin in patients with nosocomial pneumonia
6 with a focus on MRSA.

7 274 sites in 38 countries enrolled patients
8 from early 2005 to mid 2007. A little less than a
9 quarter of the patients were enrolled from U.S. sites.

10 The primary study objective was to
11 demonstrate non-inferiority of Telavancin compared with
12 Vancomycin in clinical response at a test of cure visit
13 in the all- treated, otherwise known as a modified ITT
14 population, and the clinically-evaluable protocol
15 adherent population.

16 This was consistent with the FDA nosocomial
17 pneumonia guidance available at the time and was agreed
18 to by the agency prior to initiating the Phase III
19 program.

20 A key secondary objective was to assess the
21 potential superiority of Telavancin and clinical
22 response in the pooled population of patients who had

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1 MRSA as a baseline pathogen.

2 On-study mortality was also a secondary
3 endpoint while Day 28 all-cause mortality was not pre-
4 specified.

5 Clinical response was based on the
6 investigator's assessment of the resolution of clinical
7 signs and symptoms of nosocomial pneumonia at a follow-
8 up visit seven to 14 days following the end of therapy.

9 Safety assessments included the usual vital
10 signs, adverse event determinations, electro-
11 cardiograms, and various laboratory parameters.

12 Let's now turn to study design. Patients
13 were randomized 1:1 to treatment groups using a
14 modified block algorithm. They were stratified on
15 ventilatory status, diabetic status, and geographic
16 region. Patients were randomized to Telavancin,
17 received 10mg per kg once daily with the dosage
18 modified for renal insufficiency. Patients randomized
19 to Vancomycin received the FDA- approved dose of one
20 gram every 12 hours. However, dosage could be modified
21 for body weight, renal function, or drug trough
22 concentrations, as long as the blinding was maintained

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1 at the study site.

2 Treatment continued for seven to 21 days.

3 Daily assessments of signs and symptoms of pneumonia
4 were collected and clinical response and safety
5 parameters were assessed also at an end-of-therapy
6 visit.

7 Seven to 14 days after the end-of-therapy
8 visit, a follow-up visit was conducted where a test of
9 cure was evaluated in those patients who were not
10 deemed failures at the end of therapy. For patients
11 who were failures at the end of therapy, this was
12 carried forward to the follow-up visit and only safety
13 assessments were performed.

14 The follow-up period varied, depending on the
15 length of treatment and the timing of the follow-up
16 visit.

17 The inclusion and exclusion criteria for the
18 two studies were identical and matched those for a
19 prior successful registrational trial of Linezolid in
20 nosocomial pneumonia. These criteria were agreed to by
21 the FDA prior to the initiation of the studies. They
22 were designed to enroll patients who had pneumonia and

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1 excluded patients with other deep-seated infections or
2 who were heavily amino-suppressed.

3 The criteria were intended to enroll patients
4 who would respond to either study medication and
5 excluded patients who had Vancomycin non-susceptible
6 organisms recovered.

7 Additionally, to focus the outcomes on the
8 use of the study medication, prior antibiotic therapy
9 was limited to less than or equal to 24 hours, unless
10 the recovered pathogen was resistant to the prior
11 therapy, if the patient was deemed to failure by the
12 investigator after at least three days of prior
13 therapy, or if they developed pneumonia while on
14 antibiotics for another indication.

15 Finally, to avoid or minimize any potential
16 confounding factors, such as non-study antibiotics, the
17 choices for Gram-negative coverage were limited in the
18 protocol to either Aztreonam or Piperacillin
19 Tazobactam, the latter to be used only if Aztreonam
20 resistance was suspected or documented. These drugs
21 were to be used only for short durations empirically
22 and discontinued unless culture results dictated

1 otherwise.

2 I'd like to now discuss certain important
3 considerations for the analysis of the data in our
4 studies.

5 With regard to outcome evaluations, the
6 investigator's assessment of clinical response as an
7 endpoint is based on objective criteria, such as body
8 temperature, white blood cell count, oxygenization, and
9 the like, and included an objective criterion which was
10 death due to nosocomial pneumonia.

11 This reflects how physicians take care of
12 patients with pneumonia and leads to their management
13 decisions regarding initiation or discontinuation of
14 antibiotic therapy and other supportive measures.

15 While an all-cause mortality endpoint in this
16 disease is objective, it is relatively insensitive to
17 treatment effects since the attributable mortality, as
18 Dr. Kollef mentioned, is quite low, estimated to be no
19 greater than 10 percent, with the remainder of the
20 deaths due to the patients' underlying conditions.

21 So our outcome definitions evaluations were
22 defined as follows: cure was where the signs and

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1 symptoms of pneumonia had resolved and baseline
2 radiographic findings either had improved or did not
3 progress and where antibiotic therapy was deemed no
4 longer necessary at the end-of-therapy evaluation,
5 failure included failure at the end of therapy,
6 relapsed pneumonia after the end of therapy due to the
7 same Gram- positive pathogen, and death on or after day
8 three attributable to nosocomial pneumonia, and,
9 finally, an indeterminate category was given to the
10 investigators where they were unable to determine an
11 outcome.

12 These criteria were agreed to by the agency,
13 including the investigator-attributable deaths, as part
14 of the failure definition.

15 The pre-specified analysis populations
16 included the following: we have an all-treated
17 population similar to a modified ITT, we have all
18 patients who received any amount of study medication,
19 we refer to this as our AT population, we have the
20 modified all-treated population or microbiological all-
21 treated population or all those patients in the all-
22 treated population who had a baseline respiratory

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1 pathogen Gram-positive or Gram-negative or both

2 recovered from respiratory tract or blood cultures.

3 The clinically-evaluable population were all

4 those in the all-treated population with adherence to

5 the protocol and (2) who died on or after study day

6 three where death was attributable to the nosocomial

7 pneumonia episode under study.

8 And, finally, the microbiologically-evaluable

9 population or all those who were clinically evaluable

10 who had a Gram-positive pathogen recovered from

11 respiratory tract specimens or blood cultures and this

12 could include patients with mixed Gram-positive/Gram-

13 negative infections.

14 The all-treated and clinically-evaluable

15 populations were considered co-primary for the efficacy

16 endpoint.

17 The statistical analysis plan that was filed

18 prior to unblinding of the data pre-specified that the

19 two studies were to be pooled to examine the efficacy

20 in the group of patients with nosocomial pneumonia due

21 to MRSA. The protocols were identical. Therefore, the

22 studies are random samples from the same population of

1 patients with nosocomial pneumonia.

2 Patients with nosocomial pneumonia are
3 already hospitalized for other serious underlying
4 conditions prior to developing their pneumonia. Both
5 Study 15 and Study 19 enrolled complex patients, each
6 patient with their list, their own list of co-morbid
7 conditions, some of which confounded clinical cure,
8 some of which may have confounded all-cause mortality.

9 So there are, in effect, hundreds of
10 potential subgroups of patients if one examines the
11 subsets of all these multiple co-morbid conditions.
12 Therefore, differences that might have been observed
13 between the samples will likely be observed due to the
14 complexity of the population. So we viewed these
15 observed differences between the studies as random
16 effects, given their conduct under identical protocols.

17 Together, these studies are a more
18 representative sample of the entire NP population from
19 the perspectives of efficacy, pooling results,
20 insufficient statistical power for the analysis of
21 subgroups.

22 Therefore, for the remainder of the

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1 presentation, the primary efficacy endpoints with both
2 pre-specified and post-hoc will be presented as the
3 individual studies without need for pooling of data. In
4 the efficacy subgroups where statistical power's
5 lacking, the studies will be pooled to provide
6 statistically-sound results.

7 For safety analyses, the studies are pooled
8 to increase the relative size of the subgroups that I
9 mentioned earlier in order to understand and
10 investigate them thoroughly.

11 I'd like to now discuss the results of the
12 randomization and certain baseline characteristics of
13 the two treatment groups.

14 Of the patients randomized, 29 patients never
15 received treatment, largely due to withdrawal of
16 consent, leaving 749 randomized to Telavancin and 754
17 randomized to Vancomycin. There were two patients who
18 were randomized to Vancomycin in Study 19 but
19 inadvertently received Telavancin.

20 These two patients are kept in the Vancomycin
21 group for assessment of efficacy but are moved to the
22 Telavancin group for the assessment of safety.

1 The number of patients in the analysis
2 populations are shown in the lower half of the slide.
3 Note the similar proportions that are found in each
4 treatment group and this is also true in the individual
5 studies.

6 Nearly three-quarters of patients had a
7 respiratory pathogen that was recovered from baseline
8 cultures and nearly 45 percent met the clinically-
9 evaluatable criteria. Approximately one-third of
10 patients had a Gram-positive pathogen which could
11 include mixed infections that were recovered from
12 baseline cultures.

13 These were the baseline characteristics of
14 the all-treated population for the individual studies.
15 Proportions or values of the various characteristics
16 were generally similar in each treatment group in the
17 individual studies. Patients averaged 62 years of age
18 with nearly a third over 75 years. Nearly 60 percent
19 were in an ICU at baseline with substantial proportions
20 of patients having one or more acute or chronic
21 underlying co-morbid conditions.

22 A third of the patients had moderate to

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1 severe renal impairment, defined at baseline, defined
2 as a creatinine clearance, less than 50mls per minute.
3 There were more diabetics and patients with chronic
4 kidney disease in Study 15 versus Study 19. However,
5 the mean APACHE scores, APACHE-2 scores in the two
6 studies and in the treatment groups were about 16 in
7 both studies and in both treatment groups, indicating a
8 very sick population of patients with a high
9 probability of death.

10 The proportions of patients with ventilator-
11 associated pneumonia was similar in both studies at
12 about 30 percent, most of which was late ventilator-
13 associated pneumonia that's generally associated with
14 poor outcomes.

15 There was more ARDS ALI in Study 15 than 19
16 but there were 50 percent more patients in the
17 Telavancin group in Study 15 compared to the Vancomycin
18 group.

19 Notably in Study 19, there were more prior
20 treatment failures and while not shown, there were more
21 patients in Study 19 who had isolates of Pseudomonas
22 aeruginosa and Azineda bactro-species, often multi-drug

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1 resistant, recovered from baseline cultures.

2 Most patients had multi-lober infiltrates on
3 baseline chest x-ray indicating more diffuse pneumonic
4 involvement and there were relatively small proportions
5 of patients who were in shock at baseline.

6 Similar distribution of pathogens were seen
7 in both studies, so we again display the aggregate
8 data. An overview of the baseline Gram-positive
9 pathogens and the modified all-treated population
10 reveals that Staphylococcus aureus was the causative
11 pathogen amongst this group in more than 90 percent of
12 cases with pneumococci accounting for the rest.

13 Of the Staphylococcus aureus, approximately
14 60 percent overall were MRSA as would be expected,
15 making this the largest program to evaluate MRSA
16 pneumonia. Among the MRSA, seven percent and 10 percent
17 in each of the groups, treatment groups were found to
18 be hetero- VISAs by population analysis profiling,
19 similar to the rates as described by Dr. Kollef. More
20 than one-third of patients had mixed Gram-
21 positive/Gram-negative infections.

22 Similar proportions of each type of organism

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1 were also found in the microbiological-evaluable
2 population.

3 With regard to antibiotic therapy, prior to
4 and during the study, only a small proportion of
5 patients had been exposed to an antibiotic with
6 activity against MRSA, such as Vancomycin, during the
7 pre-study window when brief durations of antibiotics
8 were allowed. There were similar proportions between
9 the two treatment groups. Negligible numbers of
10 patients received other antibiotics with activity
11 against MRSA, such as Linezolid or Trimethicillium
12 sulfamethoxicol.

13 The majority of patients received Gram-
14 negative coverage during the study with most patients
15 receiving Aztreonam, 22 percent receiving Piperacillin
16 Tazobactam, and about 10 percent receiving Imipenem.

17 An assessment of the adequacy of Gram-
18 negative coverage was deemed very important and we
19 conducted two separate blinded evaluations in order to
20 determine this for each patient with relevant baseline
21 pathogens, particularly those patients with mixed
22 infections.

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1 Now I'll review the results of the pre-
2 specified efficacy endpoint of clinical response.

3 Shown here is the primary endpoint of
4 investigator-determined clinical cure at the test of
5 cure with Study 15 at the top of the slide and Study 19
6 at the bottom. In both studies and in both primary
7 analysis populations, the all-treated and clinically-
8 evaluatable, Telavancin was shown to be non-inferior to
9 Vancomycin since the lower or better than 95 percent
10 confidence interval for the difference in treatments
11 exceeded the pre-determined non-inferiority margin.

12 In fact, in each of the studies and in both
13 populations, the lower than of the 95 percent
14 confidence interval exceeded minus 10 percent.

15 To address the FDA's concern regarding the
16 administration of potentially effective concomitant
17 antibiotics, we conducted a sensitivity analysis
18 excluding patients who received these concomitant
19 medications. The cure rates were nearly identical in
20 the two treatment groups in this analysis, indicating
21 no differential effect.

22 The agency has noted that there were 33

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1 patients who died on or before day 28 following an
2 investigator determination of cure. There were 17
3 patients in the Telavancin group and 16 patients in the
4 Vancomycin group with a small number of patients who
5 died within the first couple of days following their
6 cure.

7 They note that this is a large number of
8 patients, suggesting that the clinical response
9 endpoint may not be reliable. However, what the FDA
10 characterizes as a large number represents less than
11 four percent of all of the patients who were cured.

12 Thus, more than 96 percent of the cured
13 patients were alive at 28 days. Furthermore, deaths
14 following a clinical response in critically-ill
15 patients would not be totally unexpected, particularly
16 at death due to their underlying conditions.

17 Let's now turn to cure rates by baseline
18 pathogens.

19 Displayed here are the cure rates for
20 Telavancin and Vancomycin in the microbiologically-
21 evaluable population using data aggregated from both
22 studies. The difference between treatment for all

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1 Staph aureus infections, including those with mixed
2 infections, was 78 percent for Telavancin versus 75
3 percent for Vancomycin.

4 If patients with mixed infections are
5 considered separately, cure rates for patients with
6 only Staph aureus infections were significantly higher
7 in the Telavancin group, 84 percent, versus 74 percent.
8 This difference, albeit not significant due to smaller
9 sample size, has held true in patients with MRSA where
10 there was nearly an eight-percent difference, and MSSA
11 where there's nearly a 13-percent difference.

12 If we examine cure rates by the Vancomycin
13 MIC of Staph aureus, the cure rates for Telavancin were
14 again significantly 13 percent higher for Telavancin
15 than Vancomycin among those patients whose Staph aureus
16 had a Vancomycin MIC of at least one mcg per ml.

17 Finally, cure rates were similar among the
18 small group of patients who had pneumococci as baseline
19 pathogens.

20 Several subgroups of potential clinical
21 interests were prospectively defined. In patients with
22 ventilator-associated pneumonia, the cure rates for

1 Telavancin were 80 percent versus 66 percent for
2 Vancomycin. For other patients at risk of poor
3 outcomes, such as those who were bacteremic at
4 baseline, the elderly, and those with high APACHE
5 scores, the cure rates for Telavancin were numerically
6 higher, about five to 10 percent, than for patients who
7 received Vancomycin.

8 In the small group of patients with hetero-
9 VISA as a sole baseline pathogen, the cure rates were
10 five of seven in the Telavancin group, 71 percent, and
11 three of eight in the Vancomycin group or 38 percent.
12 Notably, one of the seven patients in the Telavancin
13 group died compared with five of the eight Vancomycin-
14 treated patients.

15 In summary, Telavancin was shown to be non-
16 inferior to Vancomycin in the pre-specified analysis
17 populations for the primary efficacy endpoint of
18 clinical cure in both studies. Higher cure rates for
19 Telavancin are observed in patients with only Staph
20 aureus infection, both MSSA and MRSA, among patients
21 with Staph aureus with higher Vancomycin MIC, and in
22 subgroups of at risk for poor outcomes, such as

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1 patients with ventilator- associated pneumonia, those
2 who are bacteremic, the elderly, those with high APACHE
3 II scores, and patients infected with hetero-VISA.

4 I'll now turn to the post-hoc analysis of 28-
5 day all-cause mortality.

6 Although the original dataset did not include
7 survival status at 28 days for a large number of
8 patients, as Dr. Laessig showed you, these data have
9 been obtained for about 95 percent of all of the
10 patients in the study through subsequent data queries
11 to all the study sites.

12 In the Draft FDA Guidelines for Hospital-
13 Acquired Pneumonia and Ventilator-Associated Pneumonia,
14 studies with the non-inferiority design may use a 10-
15 percent non-inferiority margin as long as the control
16 mortality rate is at least 20 percent. This applies
17 since the Vancomycin mortality rate in recent studies,
18 as well as the studies under consideration here, are at
19 least 20 percent.

20 For non-inferiority to be demonstrated, the
21 lower bound of the 95-percent difference confidence
22 interval for the difference in survival rates, which is

1 the way we will express them, have to exceed minus 10
2 percent.

3 For this analysis, the primary endpoint is
4 mortality or survival, as we express it, at 28 days
5 post- randomization where survival is expressed as a
6 Kaplan- Meier Estimate, owing to the small amount of
7 censored data.

8 In the all-treated population, there was a
9 higher rate of 28-day mortality in the Telavancin group
10 in Study 15 and the reverse was observed in Study 19.
11 However, the post-hoc analysis of all-cause mortality
12 as affected by antibiotic therapy should be performed
13 in a population refined to be potentially more
14 sensitive to detecting antibiotic effects.

15 We had noted the ATS IDSA criteria for
16 pneumonia as a potential analysis population shortly
17 after submitting the original NDA, that is, in early
18 2009. These were published following the initiation of
19 our studies in the 2005 ATS IDSA Guidelines for the
20 Diagnosis and Management of Nosocomial Pneumonia.

21 Therefore, for the purposes of our mortality
22 analysis, and given the relative insensitivity of the

1 all-cause mortality endpoint, we refined the primary
2 analysis population using the criteria as suggested by
3 the agency, proposed in the ATS IDSA Consensus
4 Guidelines and contained in the most recent FDA Draft
5 Guidance.

6 These criteria have been shown to identify
7 patients who should be treated for nosocomial pneumonia
8 with the optimal balance of sensitivity and specificity
9 for the diagnosis.

10 Baseline characteristics of the ATS IDSDA
11 analysis group were similar to those of the overall
12 population across both studies and between treatment
13 groups. However, there were fewer patients with
14 chronic cardiopulmonary disease, such as congestive
15 heart failure and chronic lung disease, and larger
16 proportions of patients with the objective signs and
17 symptoms of pneumonia.

18 The primary analysis group for the mortality
19 analyses are shown here. The ATS IDSDA all-treated
20 group is all patients who met the ATS IDSA criteria and
21 received any amount of study medication. Applying
22 these criteria to the overall AT population resulted in

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1 a group of patients that was about 86 percent of the
2 total.

3 As requested by the agency, we also defined
4 microbiologic subgroups of interest. What we refer to
5 as APP group are those patients in the AT ATS ISDA
6 population who had a Gram-positive respiratory pathogen
7 at baseline. This represents nearly one-half of the
8 population overall. This population is analogous to
9 the FDA-defined MAT Gram-positive group. This group
10 included patients with mixed Gram-positive and Gram-
11 negative infections.

12 We also defined an MPP group that is patients
13 who only had Gram-positive pathogens at baseline and
14 here we have nearly one-third of the overall population
15 or about 450 patients.

16 The power of the principal analysis groups
17 for mortality are presented here. In both studies,
18 there is sufficient power, about 90 percent, to
19 demonstrate non-inferiority for the primary analysis
20 population, as well as in the aggregate of the two
21 studies.

22 But, however, in the PP and MPP groups, those

1 with a Gram-positive pathogen or those with only Gram-
2 positive pathogens, the individual study power is
3 insufficient but there is sufficient power in the
4 aggregated studies for these groups, and the subsequent
5 displays that I'll show you of survival curves will be
6 for the aggregated studies in these subgroups.

7 In addition, the aggregated results are
8 presented to provide a more representative and thus
9 more exhaustive sample of the entire MP population.

10 Let's now turn to the results of the post-hoc
11 analysis of mortality.

12 The ATS IDSA AT population, non-inferiority
13 is demonstrated for Telavancin versus Vancomycin in
14 each study as the lower bound for the 95-percent
15 confidence interval for the survival difference exceeds
16 minus 10 percent. In Study 15, the lower bound is
17 minus 9.7, and in Study 19, the lower bound is minus
18 5.4.

19 In the group of patients who met the ATS IDSA
20 criteria and who had a Gram-positive pathogen,
21 including mixed infections, non-inferiority is also
22 demonstrated for Telavancin versus Vancomycin in the

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1 aggregate of the two studies where there is sufficient
2 power as the lower bound of the 95-percent confidence
3 interval for the survival difference exceeds minus 10
4 percent.

5 Again, this group is analogous to the FDA MAT
6 Gram-positive population but as refined by the ATS IDSA
7 criteria.

8 And, finally, in the ATS IDSA group who had
9 only Gram-positive pathogens at baseline, non-
10 inferiority is again demonstrated for Telavancin versus
11 Vancomycin in the aggregate of the two studies as the
12 lower bound for the 95-percent confidence interval for
13 the survival difference exceeds minus 10 percent.

14 This population is not identified by the FDA
15 in their Briefing Document. This analysis group
16 represents the purest test of the effectiveness of a
17 drug designed to treat Gram-positive infections,
18 unconfounded by the presence of mixed infections and
19 the attendant issue of the adequacy of Gram-negative
20 treatment.

21 In conclusion, Telavancin is non-inferior to
22 Vancomycin in the treatment of nosocomial pneumonia,

1 including ventilator-associated pneumonia, in two
2 adequate well-controlled studies. In the prospective
3 analysis of clinical cure rates, Telavancin was non-
4 inferior to Vancomycin and higher cure rates were seen
5 among patients with pure Staph aureus infection,
6 including a small cohort of patients with hetero-VISA
7 pneumonia.

8 In patients with Staph aureus with higher
9 Vancomycin MICs and in patient subgroups of clinical
10 interest who are at risk for poor outcomes, such as
11 those who are bacteremic at baseline, the elderly, or
12 with high APACHE II scores.

13 Non-inferiority was also shown in the
14 retrospective analysis of all-cause mortality in the
15 ATS IDSA AT group in each study and the ATS IDSA Gram-
16 positive group and the ATS IDSA Gram-positive-only
17 group.

18 Thank you for your attention. I'd like to
19 now introduce Dr. Mathai Mammen, who will discuss
20 Safety Findings in the studies. Safety

21 DR. MAMMEN: Good morning. My name is Mathai
22 Mammen. I'm Senior Vice President of Theravance, Head

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1 of Research and Early Clinical Development.

2 I will address the general safety of
3 Telavancin as observed in our Nosocomial Pneumonia
4 Program. I'll also provide an overview of what we've
5 learned from the post-marketing surveillance data
6 accumulated since the product's introduction to the
7 U.S. in 2009.

8 I will begin with a description of the
9 patient exposures to date. I'll define the safety
10 population, then review adverse events and serious
11 adverse events.

12 I'll address safety in special populations
13 and treatment discontinuations secondary to adverse
14 events. The bulk of my attention will be spent on two
15 areas of special interests: renal safety and all-cause
16 mortality. Next, I'll discuss our post-marketing
17 experience. Finally, I'll summarize the results of our
18 diligence and provide recommendations for safe use of
19 Telavancin to treat nosocomial pneumonia.

20 The Safety presentation today will focus on
21 the 751 patients exposed to Telavancin relative to the
22 752 exposed to Vancomycin in our pneumonia trials for a

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1 total of 1,503 patients studied.

2 We previously disclosed in an earlier NDA the
3 experience from 1,029 patients with complicated skin
4 and skin structure infections.

5 Additionally, we now have approximately a
6 125,000 patient exposures in our post-marketing
7 experience with Telavancin. Importantly, the safety
8 profile is consistent across these three experiences.

9 A key point to remember is that the
10 population in this study was particularly ill with
11 patients being hospitalized for a wide range of
12 reasons, a large portion of them in an intensive care
13 unit. They developed pneumonia while hospitalized and
14 were enrolled in our study. Many of the AEs, SAEs, and
15 deaths in our study were related to the conditions for
16 which the patients were initially hospitalized.

17 Next, I will discuss treatment-emergent
18 adverse events.

19 82 percent of the patients in both Telavancin
20 and Vancomycin group experienced at least one AE while
21 in the study. SAEs were somewhat higher on Telavancin
22 with a small number of events considered possibly drug-

1 related. Discontinuations were also somewhat higher on
2 the Telavancin arm.

3 Here is a list of the most common adverse
4 events that have been reported in at least five percent
5 of patients in either treatment group. In general, AEs
6 were comparable with somewhat more anemia and
7 hypocalcemia reported with Vancomycin.

8 Incidences of individual SAEs were similar
9 between the two treatment groups. There was a slightly
10 greater incidence of multi-organ failure and acute
11 renal failure with Telavancin and a greater incidence
12 of nosocomial pneumonia and congestive heart failure
13 with Vancomycin.

14 We next turn to AEs that resulted in drug
15 discontinuation.

16 In general, AEs resulting in drug
17 discontinuation were very infrequent, mostly due to
18 either renal events or QTC prolongation. The prolonged
19 QTC reads leading to discontinuation on study were
20 largely not confirmed by the core reading lab. Of the
21 three confirmed occurrences in the Telavancin arm, two
22 were associated with drugs known to prolong the QTC

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1 interval and the third had cardiac ischemia at baseline
2 and for the duration of therapy, a condition known to
3 be associated with prolonged QT.

4 We were especially interested in AEs relating
5 to the cardiovascular system. This table includes all
6 common categories of cardiac AEs. There were more
7 events in the Vancomycin group than in the Telavancin
8 group in a number of these subgroups, especially
9 ventricular tachycardia.

10 When examining patient subgroups of interest,
11 there were no meaningful differences in AEs on
12 Telavancin and Vancomycin in males and females,
13 patients that varied substantially in body mass index,
14 and patients of different races. The incidence of
15 adverse events was higher in both arms in certain
16 population; for example, in the elderly and in
17 diabetics.

18 There were higher rates of renal AEs in the
19 Telavancin group when there were renal risk factors at
20 baseline. For patients without renal risk factors at
21 baseline, the renal AE rate was equal across
22 treatments.

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1 Renal toxicity is a known effect of
2 Telavancin as we identified in the Telavancin
3 Complicated Skin Development Program and included in
4 the current labeling. We investigated Telavancin's
5 effects on the kidney in our Phase III Nosocomial
6 Pneumonia Program.

7 I will cover here renal AEs, renal SAEs,
8 followed by rises in serum creatinine. All the data
9 presented here are consistent with our current label.

10 Incidents of acute renal failure, worsening
11 of chronic renal failure, increased serum creatinine,
12 and several other terms are collected and summarized
13 here on this slide as renal AEs and SAEs. This table
14 also captures rises in serum creatinine by greater than
15 50 percent. In general, higher reports of renal events
16 occurred on Telavancin.

17 I'll now show you that the reversibility was
18 similar between the two treatments.

19 To look at reversibility of renal injury, we
20 examined the 14 Telavancin and seven Vancomycin
21 patients that discontinued therapy because of a renal
22 AE and followed their renal function. None of the

1 Telavancin patients died, one Vancomycin patient died,
2 12 of the 15 Telavancin patients recovered or improved,
3 as did two of the seven in the Vancomycin group. The
4 condition was present and unchanged in three and four
5 of the Telavancin and Vancomycin patients,
6 respectively.

7 In summary, an evaluation of the effects on
8 the renal system of Telavancin and Vancomycin groups
9 revealed that there was more evidence of nephrotoxicity
10 in the Telavancin group. We see this relative signal
11 in renal AEs, renal SAEs, rises in serum creatinine,
12 and sensitivity to baseline renal risk factors.

13 Reversibility is comparable in a large
14 majority of the Telavancin patients who discontinued
15 due to renal injury recovered or improved their renal
16 function by the end of treatment.

17 The effects on the renal system are
18 consistent with those seen in the Phase III Complicated
19 Skin Infection Trials and reflected in the current
20 label.

21 I'll now turn to a discussion of all-cause
22 mortality, beginning with the comparison of Telavancin

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1 to Vancomycin in the safety population. I'll discuss a
2 detailed investigation we conducted of relative
3 mortality in subgroups of special interest. I'll then
4 provide conclusions from our diligence and guidance.

5 At 28 days after randomization, there were
6 similar numbers of deaths in each treatment group with
7 two percent more deaths on Telavancin. We have
8 additional mortality data out to 49 days with no
9 further separation of the Kaplan-Meier curves.

10 We examined the reasons for death in the 179
11 patients on Telavancin and a 163 on Vancomycin.
12 Overall, the distribution of the causes of death is
13 similar. There were more deaths on Vancomycin
14 attributed to nosocomial pneumonia and cardiac
15 cerebral-vascular causes. There were more deaths on
16 Telavancin attributed to multi-organ failure and
17 sepsis.

18 To further understand mortality in a safety
19 population where there are a high number of co-morbid
20 conditions, we conducted an exhaustive exploratory
21 statistical investigation with the goal of evaluating
22 objectively as many factors as possible. We followed a

1 three-step process.

2 First, we used Cox Proportional Hazards
3 Regression Models, one factor at a time, to identify
4 all possible factors associated with mortality,
5 irrespective of treatment.

6 Second, once this group of factors were
7 identified, we added treatment into the models to
8 assess significance.

9 Third, for these factors, we explored
10 interaction with Telavancin versus Vancomycin
11 treatment.

12 A clinical investigation at the patient level
13 followed the statistical investigation to ensure that
14 the results were clinically sensible. We identified 18
15 baseline factors that were associated with mortality in
16 the safety population. A treatment interaction with
17 estimated baseline creatinine clearance as a
18 categorical variable of none, mild, moderate, or severe
19 was identified.

20 Estimated baseline creatinine clearance
21 accounted for the majority of the observed variance in
22 mortality rates with Telavancin being higher than

1 Vancomycin in severe renal impairment.

2 To identify an appropriate threshold,
3 estimated creatinine clearance was evaluated as a
4 continuous variable. Using a decision tree approach,
5 we identified estimated creatinine clearance less than
6 33mls per minute rounded to less than 30mls per minute
7 as the pivot point that divided the safety population
8 into a group with and without increased risk of
9 mortality. This threshold is clinically relevant as it
10 commonly defines severe renal insufficiency.

11 For patients with estimated baseline
12 creatinine clearance greater than 30, there was no
13 difference in mortality. Additionally and importantly,
14 there were no by-treatment interactions with other
15 baseline factors, such as diabetes, congestive heart
16 failure, or age.

17 We will refer to estimated creatinine
18 clearance with its limitations from this point forward
19 simply as creatinine clearance.

20 We show here that Kaplan-Meier curves for the
21 entire safety population in our study divided into two
22 groups. On the left are patients with baseline

1 creatinine clearance greater than 30mls per minute
2 which make up the large majority of the safety
3 population. In this group, there was no difference
4 between treatments.

5 On the right are patients with baseline
6 creatinine clearance less than 30, a subset that
7 contains 13 percent of the total group. For these 191
8 patients with severe renal insufficiency, the mortality
9 rate was much higher in both treatment groups with the
10 number of deaths on Telavancin being greater than on
11 Vancomycin.

12 Of the 86 patients that died in this
13 category, 50 were on Telavancin and 36 on Vancomycin.
14 An observed observation here is that it appears that
15 the entire mortality imbalance is localized to patients
16 with severe renal dysfunction prior to start of
17 therapy.

18 We undertook an extensive series of analyses
19 in the population with severe renal insufficiency at
20 baseline to try to understand what might be driving
21 this 14-death difference in these 191 patients. We
22 explored various hypotheses for the relatedness of

1 factors to deaths in this group.

2 In the interest of time, let me discuss the
3 following four hypotheses: underlying co-morbid
4 conditions, resistant Gram-negative infections, over-
5 exposure, and nephrotoxicity to Telavancin. I'll take
6 these in order, presenting our analyses. I'll start
7 with the causes of death in this subgroup.

8 Shown here are the investigator-assessed
9 causes of death within the group of a 191 patients with
10 baseline creatinine clearance less than 30. It's worth
11 noting the mean baseline APACHE II score in this
12 subgroup was 21, signifying a relatively high severity
13 of disease and expected high rate of mortality.

14 Half of the imbalances in our safety
15 population is deaths due to multi-organ failure. So I
16 will next summarize these patients that are highlighted
17 on the slide.

18 This slide first shows that three deaths on
19 Vancomycin. All three patients entered the trial with
20 multi-organ failure which I'll abbreviate as MOF. Two
21 of the patients had sensitive MSSA or MRAS at baseline
22 with no Gram-negative infections. One of the patients

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1 had no isolated pathogen at baseline, group Candida at
2 day seven, became septic on day eight, and died on day
3 21.

4 On detailed review of these patients, the
5 data suggests that these deaths on Vancomycin were
6 likely progression of their baseline condition and not
7 related directly to Vancomycin.

8 Shown here are the MOF deaths on Telavancin
9 arranged in order of day of death. My objective here
10 is to provide you with baseline information to make
11 clear that these patients were critically ill prior to
12 entering the study and that their underlying condition
13 in most cases was the cause of death. Seven of these
14 10 patients that died of MOF had MOF at baseline.

15 Let me describe the two very early deaths in
16 this category shown in the first two rows.

17 The first patient here had extensive cold
18 exposure, had frostbite, was hypothermic, and was
19 treated for pneumonia. He received one dose and died
20 on day two before his second dose.

21 The second patient here came in with MOF,
22 status post-MI cavage, received one dose of Telavancin,

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1 and died within 15 hours.

2 I'll now describe the three deaths of
3 patients that did not have MOF at baseline and they're
4 shown here.

5 Two had Gram-negative infections at baseline
6 that were resistant to the treatment administered. The
7 third patient had cerebral hemorrhage at baseline, no
8 pathogen was discovered by culture, and the patient
9 died of MOF on day three of therapy.

10 I won't discuss the remaining patients in
11 this subgroup further, except to remind you that all of
12 these patients began therapy with MOF. The
13 investigators assessed that these deaths were not
14 attributable to treatment.

15 There are two Telavancin patients that I come
16 back to that the investigator judged died due to renal-
17 related causes which we paid especially close attention
18 to.

19 The first patient here was on chemotherapy
20 for lymphoma, was malnourished, withdrew consent for
21 any medications on day three, and died on day four in
22 acute renal failure.

1 The second patient came into the trial with
2 renal and cardiac failure and a pan-drug-resistant
3 acenida bacter. This patient received Colistin, a
4 known nephrotoxin, on day three, grew both Pseudomonas
5 aeruginosa and Clebciella pneumonia from blood
6 cultures. This patient's renal function worsened on day
7 four and the patient died on day nine.

8 In summary, these patients with multi-organ
9 failure and these two with renal-related deaths were
10 very complicated medically. Most had serious pre-
11 existing conditions that, unfortunately, made death a
12 very high probability outcome. Death occurred
13 frequently in this group, in many cases apparently for
14 reasons unrelated to treatment.

15 For the patients we discussed in the last
16 three slides, whose cause of death was MOF or renal-
17 related, we noted with interest that five had
18 treatment-resistant Gram-negative pathogens at
19 baseline, whether as part of a mono-microbial or mixed
20 infection.

21 The treatment provided to these patients was
22 inadequate to treat their Gram-negative infection. This

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1 observation suggested a hypothesis that we then
2 followed further.

3 We chose to step back and look at deaths in
4 patients with Gram-negative infections at baseline
5 among the group of patients with baseline creatinine
6 clearance less than 30. Some of these patients had
7 only Gram- negative infections as the cause of their
8 pneumonia and were inadequately treated. Others had
9 mixed infection with a resistant Gram-negative
10 organism.

11 We conducted an exploratory analysis
12 excluding one then both of these groups from the 191
13 patients with creatinine clearance less than 30. The
14 results are shown here.

15 Removing inadequately-treated Gram-negative
16 infections led to a reduction in the imbalance from 14
17 deaths to seven deaths. Further removing patients that
18 had inadequately-treated mixed infections reduced the
19 difference to three deaths.

20 While we cannot tell if it is the Gram-
21 negative infection that directly led to death in the
22 patients excluded from this analysis, deaths associated

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1 with resistant Gram-negative infections because of pre-
2 treatment imbalances appear to be a contributor to the
3 mortality differences seen in this group.

4 Notably, we conducted thorough drug-drug
5 interaction studies and found no pharmacodynamic or
6 pharmacokinetic interactions of Telavancin with
7 commonly- used Gram-negative antibiotics across a range
8 of relevant organisms.

9 We next investigated whether there was
10 evidence for over-exposure of Telavancin in patients
11 with severe renal insufficiency. As seen on this
12 graph, exposures were very similar across all
13 categories of renal dysfunction.

14 I remind you that dosing was a function of
15 creatinine clearance, hence the patients with severe
16 renal insufficiency received less drug than those with
17 normal kidney function. We concluded that over-
18 exposure did not contribute to the poor outcome in this
19 group.

20 Let me summarize what we learned from our
21 analysis of all-cause mortality.

22 Our most significant learning is that

1 dividing the patients into two groups, based on
2 baseline creatinine clearance on either side of 30mls
3 per minute identifies almost all of the increased risk
4 of mortality in patients with baseline less than 30mls
5 per minute.

6 87 percent of patients in our study did not
7 have severe renal impairment at baseline and these
8 patients had comparable rates of death with the
9 Vancomycin arm. With respect to patients that began
10 therapy with severe renal impairment, we drew four
11 conclusions.

12 First, the majority of patients appeared to
13 die from progression of their underlying conditions and
14 these deaths often appeared to be unrelated to
15 treatment.

16 Second, Gram-negative infections with
17 inadequate coverage possibly played a role in
18 addressing a portion of the 14-death difference.

19 Third, we ruled out over-exposure as a likely
20 contributor.

21 Fourth, however, despite these confounders,
22 we cannot rule out some role for nephrotoxicity.

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1 A creatinine clearance of less than 30mls per
2 minute is a statistically- and clinically-meaningful
3 threshold that informs the benefit-risk decision. Our
4 use of less than 30mls per minute is therefore both
5 based on our data and leverages a widely-accepted
6 threshold for caution.

7 Consistent with this recommendation for
8 baseline renal function, we also recommend that caution
9 be used in patients whose creatinine clearance drops to
10 below 30 while on treatment. In this event, and as
11 with other potentially nephrotoxic treatments,
12 Telavancin use should be reconsidered and continued
13 only if the intended benefit warrants the risk relative
14 to alternatives. Our caution is consistent with
15 standard clinical practice in this regard.

16 I will now discuss the safety experience with
17 Telavancin since its introduction to the market in
18 2009.

19 There have been an estimated 125,000 patients
20 treated with Telavancin since its approval with 265
21 spontaneous reports as of October 1st, 2012. The most
22 commonly-reported adverse events to Theravance are

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1 listed here.

2 Renal events, highlighted in blue, constitute
3 about a quarter of these events. Hyper-sensitivity
4 infusion reactions in green are about 10 percent of
5 the reports. Nausea and dysguesia, shown in yellow,
6 which we have seen in our development programs, appear
7 in about 15 percent of reports. Thus far, we've seen
8 no evidence of a safety-related issue that has not
9 already been seen and explored in our randomized
10 clinical trials.

11 I will now provide our conclusions and
12 recommendations.

13 Overall, the rates of AEs were similar. The
14 rates of SAEs and discontinuations due to AEs were
15 somewhat more common on Telavancin than on Vancomycin.
16 We also did a thorough investigation of cardiac safety
17 and found no concerning signal at all relative to
18 Vancomycin.

19 We concluded that there was more evidence of
20 nephrotoxicity on Telavancin than Vancomycin but with
21 similar reversibility. We also observed a similar
22 incidence of 28-day all-cause mortality for the safety

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1 population in aggregate but an imbalance in mortality
2 in the patients that had severe renal insufficiency at
3 baseline.

4 Notably, there's a high level of consistency
5 of the safety results described here with those from
6 our previous complicated skin and skin structure
7 infection trials and our post-marketing experience.

8 We recommend that serum creatinine and
9 estimated creatinine clearance be used to guide
10 treatment with Telavancin. Baseline values of
11 creatinine clearance should be used to set dose
12 according to the approved product label. If creatinine
13 clearance changes, dose should be adjusted accordingly.

14 We recommend that Telavancin should be
15 considered for use in patients with creatinine
16 clearance less than 30 or who develop severe renal
17 insufficiency on therapy only after a careful
18 consideration of the risks and benefits relative to
19 alternative therapies. There are circumstances when
20 therapy with Telavancin may be a necessary choice even
21 in these patients.

22 Finally, we plan on employing a REMS program

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1 to educate treating physicians regarding the observed
2 association of mortality risk with severe renal
3 dysfunction at baseline in our trials.

4 We will now hear from Dr. Louis Saravolatz
5 from the St. John Hospital in Detroit. Benefit Risk

6 DR. SARAVOLATZ: Good morning. I'm Louis
7 Saravolatz, a Professor of Medicine at Wayne State
8 University School of Medicine and Chairman of Medicine,
9 St. John Hospital in Detroit.

10 I've been involved in the treatment and study
11 of MRSA infections for the last three decades.

12 I'm here as a consultant to Theravance and I
13 have received research support from the company.

14 I will address the issue of benefit-risk for
15 Telavancin in the treatment of nosocomial pneumonia.

16 As Dr. Kollef has described earlier this
17 morning, known or suspected MRSA represents an
18 increasing burden in the treatment of nosocomial
19 pneumonia. Over half of our isolates of Staphylococcus
20 aureus are resistant to methicillin and MRSA represents
21 the most common nosocomial pathogen in the United
22 States today.

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1 The treatment of MRSA is becoming
2 increasingly difficult not only because of the high
3 incidence but because of the associated morbidity and
4 mortality. Treatment failures remain high with an all-
5 cause mortality rate ranging between 20 and 50 percent.

6 Unfortunately today, we have a limited number
7 of treatment options and we're limited by the growing
8 problem of resistance, the issues of drug toxicities
9 with the available agents, as well as drug-drug
10 interactions.

11 It is clear from the clinician's perspective
12 that new effective antimicrobial agents are needed for
13 the treatment of patients with nosocomial pneumonia,
14 especially when MRSA is known or suspected.

15 As we approach patients with pneumonia in the
16 hospital setting, we individualize our care by
17 assessing each patient, beginning with defining the
18 extent of the infectious process. Next, based upon the
19 patient's situation, we identify the likely pathogens
20 that need to be covered with therapy. This may include
21 a history of prior antibiotic utilization or prior
22 culture results, as well as an understanding of the

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1 local epidemiology and knowing the rate of MRSA which,
2 in most urban centers, represents the majority of
3 Staphylococcal isolates.

4 Then we assess the patient's underlying co-
5 morbidities which may have implications for the
6 treatment approach. We then select the appropriate
7 empiric therapeutic regimen and dose based upon
8 considerations of renal function, the extent of the
9 infection and body weight.

10 Finally, we monitor the efficacy and safety
11 of the therapeutic intervention and reassess treatment
12 response based upon microbiologic results.

13 Thus, the benefit-risk assessment is made at
14 the individual level for both empiric and pathogen-
15 specific treatment of nosocomial pneumonia.

16 The key features of Telavancin that have been
17 described already, most importantly the activity
18 against strains resistant to other drugs that are used
19 in the treatment of nosocomial pneumonia.

20 Second, the dual mechanism of action, being
21 active against both cell membrane and cell wall.

22 Third, the low potential for the development

1 of resistance which may be related to the dual
2 mechanism of action.

3 Other key Telavancin features include its
4 bactericidal activity, the excellent penetration to
5 epithelial lining fluid in alveolar macrophages, and
6 the lack of inactivation by pulmonary surfactant.

7 Finally, the once-daily dosing is an
8 attractive pharmacokinetic feature of this drug.

9 The benefits of Telavancin are, first, the
10 effectiveness in the treatment of nosocomial pneumonia,
11 including ventilator-associated pneumonia, shown for
12 both clinical response as well as all-cause mortality.
13 These clinically-relevant results have been
14 demonstrated in what has been the largest nosocomial
15 MRSA pneumonia clinical trial program to date.

16 The population that was treated is
17 representative of the broad population of patients with
18 multiple medical co-morbidities that we frequently
19 encounter in urban medical centers.

20 A second noteworthy benefit has been the lack
21 of emergence of resistance demonstrated through in
22 vitro studies, surveillance programs, and the clinical

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1 experience to date.

2 The benefits of Telavancin also include the
3 fact that in the treatment of nosocomial pneumonia, we
4 could be dealing with strains with reduced
5 susceptibility to Vancomycin. Clearly, the experience
6 with treating strains with Vancomycin MICs greater than
7 or equal to one mcg per ml suggests a benefit of
8 Telavancin.

9 Also, the activity against VISA from our in
10 vitro work and h-VISA from the clinical trials is
11 promising.

12 Telavancin also has activity against the
13 Linezolid-resistant strains that have caused several
14 clinical outbreaks.

15 The final potential benefit is that
16 Telavancin has performed favorably in the more
17 difficult-to-treat patients with nosocomial pneumonia
18 who are bacteremic or with high APACHE scores.

19 Telavancin has manageable risks. The
20 identified risks are considered with clinical
21 situations that we frequently encounter in the hospital
22 setting and for which we routinely monitor.

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1 There's increased risk for mortality in
2 patients with severe renal impairment, as you have just
3 heard in great detail. Although this risk is
4 confounded by mixed infections, as well as complex
5 cases of multi-organ failure, the proposed labeling
6 warns against the use in these patients, unless the
7 potential benefit justifies the increased risk.

8 The risk of nephrotoxicity requires the
9 clinicians monitor creatinine during therapy and we
10 know that we have to be vigilant about renal function,
11 whether we are using Telavancin or Vancomycin.

12 The risk for QTC prolongation also needs to
13 be mentioned. However, the QTC prolongation is seldom
14 more than four or five milliseconds, less than what we
15 see when we use other agents that we use in the
16 treatment of pneumonia, including macrolytes and
17 fluoroquinolones, such as moxifloxacin.

18 Finally, the Pregnancy Category C is a
19 potential risk related to pre-clinical studies and the
20 recommendation is to avoid the drug in pregnancy.

21 Now I'd like to address how the benefits and
22 risks of Telavancin factor into the primary treatment

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1 consideration for patients with nosocomial pneumonia.

2 As Dr. Kollef described, our first
3 consideration is to ensure early effective empiric
4 therapy for the pathogens of concern. Telavancin is
5 active against all of the relevant Gram-positive
6 pathogens in nosocomial pneumonia, including MRSA,
7 MSSA, h-VISA, and VISA, and Streptococcus pneumonia,
8 including the penicillin- resistant strains.

9 Of course, adequate coverage must also be
10 provided for any known or suspected Gram-negative
11 pathogens.

12 The next consideration is to understand the
13 patient's co-morbid conditions, particularly renal
14 function, when considering Telavancin.

15 Now let me share with you two specific cases
16 where these considerations make Telavancin a preferred
17 choice for therapy.

18 A case for empiric use of Telavancin would be
19 a patient with typical co-morbidities we see in
20 patients with MRSA. A 75-year-old woman transferred
21 from a nursing home but who had previous exposure to
22 the hospital in the form of an exacerbation of her

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1 chronic obstructive pulmonary disease requiring
2 antimicrobial therapy in the last month, a history of
3 coronary disease as well as diabetes mellitus. She
4 develops cough and shortness of breath for two days
5 while in the nursing home and then presents to the
6 hospital meeting systemic inflammatory response
7 syndrome criteria. She's also neutropenic and
8 thrombocytopenic.

9 She has localized findings on physical
10 examination that are confirmed by imaging to support a
11 left lower lobe pneumonia and a sputum Gram stain
12 reveals numerous polymorphonuclear leukocytes along with
13 Gram- positive cocci.

14 Her creatinine clearance is 44 and so this
15 patient, who has classic risk factors for MRSA,
16 develops pneumonia. Vancomycin, Linezolid, and
17 Telavancin are all suitable options in our hospital.
18 However, we have a significant rate of Staphylococcus
19 aureus with strains with MICs to Vancomycin of one or
20 higher and her myelosuppression and, in addition, this
21 patient's neuropathy might be exacerbated by Linezolid.

22 Of the three options, Telavancin would be the

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1 most appropriate agent for empiric therapy in this
2 case.

3 Another candidate for Telavancin would be
4 this case that I saw last month. A 57-year-old woman
5 with lung cancer who was hospitalized with trauma and
6 after the appropriate surgical intervention, she
7 remained ventilator-dependent.

8 On her fourth hospital day, she developed
9 fever with new infiltrates. Her white count did not
10 become elevated but she did have a left shift. Her
11 serum creatinine was good with a clearance of 96.
12 Microscopy of her sputum demonstrated numerous Gram-
13 positive cocci in clusters which eventually grew MRSA
14 with a Vancomycin MIC of 1.5mcgs.

15 She had been on treatment with Paroxetine and
16 Trazadone and thus we were concerned about using
17 Linezolid in the treatment of her pneumonia. In
18 contrast, Telavancin does not have these types of drug
19 interactions.

20 She was diagnosed with ventilator-associated
21 pneumonia due to MRSA and she was treated empirically
22 with Vancomycin but did not survive and expired on the

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1 10th day of her hospitalization.

2 This is the kind of patient for which,
3 because of the absence of Telavancin drug interactions,
4 the MIC of the organism, and the favorable data that
5 we've seen today in ventilator-associated pneumonia and
6 nosocomial pneumonia, Telavancin would have been the
7 preferred agent empirically or certainly after the
8 confirmation of the elevated MIC.

9 So, in summary, we see that MRSA represents
10 an increasing burden in the treatment of nosocomial
11 pneumonia. We have just two treatment options,
12 Vancomycin and Linezolid, and the limitation of these
13 agents include the fact that we're seeing increasing
14 resistance along with well-established toxicities of
15 these drugs and the common problems of drug
16 interactions.

17 In this context, the evidence indicates that
18 Telavancin has a positive benefit-risk profile and
19 should be available as a treatment option for patients
20 with nosocomial pneumonia.

21 Thank you very much. Conclusion

22 MR. BARRIERE: Good morning again. My

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1 conclusions will be quite brief.

2 Our conclusions are that there is a
3 significant medical need and appropriate empirical
4 therapy is critical. There are only two treatment
5 options with significant limitations, as already
6 described by our speakers this morning.

7 Telavancin is active against Gram-positive
8 pathogens, including MRSA, that are non-susceptible to
9 other agents. We've identified no resistant strains to
10 date.

11 The risks of nephrotoxicity are recognized
12 and consistent with our findings in the earlier
13 complicated skin and skin structure infection trials.

14 The risk of increased mortality is recognized
15 in patients with severe baseline renal impairment and
16 among patients whose renal function deteriorates to
17 severe impairment on treatment.

18 The proposed labeling warns against the use
19 of drug or discontinuation in these settings, as
20 appropriate.

21 Telavancin has demonstrated efficacy in a
22 large nosocomial pneumonia clinical trial program.

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1 Higher cure rates were observed in at-risk populations,
2 among patients with pure Gram-positive infections, and
3 in patients with Staph aureus with higher Vancomycin
4 MICs.

5 This leads us to our proposed indication that
6 is indicated for the treatment of patients with
7 nosocomial pneumonia, including ventilator-associated
8 pneumonia or

9 VAP, caused by susceptible strains of the
10 following Gram- positive microorganisms: Staphylococcus
11 aureus, including methicillin- susceptible and
12 resistant isolates, or Streptococcus pneumonia.

13 I appreciate your attention very, very much.
14 We'll now introduce an addition to our two speakers,
15 Dr. Kollef and Dr. Saravolatz, other advisors with us
16 today who can assist us in answering some of your
17 questions.

18 We have Dr. Ralph Corey, who's Professor of
19 Medicine and Infectious Diseases at Duke University
20 Medical Center and Dr. Ethan Rubinstein, who's
21 Professor and Head of Infectious Diseases at the
22 University of Manitoba. Both Dr. Corey and Dr.

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1 Rubinstein were co- principal investigators in the
2 Nosocomial Pneumonia Trials.

3 We have Dr. Andrew Shorr, who's local,
4 Associate Director, Pulmonary and Critical Care, at the
5 Washington Hospital Center, like Dr. Kollef, eminently
6 published in the field of critical care nosocomial
7 pneumonia.

8 We have Dr. Jamie Dwyer, Assistant Professor
9 in the Division of Nephrology at Vanderbilt University
10 Medical Center, an expert on nephrology and drug
11 toxicity.

12 Dr. Gary Koch, who's Professor of
13 Biostatistics at the University of North Carolina in
14 Chapel Hill, and, finally, Dr. Anthony Scialli, who's
15 the Senior Scientist in Developmental Toxicology at
16 TetraTech, Incorporated.

17 Thank you very much. Clarifying Questions
18 from the Committee

19 DR. MOORE: Thank you, Dr. Barriere. Let's
20 proceed now with Clarifying Questions of the sponsor.

21 Dr. Kaplan, why don't you start off?

22 DR. KAPLAN: I just wanted to clarify the

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1 method of MIC determination for the nosocomial
2 pneumonia trials.

3 MR. BARRIERE: The MIC methodology that was
4 used was at a standard central laboratory for all
5 isolates and it was micro-broth dilution.

6 DR. KAPLAN: Did you compare it at all to e-
7 test?

8 MR. BARRIERE: We did not, not in this study.

9 DR. MOORE: Dr. Stevenson?

10 DR. STEVENSON: Yeah. This is Kurt
11 Stevenson. I have a number of questions, but let me
12 just ask two initially and I can come back to the
13 others.

14 On the study design, you mentioned that the
15 Vancomycin dosing was adjusted per institutional
16 policy. So I was just wondering what confirmatory
17 evidence that you have that the Vancomycin was adjusted
18 appropriately based on Vancomycin levels being in the
19 therapeutic range. So that's one question.

20 The other question is you have -- the cases
21 that have the hetero-resistant VISA strains, I was
22 wondering if you have a subgroup analysis where you

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1 looked at outcomes when -- because you would not expect
2 the Vancomycin to be effective in those settings where
3 you removed those cases from both groups and did a
4 comparative analysis with those.

5 I'll come back later to the other questions.

6 MR. BARRIERE: So as you mentioned, the
7 Vancomycin dosing was per institutional policy.

8 We didn't specifically go back and assess
9 whether or not it met any particular guideline.
10 However, we did monitor the sites very carefully and
11 when we did monitor the sites very carefully,
12 Vancomycin dosing and the use of trough levels, if they
13 were to be done at that site, wasn't done at all sites,
14 was followed and monitored, as well, and we collected
15 that data.

16 PE-99 up, please. So, as we said, the
17 decision to obtain a serum sample for Vancomycin trough
18 determinations was taken at the site and they were
19 analyzed at the site.

20 What we found is that the initial average
21 trough concentrations amongst the 226 Vancomycin
22 patients who received the drug was about 12 and the

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1 average after adjustments upward was about 13.

2 DR. STEVENSON: Maybe Dr. Kollef or somebody
3 could comment just in terms of if that range would be
4 considered therapeutic, given the MIC creep that was
5 discussed.

6 I know at our institution, we're pushing
7 troughs closer to, you know, between 15 to 20, even
8 closer to 20.

9 MR. BARRIERE: Sure. Before we ask Dr.
10 Kollef to answer that, may I have PE-104 up, please?

11 So we also looked to see if there was a
12 correlation between the higher levels and better
13 clinical response or lower levels and worse clinical
14 response and we found no correlation and that's been
15 confirmed in numerous studies simply because this is
16 one factor, one variable in an incredibly complex type
17 of patient with many other things going on.

18 So amongst the patients that were cured, the
19 trough averages were 11 to 12. Amongst those who
20 failed, they were actually a little bit higher, but I'd
21 be happy to have Dr. Kollef comment on it.

22 DR. KOLLEF: I mean, the best way I can

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1 answer that question is that a number of years ago, we
2 conducted a study in Barnes Jewish Hospital and
3 Washington University. We published it in Chest where
4 we looked at a 101 consecutive patients with BAL-
5 positive MRSA BAP and in that population, we actually
6 dosed those patients with 15mg per kilo which was our
7 standard twice-a-day for Vancomycin which is a weight-
8 based dosing, and we measured at steady state after the
9 third dose trough levels and what we found was that one
10 could not predict what the trough level would be.

11 About a third of the patients had trough
12 levels less than 10, about a third were between 10 and
13 15, about a third had trough levels greater than 15.
14 There was no correlation between the trough levels and
15 any clinical outcome parameter that we could identify,
16 mortality or length of stay.

17 Similar data came out of this study. I'm
18 just not aware of any good clinical data in nosocomial
19 pneumonia or VAP correlating trough levels with
20 clinical outcome.

21 DR. MOORE: Thank you. Dr. Follman?

22 DR. FOLLMAN: I guess I'll just ask two

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1 questions now.

2 One of the concerns of the FDA, and I guess
3 one point of contention, is whether the two studies are
4 sort of combinable. Your position is that they are.
5 The FDA feels that they are inherently more different
6 in terms of outcomes and, I guess, baseline
7 characteristics.

8 So I'd like a little more discussion about
9 how they did differ and then also if you have a slide
10 similar to CE-17, we look at the breakdown between the
11 two groups in terms of baseline characteristics, I'd
12 like to see a breakdown of baseline characteristics by
13 the two studies with associated P values to see, you
14 know, is there really a substantial difference, say,
15 for diabetes or creatinine clearance between the two
16 studies, you know, when we look at all those different
17 breakdowns and so on.

18 So the entry criteria were identical but I
19 assume maybe different sites were used for the two
20 studies. Do you have some thoughts on why they seem to
21 be different?

22 MR. BARRIERE: Well, first of all, the

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1 studies were done under completely identical protocols.
2 They were done obviously at different sites. The
3 studies were also done at about the same time frame, so
4 there was not a time issue.

5 We believe that they represent random samples
6 basically from the same population. As we've already
7 mentioned, the nosocomial pneumonia population's
8 incredibly complex, patients with multiple co-morbid
9 conditions, and the differences observed in these
10 baseline characteristics really is random.

11 The pooled data is really more representative
12 of the entire population and the primary reason for
13 pooling was simply to pool for the subgroups where
14 there was insufficient statistical power and also
15 pooling in the safety analysis in order to get large
16 enough sample sizes of the various subgroups.

17 May I have BI-50 up, please? This was your
18 request for a comparison of the studies with regard to
19 differences at baseline and so here, there are a number
20 of differences between the studies that are provided
21 and the differences between 15 and 19 and the
22 percentage of that as a proportion of the entire

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1 population.

2 So, yes, there are a number of studies but
3 nearly all of this really is random.

4 DR. FOLLMAN: I guess you didn't calculate P
5 values for that? I mean, that would help interpret the
6 massive numbers for me.

7 MR. BARRIERE: No, we did not.

8 DR. FOLLMAN: Maybe the FDA will later, you
9 know, be able to talk about that, as well.

10 The other comment I had had to do with, you
11 know, concerns the effect of creatinine clearance on
12 mortality, which I'm sure we'll talk about in more
13 detail later, but one thing I wanted to bring up which
14 you didn't really in this discussion today is cure
15 rates by creatinine clearance for Telavancin and
16 Vancomycin.

17 So in the materials you gave to us, I believe
18 you showed that there was a gradient in cure rates by
19 creatinine clearance, Vancomycin versus Telavancin, but
20 you didn't really talk about that as a potential
21 explanation for the higher mortality at low creatinine
22 clearance.

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1 So if you could show that and perhaps comment
2 on it, why it wasn't discussed as a possibility?

3 MR. BARRIERE: Yeah. That particular table
4 was in the Briefing Document but we can show that one
5 again, also, but before I do, let me show you the rates
6 in the clinically-evaluable population, one of the co-
7 primaries.

8 ON-16 up, please. So here, what we have is
9 actually much higher cure rates in the less-than-30
10 group in the clinically-evaluable population comparing
11 Telavancin to Vancomycin, a little bit lower cure rates
12 in the 30 to 50, and then higher cure rates, slightly
13 higher cure rates in all of the rest compared to the
14 slight gradient that you see going from an even or a
15 little bit above to slightly lower, about four percent
16 or five percent to about eight or nine percent, less in
17 the final group.

18 As we pointed out, if patients were cured,
19 that was a very good surrogate for survival at 28 days.

20 We can have ON-15 up. This is the table that
21 you requested. This is the all-treated population. It
22 goes from five percent to minus two, minus five, minus

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1 nine. But again, this population, you have to
2 remember, includes everybody, including patients with
3 Gram-negative infections only that would not likely
4 respond and patients, unless there was adequate
5 treatment, and when there was inadequate treatment,
6 even the mixed infections might not respond.

7 DR. FOLLMAN: And so you don't really think,
8 I guess, that the increased mortality at the low
9 creatinine clearance level is due to insufficient cure
10 rates or the drug isn't working successfully enough
11 relative to Vancomycin?

12 MR. BARRIERE: No, we do not.

13 DR. MOORE: Dr. Shyr?

14 DR. SHYR: Okay. Can we move to C-29,
15 please? Can you explain a little bit to the panel when
16 you say on the left-hand side, Study 0015, your delta
17 is negative 5.8, what does this number really mean from
18 the Kaplan- Meier curve?

19 MR. BARRIERE: I would ask Dr. Hopkins to
20 address that, please.

21 DR. HOPKINS: Alan Hopkins, Biostatistics at
22 Theravance.

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1 Could you just repeat the question one more
2 time?

3 DR. SHYR: The question is we looked at Slide
4 C- 29 in the Study 0015. You have a delta of minus 5.8
5 and you have 95 percent confidence interval. Can you
6 explain that from this Kaplan-Meier curve, please?

7 DR. HOPKINS: Explain how the --

8 DR. SHYR: Yeah.

9 DR. HOPKINS: -- confidence interval was
10 calculated?

11 DR. SHYR: Yes. What does this mean?

12 DR. HOPKINS: It's the proportion of deaths
13 at day 28 as estimated by the Kaplan-Meier curves and
14 the difference in those two point estimates. The
15 variance is calculated and the confidence interval is
16 created.

17 DR. SHYR: Okay. So then can you move to C-
18 34? Did you do the similar things by Study 0015 or
19 0019? Do you have that result? Now you pulled these
20 two studies together, right?

21 DR. HOPKINS: Yes.

22 DR. SHYR: You do have separate studies?

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1 DR. HOPKINS: Yes, we do. Okay. Slide up,
2 please.

3 DR. SHYR: Okay. So both of them have
4 negative 12 and a confidence interval higher than
5 negative 10, is that right?

6 DR. HOPKINS: Yes.

7 DR. SHYR: Okay. Then how about move to C-
8 35? If you stratify by each group, 0015 and 0019, may I
9 see the data, please?

10 DR. HOPKINS: Okay. Okay. Slide up. EM-
11 109.

12 DR. SHYR: Okay. All right. So I just want
13 to clarify the lower bound by each individual study.
14 That's the first question.

15 Second question. Can you move to CS-19,
16 please? Can you clarify your decision tree analysis?
17 Was this based on the single co-variate each time you
18 put them together?

19 DR. HOPKINS: All of them together.

20 DR. SHYR: Put all the 19 co-variates
21 together?

22 DR. HOPKINS: Yes.

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1 DR. SHYR: So you used Cox models to select
2 each individual co-variate? You found the 19, you
3 input all 19 into the decision tree together?

4 DR. HOPKINS: That's correct.

5 DR. SHYR: Some more tenuously?

6 DR. HOPKINS: Yes.

7 DR. SHYR: And then how about the other co-
8 variates, because you found that 30 is your cut-off? Do
9 you do any internal validation to find if 30 is valid,
10 is internally validated?

11 DR. HOPKINS: No internal validation was
12 conducted, except that we got similar results for the
13 proportional hazards regression, as we did for the
14 decision tree analysis.

15 DR. SHYR: So other than --

16 DR. HOPKINS: No cross-validation within.

17 DR. SHYR: Okay. So no cross-validation, and
18 was this 30 cut-off, how about the other co-variates,
19 any other thing you found out or just this is single
20 co-variate in the decision tree?

21 DR. HOPKINS: Well, from the regression, the
22 creatinine clearance was the only treatment effect

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1 modifier that we observed.

2 DR. SHYR: Okay. Then is there any clinical
3 or biological reason you used the 30 as the cut-off or
4 just pure data mining? You just thought this dataset
5 identified 30 as the cut-off?

6 MR. BARRIERE: We will have Dr. Jamie Dwyer,
7 our nephrologists, respond to that.

8 DR. DWYER: Jamie Dwyer, Vanderbilt
9 University. I'm here as a consultant to Theravance.

10 May I have SR-110 up? So there is a biologic
11 plausibility for creatinine clearance cut points of
12 less than 30. This is a traditionally-accepted level
13 by the National Kidney Foundation. It defines mild,
14 moderate, and severe renal failure or renal
15 insufficiency, and the cut point of creatinine
16 clearance less than 30 is approximately where symptoms
17 of kidney failure begin.

18 DR. SHYR: So, in other words, this is not
19 pre- determined. Your data mining found out the
20 results just matches the clinical results, is that
21 true?

22 MR. BARRIERE: These categories of creatinine

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1 clearance were pre-specified as an analysis, part of
2 the analysis.

3 DR. SHYR: Okay. The decision tree defined
4 optimal cut-off?

5 MR. BARRIERE: The decision tree validated
6 that 33 was the precise cut-off which we rounded to 30.

7 DR. SHYR: Okay. Thank you.

8 DR. MOORE: Thank you. Dr. Alston?

9 DR. ALSTON: Just a couple quick things in
10 follow-up to Dr. Stevenson about the Vanco. I was just
11 curious practically.

12 If you're doing Vancomycin levels and the
13 dosing Vancomycin dosage is based on that, how do you
14 maintain blinding in a practical sense?

15 And in follow-up to Dr. Follman, also when
16 you have identical trials performed at the identical
17 time with the anticipation of combining all along, why
18 isn't that a single trial, and is that purely because
19 we're told we need two trials, and what makes a trial a
20 trial and why isn't this a single trial instead of two
21 trials? That escapes me.

22 And then my question was one of the outcomes

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1 available to investigators was to code someone as
2 indeterminant and, you know, the problem with non-
3 inferiority in this type of thing is that you can't
4 tell who has nosocomial pneumonia and you can't tell
5 who's getting better. So everybody just all looks the
6 same and no matter what you do looks non-inferior.

7 I was wondering how often that indeterminant
8 outcome was used and how that was handled in data
9 analysis.

10 MR. BARRIERE: So the three questions then
11 are the Vancomycin trough obtaining, looking at
12 blinding and how the blind was maintained. The last
13 part of your question had to do with what the
14 indeterminant outcome was, and the --

15 DR. ALSTON: How often.

16 MR. BARRIERE: How often, how often that
17 occurred. That was about 20 percent of the time there
18 was an indeterminant most commonly because patient had
19 a Gram-negative infection and the investigator decided
20 that they couldn't determine the effects of study
21 treatment, so they made that indeterminant call.

22 Your second question? I'm sorry.

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1 DR. ALSTON: About calling them two separate
2 trials.

3 MR. BARRIERE: Oh, separate trials. Well,
4 the two separate trials were done because two separate
5 trials were required. Okay.

6 So with regard to the blinding and
7 maintaining the blinds, very extensive blinding plans
8 had to be -- GP-118 up, please -- had to be put into
9 place at each site. So they had to document the roles
10 for the blinded and unblinded staff and the responsible
11 individuals.

12 So there was a complete unblinding staff and
13 there was a separate blinded and unblinding monitoring
14 staff. So the blinded staff took care of patient
15 identification, the consent, screening, patient
16 management, and study assessments.

17 The unblinded staff did the randomization
18 calls, the drug preparation, and the blinding, the
19 Vancomycin levels and dose adjustments and every effort
20 was made, depending on what the site practices were, to
21 keep any information about Vancomycin levels out of the
22 patient record that would be accessible to the

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1 clinician taking care of the patients.

2 So we identified specific separate procedures
3 needed for Vancomycin levels, as needed, for each
4 individual site. So all these plans had to be
5 completed by each site. They had to be signed by the
6 investigator, reviewed by RCOs and also reviewed and
7 approved by us. So we made every effort we possibly
8 could to do that.

9 Even if a patient was receiving Telavancin
10 and a Vancomycin order was placed because the
11 investigator didn't know, blood was obtained and sent
12 to the central laboratory but, of course, that result
13 was kept from the investigator.

14 DR. MOORE: Dr. Goetz, you had a question?

15 DR. GOETZ: Yeah. I wanted to follow up on
16 the renal function issues, in particular, and the
17 analyses that you presented are based on your threshold
18 analysis showing 33 to be important.

19 In the FDA documents, there were discussions
20 of other thresholds. So for the purposes of sort of
21 clarifying things, I wonder if you have slides similar
22 to CS-20 that look at people with, say, creatinine

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1 clearances between 30 and 50 and look at all-cause
2 mortality across the two studies in that regard.

3 Then I have a second question in that you
4 looked at the relationship particularly between multi-
5 organ failure and mortality in the patients with
6 creatinine clearances less than 30.

7 I don't recollect a presentation in the data
8 as to what the distribution of multi-organ failure was
9 across the two studies and I wondered if you're going
10 to also show us that.

11 MR. BARRIERE: So looking for higher cuts of
12 creatinine clearance, looking at the individual
13 studies, also wanting to know, in particular, about --
14 the second part of your question again?

15 DR. GOETZ: The second question was at
16 baseline, the distribution of multi-organ failure
17 across the studies.

18 MR. BARRIERE: Correct. Yeah. I don't
19 believe we have the full distribution of multi-organ
20 failure. No, I'm sorry, we don't have that. We can
21 certainly get that for you and provide that for you
22 later, a little later today.

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1 However, to address the issues that you did
2 bring up about other levels of creatinine clearance,
3 I'd like to ask Dr. Mammen to address them.

4 DR. MAMMEN: So your question is an important
5 one that we gave a great deal of consideration to. It
6 has a safety component and an efficacy component. I'll
7 talk about the safety considerations.

8 We did do a thorough analysis on various ways
9 to look at creatinine clearance and we think our
10 analysis justifies a cut of 30 and the data does not
11 justify cuts above 30 and so what we showed you is that
12 we took an entirely objective approach to the safety
13 population as a whole and looked at every factor that
14 associated with mortality and the only treatment effect
15 modifier we were able to pull out was baseline
16 creatinine clearance and when baseline creatinine
17 clearance was considered as this continuous variable,
18 33mls or 30mls split the population into a group with
19 risk and without risk, not higher thresholds but 30.

20 You might be referring to an FDA Briefing
21 Document figure that we can put up. FD-37, please. So
22 in this figure from FDA, they look at creatinine

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1 clearance thresholds, different creatinine clearance
2 thresholds in the two studies, 15 and 19, and what we
3 note here is that the patterns are inconsistent across
4 the two studies.

5 We also note that this is a very complex
6 population and a given subgroup, and there are eight
7 subgroups, four in each study here, have a lot of
8 things going on and it's not necessarily creatinine
9 clearance that's the most important variable in any
10 given subgroup.

11 The other point to make about this figure
12 that's important is that it doesn't capture the
13 entirety of the guidance we as sponsors are giving. Our
14 guidance is to treat patients, focus on patients with
15 baseline creatinine clearance above 30, and discontinue
16 patients that drop below 30 while on treatment.

17 So these set of graphs here illustrate the
18 full set of patients and not the ones that reflect our
19 guidance.

20 ON-71 up, please. We have tried to capture a
21 similar display here across the two studies, Study 15
22 and 19, that look at the patients that are the large

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1 majority in our population that reflect our guidance;
2 that is, start with baseline creatinine clearance over
3 30 and stay there for the duration of therapy, and,
4 once again, we don't see any particular pattern here.

5 ON-36 up, please. My final table here is
6 this is the entirety of the population where we've
7 pooled across the studies in an effort to draw as
8 robust a conclusion as possible and what you see on the
9 left are the different baseline renal function
10 categories, 30 to 50, 50 to 80, and greater than 80,
11 for Telavancin and Vancomycin.

12 Shown on the bottom is the less-than-30 as a
13 reference value and there, I showed you in the
14 presentation 50 deaths and 30 deaths on Telavancin and
15 Vancomycin. So shown above there are the equivalent
16 number of deaths and the denominators for these
17 different baseline cuts. We do notice that there's 23
18 and 20 deaths on Telavancin and Vancomycin, so a three-
19 death difference among the 222 people in that group.

20 A deep dive into those patients led us to
21 conclude that there's no meaningful difference between
22 the deaths in that category or any other category.

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1 I'd point to the very top line in that table
2 with some interest. This represents all the patients
3 that have baseline creatinine clearance above 30 and
4 stay above 30 on study. Those are the patients we
5 recommend focus on and in that population, there were
6 79 deaths on Telavancin and 99 deaths on Vancomycin in
7 total.

8 DR. GOETZ: If I could just briefly follow up
9 on that, I respect the analyses you show are consistent
10 with what you propose, in particular, into
11 discontinuing Telavancin should the creatinine
12 clearance drop to less than 30.

13 As a clinician, I find that I'm often
14 challenged in predicting which patient will drop to a
15 creatinine clearance of less than 30 and I have to make
16 decisions on therapy based upon what I know about the
17 patient at baseline.

18 So, with all due respect, I would appreciate
19 showing those slides with those cut points with what
20 the patient's creatinine clearance actually is at the
21 time that a clinician needs to make a decision.

22 MR. BARRIERE: We have Dr. Andy Shorr who can

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1 address that, I believe.

2 DR. SHORR: So Andy Shorr. I'm an Academic
3 Intensivist here in Washington, and I've served as a
4 consultant to the sponsor.

5 I understand your point precisely. I make a
6 decision on day zero and I have no guesses that are
7 distractory and if I did, I wouldn't be practicing
8 medicine. I'd be doing something much more lucrative,
9 of course.

10 The point is, is that, if you actually look
11 at the data, first of all, realize that in terms of the
12 unmet need and the burden of nosocomial pneumonia, the
13 vast majority of patients that you and I care for in
14 ICUs are in that 30-to-50 GFR range to start with. So
15 this is where the real challenge of treating the
16 patients are.

17 This is where the burden of the unmet need is
18 and that's also the group of patients who are at very
19 high risk for treatment failure because they're more
20 likely to be bacteremic and they're going to have
21 higher APACHE II scores and, as was shown earlier,
22 that's the population where there's some suggestion of

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1 Telavancin being very efficacious.

2 If you look at the dataset of the patients
3 who had GFRs of 30 to 50, the minority of them fell
4 below 30 after that and, as you know as well as I do,
5 the GFR may be 28 today, may be 37 tomorrow, and so
6 that's why, as a clinician, I would make the argument
7 that, in that population, I need to have the ability,
8 the authority to exercise my clinical acumen and my
9 judgment because a creatinine variability from day to
10 day may be a function of regression to the mean, may be
11 a function of my fluid resuscitation status, may be a
12 function of other things that has to be weighed against
13 the patient's clinical response.

14 Are there parameters of oxygenization
15 improving? Am I getting ready to liberate them from the
16 ventilator? Is their fever resolving? It's a very
17 messy population. So that decision about how to weigh
18 the risks and benefit that's going to happen from day
19 zero to day one to day two, I think, can only be made
20 best and most appropriately by the clinician at the
21 bedside trying to sift signal from noise in a
22 complicated setting.

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1 DR. MOORE: Thank you. Mr. Mullins, did you
2 have a question or comment?

3 MR. MULLINS: My questions, I have a couple
4 of questions. My questions are related to the
5 developmental toxicity of Telavancin, and I know that
6 the Applicant was required to do risk evaluation and
7 mitigation strategy in the Pregnancy Registry.

8 So I want to better understand. I think
9 there wasn't a lot of information given on the impact
10 or the effects, SAEs, on -- we address the issue of
11 pregnant women, but I'm curious about lactating women.
12 Are there any studies on that?

13 And then, secondly, I wanted to get some
14 information on CS-22, but we can address that first on
15 the REMS Study.

16 MR. BARRIERE: So I'd like to ask Dr. Mike
17 O'Connor, our toxicologist, to address that and perhaps
18 he'll ask Dr. Scialli to address it further with regard
19 to the data that you're looking for.

20 DR. O'CONNOR: So the findings that trigger
21 the concern about pregnancy and treatment with
22 Telavancin are based on some individual animal findings

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1 that I would have Dr. Scialli review with you and,
2 appropriately, Pregnancy Category C was chosen and Dr.
3 Coleman will discuss the status of the REMS Program for
4 this, as well.

5 So, Dr. Scialli, you want to discuss the
6 actual findings?

7 DR. SCIALLI: I'm Tony Scialli. I'm an
8 obstetrician-gynecologist and a reproductive
9 toxicologist and I'm a paid consultant for the sponsor.
10 Two teratologists, independently of the
11 company, evaluated the developmental experimental
12 animal data. I was one of them. We found minimal
13 risk. However, the product does carry the Category C
14 rating.

15 With respect to the lactation question, could
16 I have NE-21 up, please?

17 These are the data of the pre- and post-natal
18 studies in rats and just to orient you, these animals
19 were exposed during a part of pregnancy and then were
20 exposed for the entire lactation period to extremely
21 high exposure levels compared to human exposure levels
22 and you can see there were no abnormal findings. There

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1 are no lactation data in women but these data are
2 reassuring.

3 MR. MULLINS: I guess I'm just a little
4 confused. If there are no findings, then why do we
5 have the warnings on the label?

6 MR. BARRIERE: Dr. Scialli?

7 DR. SCIALLI: Could I have Slide NE-3 up,
8 please?

9 This is a summary of the experimental animal
10 findings. There were studies in rats, rabbits, mini
11 pigs, and these findings were consistent in my opinion
12 and that of the other teratologists who investigated
13 the findings with random appearance of occasional
14 malformations which we see virtually all the time in
15 experimental studies.

16 However, the Category C definition is that
17 there are positive findings in experimental animals and
18 certainly these can be characterized as positive
19 findings.

20 So, although I would not predict any risk in
21 human pregnancies from these findings, they do satisfy
22 the definition of Category C.

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1 MR. BARRIERE: Dr. Coleman can talk about the
2 REMS Program and our results.

3 MS. COLEMAN: So we have a REMS Program in
4 place and we have had since the approval of product for
5 complicated skin infections, so since late 2009.

6 The program includes the REMS Program itself
7 is a communication plan which includes a medication
8 guide which is provided to each patient who receives
9 the product and a Dear Healthcare Provider letter which
10 has been mailed in multiple waves to all clinicians who
11 are included in the group of clinicians who are
12 prescribers for the product. So that mass mailing has
13 gone out now in three different waves over the life of
14 the product.

15 We have done assessments per the REMS
16 guidance and assessed the uptake of the messages which
17 is basically warning or reminding clinicians of the
18 warning around the use in pregnancy and the uptake has
19 been between 20 and 70 percent based on the type of
20 clinician with regard to knowledge of the warning and
21 the need to assess pregnancy before initiating therapy
22 in the woman who's of child-bearing potential.

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1 We also have a Pregnancy Registry which is
2 another post-approval requirement for the product and
3 we have no registrations in the Pregnancy Registry.

4 DR. MOORE: Thank you. Mr. Mikita, did you
5 have a question?

6 MR. MIKITA: Thank you, sir, for your
7 presentation. I found it very helpful.

8 I'm not a statistician or a clinician or
9 anyone with any kind of technical assessment. I have
10 had pneumonia nine times over my lifetime and I've been
11 on a ventilator twice. Those were perhaps the most
12 frustrating days of many hospitalizations that I've
13 experienced.

14 Having said that, I have a couple of
15 questions.

16 In reviewing the materials, getting to the
17 crux of the matter, it seems to me that Theravance is
18 saying to the FDA, FDA, you moved the goal post on us
19 halfway through this game and notwithstanding the fact
20 of you moving the goal posts, we can still take the
21 ball over the goal line.

22 So I would like you in perhaps less technical

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1 terms to tell me as a patient representative and other
2 patients who are going to be faced with these kinds of
3 really disorienting questions when we're really, really
4 sick how is it, sir, that this drug meets that
5 substantial evidence threshold?

6 MR. BARRIERE: Thank you for the question,
7 very good question, and obviously we have developed
8 this drug for patients, such as yourself and other
9 patients, who would have suffered from pneumonia,
10 particularly pneumonia due to Staphylococcus aureus,
11 and our data demonstrate that for clinical response,
12 which is how physicians take care of their patients,
13 when your physician was taking care of you, he or she
14 was looking for your signs and symptoms to be approved
15 for you to be taken off the ventilator and sent home
16 and to lead as productive a life and as great a life as
17 possible.

18 So in our studies, CE-22 up, please, we
19 showed that with regard to clinical response, the
20 accepted primary specific endpoint at the time that we
21 have found that Telavancin was comparable non-inferior
22 to Vancomycin in two separate studies which met the

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1 regulatory requirement at the time.

2 We also showed that in subgroups, sicker
3 patients, patients with poorer outcomes, who are at
4 risk, that were bacteremic or who had ventilator-
5 associated pneumonia, that we had higher cure rates in
6 the group of patients who were at risk, including
7 patients who had higher APACHE scores, who were at
8 special risk for not doing well or dying.

9 So we've made a concerted effort in a large,
10 large program over 1,500 patients, including many
11 patients who were critically ill, many of whom died
12 very quickly during the study, regrettably, that the
13 drug is effective.

14 DR. MOORE: Thank you. Dr. Stevenson?

15 DR. STEVENSON: I'd like to come back. I
16 asked the question before about the subgroup analysis
17 of removing the hetero-resistant VISA.

18 MR. BARRIERE: Yes.

19 DR. STEVENSON: If you could comment on that,
20 and also if you have any analysis of outcomes in
21 patients that had secondary bacteremia, and then the
22 third thing to follow up, I think, on the question of

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1 Dr. Shyr asked is on Slide CS-20, can you display or
2 show the lower bounds of the confidence intervals on
3 that slide, as well?

4 MR. BARRIERE: So there were a total -- to
5 address your first question first about the hetero-
6 VISA, there was a very small proportion of patients who
7 had hetero-VISA infections and when we looked
8 specifically at the patients who had pure hetero-VISA
9 as opposed to confounded with mixed infections, almost
10 all of whom, interestingly, in the Telavancin group
11 were also infected with Pseudomonas acedovactor which
12 were highly resistant, there were better cure rates,
13 but there was such a small number that it made no
14 difference.

15 We haven't done a sensitivity analysis where
16 we removed those, but it would have been very unlikely
17 to have affected the overall response or cure rates.

18 The other question that you asked had to do
19 with secondary bacteremia and I'm presuming that you're
20 asking about bacteremia that may or may not have been
21 associated with pneumonia.

22 DR. STEVENSON: No. I was talking

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1 specifically if you had, for example, MRSA pneumonia
2 with an associated bacteremia.

3 MR. BARRIERE: Bacteremia. We did. Well,
4 that's the group of patients that were referred to as
5 bacteremic on the slide that we showed you a moment
6 ago. CE-25 up, please.

7 So there were 29 patients who had bacteremia.
8 This was bacteremia with the same pathogen that was
9 found in the lung and this is the clinically-evaluable
10 population. There was a larger proportion of patients
11 who had bacteremia in the all-treated population but
12 focusing on those patients, those were the patients who
13 had bacteremia, again with the same pathogen that was
14 in the lung.

15 And your third question had to do with
16 confidence intervals for the less-than-30 and greater-
17 than-30. So SA-4 up, please. This provides you with
18 the confidence intervals for that.

19 So in the patients with creatinine clearance
20 greater than 30 in the aggregate there, you know, we've
21 demonstrated non-inferiority with a very tight
22 difference.

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1 DR. MOORE: Okay. Thank you. Dr.
2 Cappelletty?

3 MS. CAPPELLETY: You broke down for us the
4 elimination of Gram-negatives in the under-30 group
5 that you felt were inadequately treated and I'm still
6 having an issue sort of resolving that a little bit
7 through the individual studies.

8 You had indicated that the 19 study had a
9 higher incidence of Pseudomonas and Stenotrophomonas,
10 yet it appears that the mortality differences in that
11 individual study were not present. There was a greater
12 proportion from what I see in the data of individuals
13 inappropriately treated in the 19 study versus the 15.

14 So I'm still struggling a bit within the 15
15 study the mortality differences that were seen there,
16 despite an appearance, at least, overall that there was
17 more inappropriate therapy and more Gram-negative
18 infections in the 19.

19 I was wondering if you had a further
20 breakdown of that for each individual study and not
21 just in the less-than-30 creatinine clearance group.

22 MR. BARRIERE: So, Dr. Cappelletty, what

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1 you're asking is a breakdown of that slide that talked
2 about the exclusion of the patients from the less-than-
3 30 population with inadequate by study.

4 I don't believe we've done that by study. So
5 we can certainly do that for you.

6 But let me just respond, though, that, while
7 it is true that there were more patients in the 19
8 study with Gram-negative, highly-resistant Gram-
9 negative organisms that were -- rate that was
10 inadequately treated, while there may have been fewer
11 in Study 15, there were still a substantial number and
12 there were again the similar number that were not
13 adequately treated in Study 15, which probably explains
14 the finding across the two studies.

15 DR. MOORE: Thank you. Dr. Parise?

16 CAPT PARISE: Monica Parise. You showed some
17 data that, you know, a relatively small proportion of
18 those with the renal adverse events were not improving
19 or hadn't recovered and had survived.

20 Do you have any data from your -- any
21 additional data from post-marketing about the
22 persistence of -- I mean, I know these patients have a

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1 lot of co-morbid conditions, but is there anything that
2 comes out about the irreversibility of this or?

3 MR. BARRIERE: The only data from post-
4 marketing that we have available -- well, there's two
5 sources, of course, from post-marketing and that would
6 be the spontaneous reports that are submitted to us
7 which are very limited in their information and very
8 difficult to get follow-up information on, even very
9 difficult to get primary information on, over and above
10 what they provide in the first MedWatch to us.

11 The other source is the literature and there
12 have been -- there's at least one case series that was
13 presented or a couple of case series that was presented
14 looking at efficacy and safety and then there was a
15 poster that was presented by the agency. Dr. Lorenz
16 presented a poster a couple of years ago, I believe it
17 was ICAAC, where they reported on their report, their
18 spontaneous reports of acute renal failure, and I'd
19 have to refer to Dr. Lorenz to remind me what the
20 reversibility was in those cases. I believe they were
21 mostly reversible.

22 And in the literature that we've seen, again

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1 the majority of the cases appeared to be reversible, as
2 I recall, but I don't have that on the tip of my
3 tongue.

4 DR. MOORE: Thank you. Dr. Chatterjee?

5 DR. CHATTERJEE: Every time a new or newer
6 antimicrobial is developed, we are told that there is
7 little resistance or no resistance of the existing
8 organisms to it.

9 I'm curious as to whether there have been any
10 in vitro studies looking at Telavancin, the mechanisms
11 of resistance, and whether these organisms actually do
12 develop resistance to this agent.

13 MR. BARRIERE: I'd like to ask Dr. Benton,
14 our microbiologist, to respond.

15 DR. BENTON: Good morning. Brett Benton,
16 microbiologist with Theravance.

17 We have in our own laboratory and in several
18 academic laboratories, we've sponsored studies of in
19 vitro resistance to element. Only in a single study
20 has identified resistance and we've done studies that
21 include both spontaneous challenge where organisms are
22 plated on auger-containing antibiotic, and then serial

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1 passage for multiple days, and the most rigorous study
2 was a 50-day serial passage study.

3 Slide MI-20 up, please, and this slide
4 summarizes the clinical experience which you've heard
5 before earlier today and then the in vitro study then
6 describing is part of what's summarized in the second
7 half of the slide and a single isolate of MRSA among 10
8 studied developed resistance on day 43 of eight-fold
9 MIC increase. That was continued. That strain was
10 continued to be passage for seven additional days and
11 no additional MIC increases were observed.

12 The mechanism of resistance to this strain
13 was evaluated more recently in a subsequent lab of Dr.
14 Brian Wilkinson at Illinois State University and he's
15 sequenced the genome. He's compared the whole genome
16 transcriptome, both of those to the wild-type parental
17 strain, and could I have Slide MI-22 up, please? What
18 we see is the eight-fold increase in MIC for
19 Telavancin. We don't see significant cross-resistance
20 with any other antibiotics.

21 Notably, there was a reduced in vitro
22 fitness. So the reduced susceptibility came at a cost

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1 of about 50 percent growth rate reduction. We saw
2 altered cell envelope. An electromicroscopy study
3 showed a thickened cell wall and other physiologic
4 studies showed reduced expression of auto license and
5 also altered fatty acid composition and, notably,
6 experiments showed that the fluid indy of the membrane
7 was altered in the strain.

8 The genetic sequencing studies showed a 148
9 different single nucleotide alterations in the strain.
10 So a lot of genetic changes were required to get this
11 level of reduced susceptibility and that translated
12 into greater than 600 gene mis-regulation observations,
13 approximately 300 up-regulated, and approximately 300
14 down-regulated more than two-fold, and these functions
15 are described in the bottom of the slide involving co-
16 factor biosynthesis cell wall functions. Fatty acid
17 biosynthesis, you would think, would result in the
18 membrane alterations that were observed and, notably,
19 changes in regulatory function, the strain was AGR-
20 negative.

21 MR. BARRIERE: I would just add to that, that
22 we have had some patients post-approval who received

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1 the drug and also during the compassion use program
2 who've received the drug for a very long time with no
3 emergence of resistance.

4 DR. MOORE: Okay. We're overtime. I'm going
5 to allow two more questions.

6 Dr. Voynow?

7 DR. VOYNOW: I had a couple of questions. One
8 is related to Slide CE-16. The number of patients then
9 for which you had no microbiologic data that would have
10 been between about 55 to 58 percent of the patients, is
11 that correct?

12 MR. BARRIERE: No, that's not correct. CE-
13 16. So the difference that you're looking for who had
14 no pathogens whatsoever was about 25 or 25 to 30
15 percent, the difference between the all-treated and the
16 modified all-treated.

17 The 50 percent is those who had a Gram-
18 positive pathogen. So that was closer to 50 to 60
19 percent had a Gram-positive pathogen and the rest
20 either had no pathogen or only Gram-negative pathogens.

21 DR. VOYNOW: Okay. Another question that I
22 had was apropos some of the discussion about resistance

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1 and also about monitoring levels.

2 Would Telavancin levels be monitored as part
3 of a therapeutic program?

4 MR. BARRIERE: I'd like to ask Dr. Worboys,
5 our pharmacokineticist, to address the issue of
6 monitoring.

7 DR. WORBOYS: Philip Worboys,
8 Pharmacokinetics with Theravance.

9 Telavancin monitoring is not required for two
10 main reasons. CS-29. This slide was demonstrated by
11 Dr. Mammen and it displays the pharmacokinetics that we
12 obtained during the course of our studies.

13 Telavancin is dosed according to body weight
14 and adjusted for renal function. Those two features,
15 both body weight and renal function, comprise the basis
16 for the vast majority of the variants that you see
17 within the population and by adjusting for both of
18 those, body weight and renal function, you see very
19 consistent exposures across individuals. So
20 variability and pK per se doesn't lead us to think that
21 therapeutic monitoring would be required.

22 Another reason potentially for doing

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1 therapeutic monitoring is if you see an association
2 with increased exposures and something potentially
3 adverse. Well, that'd be nephrotoxicity and/or, say,
4 mortality.

5 PE-67, please. This is an analysis we've
6 done looking at exposure relative to, in this example,
7 rises in serum creatinine. This figure shows AUC but
8 we've done similar analyses for CMAX, CTROUGH. We've
9 looked at relationships for the emergence of renalase.
10 We've also looked at mortality. All of these look at
11 the data and don't show that there's any association
12 with any pK parameter, whether it's higher exposure or
13 lower exposure, with a difference in those outcomes.

14 So based on those two features, there's no
15 reason to believe that therapeutic monitoring would be
16 required for Telavancin to give an improved benefit-
17 risk profile.

18 DR. VOYNOW: I had one other question.

19 DR. MOORE: If it's quick.

20 DR. VOYNOW: Okay. Really quick. Which is,
21 the post-marketing analysis adverse events. Was there
22 any mortality, report of mortality?

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1 MR. BARRIERE: Dr. Mammen?

2 DR. MAMMEN: Could you please repeat your
3 question?

4 DR. VOYNOW: So for the post-marketing
5 experience for the skin infection indication, you
6 listed adverse events. Have there been any cases of
7 mortality reported, any deaths?

8 DR. MAMMEN: Yes. So there have been eight
9 deaths reported to Theravance since 2009. That's not
10 to say there have not been many more deaths than that
11 for patients that have been treated but these are the
12 eight that have been reported.

13 SA-157 up, please. The deaths, in general,
14 were at variable times post-treatment. There's one
15 death that actually occurred where the patient had
16 pneumonia and that's described here. This patient, as
17 you can see there, had a history of diabetes,
18 rheumatoid arthritis, coronary artery disease, and
19 ultimately developed pneumonia and died of multiple
20 organ dysfunction and development of a cavitary
21 pneumonia and death, and in this case, the physician
22 taking care of this patient considered this death as

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1 possibly related to Telavancin.

2 The other seven deaths, they were not
3 considered related to Telavancin and those are the
4 totality of the deaths that have been reported to the
5 company.

6 DR. MOORE: Okay. Dr. Katona, last question.

7 DR. KATONA: With regard to the combinability
8 of the studies, have you made a calculation as to how
9 many additional patients you'd have to enroll to be
10 able to make your point without combining the studies?

11 MR. BARRIERE: Dr. Hopkins, the question is
12 how many more patients would we need to enroll to avoid
13 combining them, and this would be particularly for the
14 subgroups where we had insufficient power?

15 DR. HOPKINS: You'll recall the slide we
16 showed where the power was estimated based on the data
17 that we had for these subgroups that we want to test
18 and they were in the 50 to 60 range.

19 Slide up, CE-32. So those ones that are
20 grayed out, we would want to raise the sample size in
21 order to get something that's greater than 80 and, you
22 know, a rough estimate, I think, would be to nearly

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1 double the sample size.

2 DR. MOORE: Thank you. All right. We're
3 going to have to go to a break at this point.

4 We'll now take a 10-minute break. Panel
5 members, please remember that there should be no
6 discussion of the meeting topic during the break
7 amongst yourselves or with any member of the audience.

8 We'll resume at 10:45ish.

9 (Recess.)

10 DR. MOORE: We will move forward now with the
11 FDA Presentations, starting with Dr. Lorenz. FDA
12 Presentations

13 Presentation of Regulatory History and

14 Safety: Telavancin for Nosocomial Pneumonia

15 DR. LORENZ: Okay. Good morning again. My
16 name is Ben Lorenz. I'm a Medical Reviewer in the
17 Division of Anti-Infective Products. I'm here to
18 discuss the first part of the FDA Review.

19 During this presentation, I'll go over the
20 following topics: briefly revisit the Regulatory
21 History, touch upon some topics in microbiology and
22 non- clinical toxicology, also give a brief overview

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1 again of the trial design with a discussion of our
2 clinical safety, particularly focusing on the
3 nephrotoxicity issue.

4 So the Regulatory History. You know,
5 Telavancin was initially approved in 2009 for
6 complicated skin and skin structure infections caused
7 or suspected to be caused by Gram-positive organisms.
8 As noted in the Warnings and Precautions Section of the
9 label, decreased efficacy was noted in patients with
10 moderate to severe baseline renal impairment, indicated
11 by creatinine clearance of less than 50.

12 As part of the approval for complicated skin,
13 the indication was accompanied by the following post-
14 marketing commitment to evaluate the effect of renal
15 function on the biologic activity of Telavancin.

16 So during the first cycle review or during
17 the first cycle submission in 2007, the final
18 statistical analysis plan was submitted for the Phase
19 III studies, two ATTAIN trials, as we know now, 15 and
20 19 were designed with the primary efficacy endpoint of
21 clinical cure using a 20-percent non-inferiority
22 margin.

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1 In July of 2008, during the discussion of
2 Doripenem at the advisory committee, the FDA presented
3 a justification for a non-inferiority margin using a
4 28-day all-cause mortality endpoint, but there was
5 insufficient evidence to justify a margin for clinical
6 cure, and subsequently, in January of 2009, the sponsor
7 submitted the NDA to the FDA.

8 In response to the submission, the division
9 submitted a complete response and in that letter, the
10 division requested the sponsor obtain all mortality
11 data and, Number 2, to specifically address consistency
12 of treatment difference for Telavancin relative to
13 Vancomycin across the trials, given the difference
14 between -- excuse me -- distribution of baseline
15 prognostic factors for mortality and the proportion of
16 patients whose mortality was censored, and, thirdly, to
17 determine if patients enrolled in the trial met the ATS
18 IDSA criteria for the diagnosis of pneumonia.

19 After recovery of the missing mortality data,
20 second cycle review was done and looking at the
21 following patient populations, not only the all-treated
22 population but a supportive population using the ATS

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1 IDSA Guidelines for diagnosis of pneumonia, as well as
2 specific microbiologic populations, including patients
3 who had microbiologically-evaluable specimens showing
4 Gram- positive organisms or patients who had only Gram-
5 positive organisms identified.

6 In December of 2010, however, the division
7 issued a second CR letter for that submission and noted
8 that, in the Study 15, there was a failure to
9 demonstrate non-inferiority using the 10-percent margin
10 for the 28- day all-cause mortality.

11 It was after that CR that the sponsor
12 submitted a Request for Formal Dispute Resolution in
13 which they stipulated Studies 15 and 19 met the
14 statutory standard for approval, based upon the pre-
15 specified endpoint clinical cure.

16 In further discussions with not only the
17 division but the Office of Antimicrobial Products and
18 New Drugs, the applicant agreed to discuss the
19 resubmission in the public forum at the advisory
20 committee, and then in July this year, the amendment
21 was submitted, including new analyses. So that leaves
22 us where we are today.

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1 Just to lead into more discussion, I just
2 want to touch upon a few topics with microbiology.

3 From these nosocomial pneumonia trials, we
4 know from about 650 isolates, Staph aureus was
5 collected and about half of those, 315, were described
6 as MRSA. Collectively, the MIC 90 was observed to be .5
7 and the highest MIC noted was one.

8 Microbiologic eradication, which was defined
9 as absence of a baseline pathogen in the last post-
10 baseline culture, was observed in approximately 83
11 percent of Telavancin-treated patients and 76 percent
12 of the Vancomycin patients.

13 Shifting slightly to touch upon some of the
14 non- clinical toxicology studies, there were several
15 studies in rats and dogs, including exposures up to six
16 months in rats with a maximum dose of a 100mg per kg
17 per day, and in dogs where there was up to three months
18 of exposure maximum of a 100mg per kg per day.

19 All studies included a drug product,
20 including the excipient insolubilizer hydroxy-beta-
21 cyclodextran or HBCD in one group, and all studies,
22 including single dose, had renal findings. These renal

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1 findings with HBCD tended to be more frequent and
2 severe, including specifically with the highest dose
3 tested of Telavancin.

4 Looking more carefully at the observations,
5 BUN and creatinine was increased in both HBCD and high-
6 dose animals. Urine volume incidence and incidence of
7 granulomatous casts, occult blood, were increased in
8 treated animals.

9 Kidney weights were increased in the rats at
10 the high dose. Renal epithelial cell vacuolization,
11 dilatation and interstitial inflammatory cell
12 infiltrates were seen in HBCD in Telavancin-exposed
13 rats. Renal tubular degeneration was observed at the
14 high dose.

15 So to delve into the safety, I first want to
16 just discuss the trial design, showing that 15 and 19
17 again were both active controlled randomized double-
18 blind non-inferiority trials where the primary efficacy
19 endpoint was clinical response at the test of cure.

20 As mentioned previously, intended to combine
21 for superiority in patients with MRSA, and in post-hoc
22 analysis, recovery of all-cause mortality data, looking

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1 at the various patient populations, including patients
2 with any Gram-positive identified or if only Gram-
3 positive organism was identified.

4 Patients were randomized 1:1 and received
5 Telavancin and Vancomycin and patients were to receive
6 a minimum of seven days and up to a maximum of 21 and
7 empiric Gram-negative coverage was allowed, preferably
8 to receive Aztreonam and/or Metronidazole but
9 Piperacillin Tazobactam was permitted if Aztreonam was
10 suspected to be ineffective.

11 So looking at the inclusion criteria, major
12 inclusion criteria included two signs, two symptoms
13 from a list of symptoms, including cough, purulence,
14 sputum, auscultatory findings, or other signs,
15 including fever, leukocytosis, along with chest x-ray
16 consistent with pneumonia, inappropriate respiratory
17 specimens.

18 The major inclusion criteria, there's more,
19 but these are the salient, more than 24 hours of
20 potentially effective systemic antimicrobial therapy,
21 respiratory specimens with only Gram-negative
22 pathogens. If patients had refractory shock or severe

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1 neutropenia, they were excluded, as well as certain
2 risk factors for sudden death, including QTC longer
3 than 500 milliseconds, congenital QT, or uncompensated
4 heart failure.

5 To go over the analysis populations, these
6 are the populations used prospectively to define these
7 patients, all treated, as mentioned, all subjects who
8 received any amount of study medication, somewhat
9 similar to an ITT population, modified all treatment,
10 which is where a patient had a baseline pathogen
11 identified, known to be a cause of pneumonia.

12 In the clinically-evaluable patient
13 population where a subset of the AT population who
14 adhered to the protocol, such that their treatment
15 effect could be ostensibly linked to the study drug.

16 Microbiologically-evaluable population were
17 subjects who essentially met the CE criteria but had a
18 Gram-positive baseline pathogen identified.

19 In some of the post-hoc analysis sets that we
20 discussed previously and just to reiterate here that
21 there might be a bit of discrepancy between the
22 nomenclature between the sponsor and the FDA, just to

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1 clarify that, you know, these patient populations were
2 as described. So patients who were in the AT
3 population who met the ATS IDSA criteria, also patient
4 populations who had at least one Gram-positive
5 respiratory pathogen which, note, may include mixed
6 infections, also patient population where we're
7 focusing only on Gram-positive baseline respiratory
8 pathogens, and likewise with MRSA, where there's at
9 least one or another population where only MRSA was
10 identified.

11 So as I mentioned, the pre-specified analyses
12 were to test both non-inferiority and superiority of
13 Telavancin with respect to clinical response at the
14 test of cure. The primary analyses were meant to be
15 the AT and CE analysis population and were considered
16 co- primary.

17 When looking at the IDSA criteria and
18 applying them retrospectively to those populations,
19 about 86 percent of those patients satisfied that
20 criteria.

21 Looking at baseline characteristics,
22 comparing the two treatment groups, 716 patients,

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1 randomization was 50/50, approximately, likewise in 19
2 where there was 771 patients.

3 Just to note that there were 22 countries
4 included in Study 15 where 31 percent of the patients
5 were from the U.S. and in 19, in 29 countries where 14
6 percent of the patients were from the U.S.

7 And again here's a breakdown of analysis
8 populations and to point out the AT population at the
9 top where the subsequent populations represent a
10 percent of those and looking at Study 15 and 19,
11 they're essentially balanced between treatment arms. As
12 you can see, the CE population represented
13 approximately 40 percent of patients but Telavancin
14 group in Study 15 had slightly less patients in the
15 clinically-evaluable group in Study 15 versus the
16 Vancomycin group.

17 But looking at the microbiologic subgroups
18 where MAT representing the Gram-positive population was
19 about 50 percent of the AT population.

20 So looking here at the baseline
21 characteristics and for simplicity's sake, I included
22 only the baseline characteristics that represent a

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1 statistically significant difference between the groups
2 and mentioned here, as listed, patients with a history
3 of diabetes, chronic renal failure, patients who had a
4 baseline creatinine of less than 50, who are diabetic
5 at baseline, also patients who are on hemodialysis,
6 noting here that significantly more patients in those
7 categories were in Study 15.

8 So this slide shows exposure of patients who
9 received various duration of treatment. Most of them,
10 seven to 10 days, approximately half of them received
11 about seven to 10 days. A handful received a little
12 bit more than 21 days.

13 So discussing the findings and clinical
14 safety, pointing out that the difference between this
15 trial and obviously the complicated skin where patients
16 tended to be older with more co-morbid conditions, and
17 this is evidenced by the baseline APACHE II scores
18 which were greater than 20 represented in both the
19 study groups, 22 percent in the Telavancin and 25 in
20 the Vancomycin group, where in more than half of the
21 patients were in the ICU at baseline.

22 So just to note what's currently in the label

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1 and directing the focus of the safety evaluation, of
2 course, we understand there's a degree of renal
3 toxicity in observations from QT studies that there's
4 an effect on prolongation and, quoting from the label,
5 the mean maximum baseline-corrected/placebo-corrected
6 QTC prolongation at the end of infusion was estimated
7 to be approximately 12 to 15 milliseconds for
8 Telavancin when receiving 10mgs per kilo.

9 Warnings and Precautions Section states that
10 you instruct the prescriber to use caution with
11 patients taking drugs known to cause QTC interval, not
12 to prolong QTC intervals.

13 Also in the label, there's a note that
14 increases in serum creatinine to one and a half times
15 baseline occurred more frequently in Telavancin-treated
16 patients with normal baseline. Serum creatinine, 15
17 percent compared with seven percent in Vancomycin
18 patients.

19 To put this in perspective and compared to
20 what we're observing in the nosocomial pneumonia
21 trials, this same increase was noted in 16 percent of
22 Telavancin patients versus 10 percent of the

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1 Vancomycin-treated patients.

2 So this slide shows premature study drug
3 discontinuations, showing here Study 15 where
4 discontinuations here were for any reason. Looking at
5 Telavancin group where approximately 46 percent dropped
6 out versus 40 percent in Vancomycin and the difference
7 reaching not quite statistical significance but a P
8 value of .07. I'll note that this wasn't seen in Study
9 19.

10 Most of these drop-outs, however, were noted
11 as to be due to death, either unsatisfactory
12 therapeutic response or the investigator felt that the
13 Gram-positive coverage was no longer indicated.

14 So these are discontinuations due to AEs as
15 determined by the investigator. In Study 15,
16 Telavancin patients dropped out six percent of the time
17 and Vancomycin three. Again, this didn't quite reach
18 statistical significance but P value using Fisher's
19 exact was 0.07. Again, this difference was mostly seen
20 just in Study 15.

21 Now this slide is looking at treatment-
22 emergent adverse events where patients were also

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1 discontinued, not necessarily correlating it to but
2 again this is a combination of patients where
3 treatment-emergent events may or may not be necessarily
4 related, but you can see in Study 15 there's a
5 difference in drop-outs and the Telavancin group had
6 approximately nine percent where in the Vancomycin was
7 4.5. This was statistically significant in Study 15.

8 The lower portion of the table where,
9 according to system organ class, there was an imbalance
10 of renal and urinary treatment-emergent events, and
11 these are grouped by preferred term in that system
12 organ class. So again, we're seeing an imbalance here
13 in the Study 15.

14 Looking at all of the renal-related
15 treatment-emergent adverse events, acute renal failure
16 was the most frequently-reported renal-related
17 treatment-emergent event in Study 15 and 19 and listed
18 here, I've included blood creatinine increased as a
19 preferred term in acute renal failure.

20 Looking just grossly at the numbers, there's
21 again that slight imbalance in Study 15, whereas the
22 number's a little bit more similar in Study 19.

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1 These are the renal treatment-emergent
2 adverse events that were determined to be serious,
3 again Study 15 and 19 listed separately, and showing
4 differences in treatment arms. Study 15 showed a
5 summation of all these events highlighted in blue at
6 the bottom where 17 patients were found to have a
7 serious renal TAE versus Vancomycin, seven patients.
8 Again, in Study 19, these results were somewhat similar
9 and the difference in 15 was statistically significant.

10 So this is the stratification by baseline
11 creatinine clearance -- excuse me -- baseline serum
12 creatinine stratified by less than 1.2 or less than or
13 equal to 1.2 or more than 1.2 and looking at the total
14 number of patients with renal TAEs, 38 patients or 10
15 percent in Study 15 versus 30 patients with eight
16 percent in Study 15. Again, in Study 19, not quite as
17 significant of a difference there.

18 This is a slide showing the trend of
19 creatinine starting at the baseline and using the test
20 of cure value to find the mean difference in serum
21 creatinine. Just focusing on the bolded numbers where
22 you can see that in Study 15, there's mean increase in

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1 creatinine in the Telavancin arm, a mean decrease in
2 Vancomycin. Comparatively in Study 19, you're seeing
3 another similar increase in creatinine throughout the
4 course of the study and in Vancomycin a slight
5 decrease.

6 Now note the standard deviations are pretty
7 wide where, you know, this could be a result of
8 significantly high outliers but just to note that there
9 is a slight trend in both of these studies.

10 So that's my talk, and I guess I'll pass the
11 baton to Scott Komo for discussion of Efficacy.

12 Presentation of Efficacy: Telavancin for
13 Nosocomial Pneumonia

14 DR. KOMO: Good morning. My name is Scott
15 Komo. I'm the Statistical Reviewer for this
16 application. I'll be giving a discussion of the
17 Efficacy Results for this application.

18 Here's the outline for my presentation. I'll
19 first talk about the protocol-defined and point of
20 clinical response. Then I will discuss the two
21 concerns that we have with this endpoint.

22 The first is the lack of historical data to

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1 justify non-inferiority margin, and the second is that
2 there were some deaths that occurred in close temporal
3 proximity to the time of the clinical cure assessment
4 with the inability to rule out pneumonia as being
5 related to death.

6 I'll then present the clinical response
7 results. I'll then move on to discuss all-cause
8 mortality. I'll first discuss how the non-inferiority
9 margin was determined for this endpoint. I'll then
10 move on to the 28-day all-cause mortality results and
11 then will discuss subgroup analyses by baseline
12 creatinine clearance and finally finish with additional
13 subgroup analyses by factors that affect renal
14 function.

15 The major issue with the protocol-defined
16 primary endpoint clinical response is that there is a
17 lack of historical data to justify a non-inferiority
18 margin. This information is critical in the
19 interpretation of a non-inferiority trial. Without it,
20 we will not be able to differentiate between an
21 effective and ineffective drug without historical data
22 demonstrating a treatment effect for the active

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1 control.

2 This lack of historical data has been
3 discussed at both the 2009 Nosocomial Pneumonia
4 Workshop co- sponsored by the FDA as well as the
5 November 2011 meeting of the Anti-Infective Drugs
6 Advisory Committee.

7 Another concern with the clinical response
8 endpoint is that some patients were classified as
9 clinical cures at the TOC assessment and died in close
10 temporal proximity to the test of cure assessment for
11 causes cited by the investigator that could not be
12 ruled out to be related to their nosocomial pneumonia.
13 There were 33 such patients in both trials that were
14 evenly distributed across treatment arms. There were
15 17 Telavancin patients and 16 Vancomycin patients.

16 This could be related to lack of a clear
17 definition of clinical response resulting in an
18 endpoint that is not well defined and reliable or also
19 possibly an issue with determining the window that
20 maximizes the number of deaths related to nosocomial
21 pneumonia and minimizes the number of non-infection-
22 related deaths.

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1 It should be noted that this phenomena has
2 been seen in several other recent submissions.

3 I will now go over the clinical response
4 definition for the test of cure assessment.

5 So cure is defined as the signs and symptoms
6 of pneumonia resolved and the baseline radiographic
7 findings improved or did not progress and failure was
8 at least one of the following: that the relapse
9 pneumonia with the same Gram-positive organisms that
10 terminated after the termination of study medication or
11 death on or after study day three and before the TOC
12 evaluation or if no TOC evaluation was done, within 28
13 days after the last study medication where the death is
14 attributable to the pneumonia episode under study, and
15 indeterminant is defined as inability to determine
16 outcome.

17 It should be noted that failures at the end
18 of the therapy were carried forward to the test of
19 cure.

20 This graph represents the data for the
21 Telavancin all-treated patients from both studies who
22 are considered clinical cures at the TOC and

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1 subsequently died by study day 28. The day that the
2 clinical response was assessed as cure is shown as a
3 blue circle and the day that the patients died is shown
4 as a red circle. The cause of death, as cited by the
5 investigator, is labeled on the left side of the graph.

6 The one patient with only a red dot as shown
7 died on the same day as the clinical cure was assessed.
8 As you can see, most of the patients died close to the
9 time that TOC cure assessment.

10 Based on discussions with my clinical
11 colleagues, it was determined that the pneumonia cannot
12 be ruled out to be related to death for many of the
13 patients.

14 Similar to the previous slide, this graph
15 represents the data for the Vancomycin-treated patients
16 from both studies who are considered clinical cures at
17 the TOC assessment and subsequently died by day 28.

18 As you can see, as was seen for Telavancin,
19 most of the patients died close to the time of their
20 TOC cure assessment and for many of the patients,
21 pneumonia cannot be ruled out to be related to their
22 deaths.

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1 This slide represents the analysis
2 populations that will be discussed.

3 The first is the all-treated population which
4 includes all patients who received study drug.

5 The next population includes all-treated
6 patients who met the ATS IDSA criteria at baseline and
7 this includes 86 percent of the treated patients.

8 The next population is the patients who had
9 at least one Gram-positive pathogen isolated at
10 baseline. This includes both mixed and Gram-positive-
11 only infections and this is made up of 53 percent of
12 the treated patients.

13 The next population is the patients who had
14 at least one MRSA pathogen isolated at baseline and
15 this included both mixed and Gram-positive-only
16 infections and this made up 31 percent of the treated
17 patients.

18 Also, the last population, the patients were
19 considered clinically-evaluable and this made up 44
20 percent of these treated patients.

21 The protocol specified that the all-treated
22 and clinically-evaluable populations were to be

1 considered the co-primary analysis populations.

2 The applicant-defined primary analysis
3 population for this submission was the all-treated
4 patients who met the ATS IDSDA criteria and the agency-
5 defined primary analysis population was patients who
6 had at least one Gram-positive pathogen isolated at
7 baseline. This population was chosen because both the
8 test and the comparator only have activity against the
9 Gram-positive pathogens.

10 To help address some of the issues raised in
11 the previous slides, we performed an analysis for
12 clinical response at test of cure which was the
13 original pre- defined primary endpoint and considered
14 patients who died by study day 28 as clinical failures.
15 Values to the right of the zero reference line favor
16 Telavancin.

17 As you can see for both trials, that the
18 clinical response is relatively similar for all of the
19 analysis populations.

20 I will now discuss the 28-day all-cause
21 mortality endpoint.

22 This endpoint with evidence of treatment

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1 effect for antimicrobials is based on an agency
2 literature review and discussion at both the 2009
3 Nosocomial Pneumonia Workshop and the 2011 Anti-
4 Infectives Drugs Advisory Committee meeting. However,
5 there is not a clear consensus on the appropriate
6 timing of assessment for evaluating all-cause
7 mortality.

8 Discussions at the workshop focused on the
9 time point of 28 days after the randomization and
10 initiation of therapy.

11 There was some concern on the sensitivity of
12 the all-cause mortality endpoint because of the
13 possible effect of non-infection-related deaths. A 10-
14 percent non-inferiority margin is felt to be
15 justifiable based on the historical data for the all-
16 cause mortality endpoint.

17 I will now briefly discuss how the non-
18 inferiority margin was determined. More can be found
19 in the 2010 Drug Information Journal by Sorbello.

20 To determine the historical evidence of
21 treatment effect with active comparator, a literature
22 search identified 36 published articles. Unfortunately,

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1 no placebo-controlled studies were identified, so we
2 were not able to directly estimate the historical
3 treatment effect. Also, no placebo data for assessing
4 clinical response was identified.

5 The placebo effect for all-cause mortality
6 could be estimated indirectly based on 12 studies of
7 patients administered inappropriate, delayed, or
8 inadequate initial treatment that reported all-cause
9 mortality. These were non-randomized observational
10 cohort studies.

11 The active control effect could be estimated
12 from nine recent randomized clinical trials of
13 effective therapy with the primary endpoint of clinical
14 response and the secondary endpoint of all-cause
15 mortality.

16 Because the active control and placebo effect
17 had to be estimated separately, it is important to
18 assure the comparability of the two groups. The
19 observational studies did not provide a lot of details
20 on the baseline characteristics of the patients. The
21 only risk factors that were consistently reported were
22 age and severity of illness.

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1 The two groups were matched with respect to
2 both age and severity of illness. In addition, we
3 tried to assure comparability of the risk factors to
4 recent registrational clinical trials to give greater
5 confidence that the effect found would be similar to
6 that seen in current trials.

7 Based on these two factors, to estimate the
8 placebo effect, two out of the 12 placebo studies were
9 selected and to estimate the active control effect,
10 five out of the nine studies were selected.

11 I will now discuss how the active control
12 treatment effect was estimated. The fixed effects
13 margin approach was used.

14 We estimated the placebo and active control
15 mortality rates separately using a DerSimonian and
16 Laird random effects meta analysis. The weighted
17 placebo mortality rate was 62 percent with a 95-percent
18 confidence interval of 52 to 71 percent, and the
19 weighted active control mortality control was 20
20 percent with a 95- percent CI of 18 to 23 percent.

21 The active control treatment effect was
22 estimated to be 29 percent. This was calculated based

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1 on the difference between the lower 95-percent
2 confidence bound for the placebo and the upper 95-
3 percent confidence bound for the active control.

4 The mortality rate estimate was thought to be
5 conservative because of how it was constructed.

6 However, there are limitations with this approach and
7 thus uncertainty in the estimate that will be discussed
8 in the following slide.

9 I will now discuss the limitations of the
10 approach used.

11 First, there were no placebo-controlled
12 studies, so historical treatment effect could not be
13 directly estimated. The observed treatment effect for
14 HAP and VAP was derived from only seven studies, two
15 placebo and five active control. Across the studies,
16 there was a variability in baseline patient
17 demographics and disease severity reported. In
18 addition, the patients in the placebo studies were not
19 always well characterized.

20 The studies assessed mortality at different
21 time points or did not state when mortality was
22 assessed and also there was a cross-study comparison

1 that creates uncertainty due to the concern of the
2 comparability of the patients and, finally, changes
3 over time in the ICU patient management lead to
4 potential concerns of the constancy of the treatment
5 effect.

6 As discussed in the previous slide, there was
7 some uncertainty in our estimate of the active control
8 treatment effect. However, given the large active
9 control treatment effect, it was still felt that a 10-
10 percent non-inferiority margin was justifiable.

11 It should be noted that there were concerns
12 using a non-inferiority margin of greater than 10
13 percent for a mortality endpoint.

14 I will now discuss the mortality in the
15 Telavancin trials.

16 Because the protocol was not designed to
17 collect 28-day mortality, there was incomplete data for
18 the 28- day period in the original NDA. For Study 15,
19 there were 35 percent and for Study 19, it was 28
20 percent.

21 The incomplete survival data occurred
22 primarily because the protocol required follow-up seven

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1 to 14 days after the end of the therapy and the
2 duration of treatment was seven to 21 days with most
3 patients receiving seven to 10 days of treatment. Thus,
4 a large number of patients were not followed up to day
5 28.

6 The applicant retrospectively determined
7 survival status and the percentage of patients with
8 incomplete survival data for the 28-day period was
9 substantially decreased. This was down to six percent
10 for Study 15 and five percent for Study 19.

11 In the analyses, patients with incomplete
12 survival data were considered to be censored on the
13 last day they were known to be alive and the mortality
14 difference was estimated using the difference in
15 Kaplan- Meier estimates at day 28.

16 This slide shows results for 28-day all-
17 cause mortality. The mortality results for the various
18 analysis populations are provided for both trials. To
19 assess non-inferiority, the upper confidence bound in
20 red should be evaluated based on the 10-percent non-
21 inferiority margin that we discussed earlier.

22 In this graph, the agency primary analysis

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1 population of patients who had at least one Gram-
2 positive pathogen isolated at baseline, as well as the
3 all-treated population, are also marked in red.

4 In Study 15, Telavancin is tending to do a
5 little worse than Vancomycin for most of the
6 populations. It should be noted that the upper bound is
7 higher than the 10-percent margin for all of the
8 populations, except for the all-treated patients who
9 met the ATS IDSA criteria.

10 Of particular concern is that the lower bound
11 of the 95-percent confidence interval in the all-
12 treated population is just below zero, showing that the
13 mortality was almost statistically significantly higher
14 for the Telavancin patients than for the Vancomycin
15 patients. Note this was not seen in Study 19.

16 In Study 19, the mortality rates are more
17 similar between groups and the upper bound of the 95-
18 percent confidence interval was less than or equal to
19 10 percent for all of the populations, except for the
20 MRSA population, which is the smallest.

21 Note that there appears to be a differential
22 treatment effect between the two trials in the all-

1 treated population.

2 It should be noted that there were more
3 patients enrolled in Study 15 from the U.S. than in 19.
4 Also, as Dr. Lorenz pointed out, there were
5 statistically significantly more patients in Study 15
6 who had a history of diabetes, had chronic renal
7 failure, had a baseline creatinine clearance of less
8 than 50 ml per minute or were on hemodialysis.

9 These graphs present the Kaplan-Meier
10 survival curves in the all-treated population with the
11 Telavancin group presented as the blue curve and the
12 Vancomycin group as the red curve.

13 In Study 15, the curves begin to diverge at
14 seven to 10 days after initiation of study drug with
15 the Telavancin curve falling below the Vancomycin
16 curve. For Study 19, the curves are relatively close
17 together.

18 Similar to the last slide, these graphs
19 present the Kaplan-Meier survival curves in the
20 patients who had at least one Gram-positive pathogen
21 isolated at baseline. Again, the blue curve represents
22 the Telavancin group and the red curve represents the

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1 Vancomycin group.

2 In both studies, the curves begin to diverge
3 at seven to 10 days after initiation of study drug with
4 the Telavancin curve falling below the Vancomycin
5 curve. However, in Study 15, the curves continue to
6 stay separated through day 28 while for Study 19, the
7 curves come together by day 28 with the Vancomycin
8 patients suffering more late deaths.

9 I will now discuss the subgroup analyses that
10 were conducted.

11 The goal of these analyses was to assess the
12 consistency of the treatment effect. As noted by many
13 authors, there is need to interpret the results
14 cautiously. There's a serious multiplicity issue
15 because of the exploratory nature of the analyses. That
16 is, we looked at multiple factors resulting in increase
17 in the chance of a false-positive finding.

18 Also, because of the interaction tests that
19 will be used to detect the subgroup effect often has
20 low statistical power, we may not detect a subgroup
21 effect, even when one exists.

22 Because of the major concern of the over-

1 interpretation of the subgroup effects, we used the
2 prior biological evidence and primarily focused on
3 factors that either measure baseline renal function or
4 are baseline risk factors for renal injury.

5 I will now present some of the prior evidence
6 of the renal effects.

7 This slide presents the pooled results for
8 the clinical response at seven to 14 days after the end
9 of therapy, stratified by baseline renal function from
10 the complicated skin and skin structure infection
11 trials that is in the current Telavancin label.

12 You can see that the efficacy decreases for
13 the Telavancin patients as baseline renal function
14 decreases. This is not the case for the Vancomycin
15 patients.

16 The current label has a statement in the
17 Warnings and Precautions Section of the label of
18 decreased efficacy among patients treated for skin and
19 skin structure infections with moderate to severe pre-
20 existing renal impairment.

21 Also, I would refer to two other points that
22 was discussed by Dr. Lorenz. These are the

1 nephrotoxicity seen in the complicated skin and skin
2 structure infection trials and also the renal effects
3 seen in the pre- clinical studies.

4 In order to assess the subgroup effects, we
5 tested for a homogeneous treatment effect across the
6 levels of the baseline variables that either measure
7 renal function or risk factors for renal injury.

8 The results are given in this table. The
9 possible effect modifiers that were identified are the
10 baseline creatinine clearance in Study 19 and
11 congestive heart failure in Study 15 and the receipt of
12 nephrotoxic drugs at baseline in both studies.

13 I will now present stratified analyses to
14 further investigate the possible subgroup effects.

15 This slide presents the 28-day all-cause
16 mortality results in the all-treated population by the
17 baseline creatinine clearance.

18 In Study 15, the results tend to favor
19 Vancomycin for patients with baseline creatinine
20 clearance less than 80 ml per minute. In Study 19, the
21 treatment effect of Telavancin relative to Vancomycin
22 decreases as baseline renal function worsens. Note

1 this is the same relationship that was seen in the
2 complicated skin and skin structure infection trials
3 for the clinical response endpoint at TOC.

4 Of note is that the applicant is proposing to
5 put a statement in the Warnings and Precautions Section
6 of the label of increased mortality for patients with
7 pre-existing severe renal impairment, that is, patients
8 with a creatinine clearance less than 30 ml per minute.

9 This slide shows the results for the 28-day
10 all- cause mortality for patients who had at least one
11 Gram- positive pathogen isolated at baseline,
12 stratified by the baseline creatinine clearance. The
13 results are similar to those seen in the all-treated
14 population.

15 These are the stratified analyses of the 28-
16 day all-cause mortality in the all-treated population
17 that are stratified by the baseline creatinine
18 clearance where patients are categorized into two
19 groups, into the two groups presented in the current
20 Telavancin label, those with baseline creatinine
21 clearance greater than or equal to 50 ml per minute and
22 those below 50 ml per minute.

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1 As you can see, the analyses favor Vancomycin
2 for patients with a baseline creatinine clearance less
3 than 50 ml per minute. This is not the case for the
4 creatinine clearance greater than or equal to 50 ml per
5 minute.

6 This slide presents the analyses of the 28-
7 day all-cause mortality in the all-treated population,
8 stratified by risk factors for renal injury.

9 The first four rows represent the results
10 stratified by baseline history of diabetes. As you can
11 see, the treatment differences do not vary, based on
12 the history of diabetes. That is true for both
13 studies.

14 The next four rows are the analyses
15 stratified by age where age groups are classified by
16 those greater than or equal to 65 years of age and less
17 than 65 years. The treatment difference also does not
18 depend on the age of the patients. This is true for
19 both trials.

20 The next four rows in the analyses are
21 analyses stratified by the history of congestive heart
22 failure. If you recall, this was identified as a

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1 possible effect modifier of Study 15. It can be seen
2 in the stratified analyses where mortality strongly
3 favors Vancomycin for patients with a history of
4 congestive heart failure where the mortality appears to
5 be more similar in patients without a history of
6 congestive heart failure. Note that this was not seen
7 in Study 19 where the two treatments appear similar,
8 regardless of the history of congestive heart failure.

9 The next four rows of the analyses are
10 stratified by the receipt of baseline nephrotoxic
11 medications. This risk factor was identified as a
12 possible effect modifier for both studies.

13 As you can see, patients who received
14 baseline nephrotoxic medications fared worse on
15 Telavancin relative to Vancomycin. In contrast, the
16 relative treatment effect in patients who did not
17 receive baseline nephrotoxic medications was different
18 than those who did. This occurred in both trials.

19 So, in summary, for the pre-defined clinical
20 response, there were similar response rates for both
21 treatment groups seen in both trials. However, the
22 interpretation of the results is not clear.

1 It is difficult to interpret the results
2 because of the lack of historical data to justify the
3 non- inferiority margin and also there was inability to
4 rule out pneumonia as being related to the deaths in
5 some patients who died in close temporary proximity to
6 the day of the clinical cure assessment. This could be
7 related to the lack of clear definition of clinical
8 response resulting in an endpoint that is not well
9 defined and reliable or it's an issue with determining
10 the window that maximizes the number of deaths related
11 to pneumonia and minimizes the number of non-infection-
12 related deaths.

13 For the 28-day all-cause mortality endpoint,
14 this is the endpoint with the evidence of a treatment
15 effect and Telavancin met the non-inferiority margin in
16 Study 19 for the agency's primary analysis population
17 of patients who had at least one baseline Gram-positive
18 pathogen. However, non-inferiority was not
19 demonstrated in Study 15.

20 Also, there was a trend of increased
21 mortality for Telavancin in Study 15 in the all-treated
22 population and also subgroup analyses identified

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1 possible effect modifiers related to baseline
2 creatinine clearance, congestive heart failure, and
3 receipt of nephrotoxic medications.

4 Thank you.

5 DR. MOORE: Thank you. Clarifying Questions
6 from the Committee

7 DR. MOORE: Are there any clarifying
8 questions for the FDA? I'm sure there are some.

9 Dr. Parise?

10 CAPT PARISE: Yes. I have two sort of fairly
11 general questions.

12 One is when -- you know, I wasn't here at the
13 advisory committee meeting but I read it in the slides
14 that the FDA presented early on. So I think, I mean,
15 my issue is sort of one -- it gets down to one versus
16 two trials at some point because in the guidance, it
17 says you need two trials but in the advisory committee
18 meeting, it says one trial, a single trial could be
19 acceptable if there was adequate supporting evidence.

20 So what is adequate supportive evidence, and
21 what is truth? We don't know.

22 And then I guess my other issue is, you know,

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1 if these seem like they were really one protocol, you
2 know, it almost seemed arbitrary to me where you would
3 divide it.

4 I mean, is there other experience with this?

5 I mean, they were in so many different countries, it
6 would be hard to say. You know, one was in -- there
7 was really a difference between these two. So I'm
8 struggling to sort of understand that.

9 DR. LAESSIG: First, I'll start with the
10 first part of your question and then maybe turn the
11 second part over to Dr. Komo to discuss poolability.

12 At the committee meeting last November, there
13 was discussion about one versus two and the committee
14 suggested that one may be reasonable with adequate
15 supportive evidence.

16 Now what was adequate supportive evidence
17 sort of varied according to committee members. You
18 know, you could say, okay, Phase II data and the same
19 indication or evidence of efficacy and other
20 indications, whether it be community-acquired
21 pneumonia. Is that acceptable as supportive evidence?

22 From my recollection, many members didn't

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1 feel that that was supportive. Is skin indication
2 supportive? Some members thought maybe yes and some
3 thought maybe no.

4 So I would sort of turn that question back to
5 you when you think about whether one trial with
6 supportive evidence is okay, what you would consider
7 adequate supportive evidence.

8 DR. COX: I just might add, too, I mean, you
9 know, a big part of the discussion, too, at the
10 November meeting focused on the issue of trial
11 feasibility. In essence, you know, what can be
12 accomplished in an area such as nosocomial pneumonia
13 and doing trials and so that that was a lot of the
14 discussion around one trial, you know, to look at ways
15 to, in essence, have feasible pathways for development
16 of drugs for nosocomial pneumonia and then try and
17 utilize supportive data, you know, in addition to a
18 single trial in nosocomial pneumonia/HAP/VAP.

19 DR. MOORE: Dr. Shyr?

20 DR. SHYR: Can we move to Slide 17, please?
21 Dr. Komo's slide. Slide 17.

22 Okay. So we do know for the -- especially

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1 for the FDA interested in one Gram-positive, that's the
2 power for that confidence interval. That power for
3 that endpoint is much smaller.

4 Have you ever done -- if assume you have 80-
5 percent power, so therefore your confidence interval
6 would be narrow, so plus/minus would be -- the half
7 width would be much narrow because of a bigger sample
8 size.

9 If you assume you have enough power for your
10 greater than one Grams for 0015 Study, what is your
11 margin would be? Because the sponsor already said,
12 based on this, your power is very, very low. So
13 therefore you may have much wider confidence interval.
14 So you have the chance over 10 percent is higher.

15 If you have 80-percent power, have you ever
16 done that? What is your confidence interval for the
17 greater than one Gram for 0015 Study? Would that still
18 be over 10 percent or that will be less than 10
19 percent?

20 DR. MOORE: Dr. Komo?

21 DR. KOMO: Scott Komo. I'm sorry. We have
22 not done that calculation yet, no.

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1 DR. SHYR: Okay. So, in addition, since we
2 know FDA study is less than 50 for the creatinine
3 clearance, less than 50 is the cut-off, if you remove
4 50, all the patients less than 50 away, have you --
5 what is this table in this Slide 17? How will that
6 change, too? Do you have that slide? Or 30, because
7 sponsor picks 30 as the cut-off.

8 DR. KOMO: Could you go to Slide 26, please?
9 So these are the individual results classified as
10 greater than 50 or less than 50.

11 DR. MOORE: Can't hear you. Could you speak
12 into the microphone, Dr. Komo? I'm sorry. Thank you.

13 DR. KOMO: These are the stratified results
14 by greater than 50 or less than 50. So I think these
15 are the results you're looking for.

16 DR. SHYR: But this is the AT population. You
17 want to focus on greater than one Gram plus, right?
18 That's what you want to, FDA want to focus on that
19 population. Greater than one Gram-positive.

20 DR. KOMO: I don't have that right now. I
21 could calculate that for you in a little while and get
22 back to you.

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1 DR. SHYR: Okay. Thank you.

2 DR. MOORE: Thank you. Dr. Calhoun?

3 DR. CALHOUN: Thanks. I have a couple of
4 questions.

5 One of the issues that came up, I think, at
6 the November 2011 meeting was the use of rate ratios as
7 opposed to absolute differences. For a simple
8 clinician, the difference between 80-percent mortality
9 and 90- percent mortality is quite a bit different than
10 the difference between 10- and 20-percent mortality and
11 so the rate ratios help to get to that.

12 Neither the sponsor nor the FDA dealt with
13 that metric at all. So I'd be interested in hearing a
14 little bit about that.

15 The second thing that strikes me is that this
16 is a new indication proposal for pneumonia and I've
17 heard really nothing about the effect of severity of
18 pneumonia on the differential efficacy, if any, between
19 these two drugs. We heard about differential efficacy
20 related to renal disease and the sponsor mentioned and
21 the FDA, I think, has shown clearly that there is a
22 renal toxicity issue that's been well known and that's

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1 not new.

2 But is there a difference in the responses of
3 people who've got really bad pneumonia compared to
4 people who have less bad pneumonia? There are
5 obviously scores for scoring pneumonia severity. We
6 haven't heard anything about that which surprises me a
7 little bit, given that this is a pneumonia indication.

8 DR. MOORE: Dr. Komo, did you want to handle
9 that?

10 DR. KOMO: Yes. In terms of the risk ratios,
11 what you're saying makes a lot of sense. I think we
12 left it as it was for this application. We were
13 primarily focused on the risk difference because these
14 were greater than 20- percent mortality as discussed at
15 that workshop, and I think it was one less thing that
16 we were going to change as opposed to changing the
17 metric at this point, too, for this application.

18 In terms of the severity, I think maybe Dr.
19 Lorenz might be better able to answer that than I am.

20 DR. MOORE: Dr. Lorenz?

21 DR. LORENZ: Yeah. I think we had that
22 analysis by APACHE but I don't think we have that data

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1 right now. I don't know. Perhaps the sponsor has more
2 information on that.

3 DR. CALHOUN: I'm just going to follow up,
4 Dr. Moore.

5 So the follow-up question is I'm a little bit
6 concerned that we're comparing apples and oranges here
7 with the various populations and subsets and so forth,
8 and I'm not sure that it's fair to call it pick and
9 choose but I'll use that terminology, that we're
10 picking and choosing particular signals that we want to
11 focus on, whether they be efficacy signals, in which
12 case we're generally conservative. We don't like to
13 pick and choose. We like to see data that are solid
14 and so forth.

15 I'm a little bit concerned that when we're
16 looking at the safety signals, we're doing the pick and
17 choosing and finding things that happen to fall out and
18 again with the multiple testing concerns that Dr. Komo
19 mentioned early on, these being exploratory analyses,
20 are these -- is this a proper way to approach the
21 assessment of the safety signal?

22 DR. MOORE: Dr. Cox?

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1 DR. COX: Yes. So, I mean, it is fair, you
2 know. Looking at the data after the studies have been
3 completed, I mean, particularly for safety, we
4 oftentimes are looking through to see what we find, in
5 essence, to see what pops out and, yes, that's inherent
6 in the process, so it's a fair comment.

7 One of the things we also do, too, is that we
8 oftentimes look at, you know, each of the two studies.
9 We may also look and see what we learn from the skin
10 infection studies. We may look for consistency of
11 effect, and then, in addition to and you saw some of
12 the information presented on the Pharm Tox studies, you
13 know, what did we learn from the animal studies?

14 So, you know, your comment is correct, you
15 know. Post-hoc analyses and looking to see what you
16 find, but that's oftentimes why we're looking for
17 consistency across, you know, multiple studies and/or
18 what we see in the animal studies to help, you know,
19 address some of those concerns about, you know, all the
20 looks that are being taken.

21 DR. MOORE: Thank you. Dr. Goetz and then
22 Dr. Parise.

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1 DR. GOETZ: So what I'm trying to get back to
2 is that question that was raised by Dr. Parise that I
3 didn't hear an answer, at least that I thought was full
4 or I didn't fully understand perhaps, and that is
5 really the criteria for combining the results of the
6 two studies.

7 I'm coming back to what I remember as being
8 part of the discussions on the November 2011 panel,
9 where I had the opportunity to contribute, where
10 there's discussions about that for the MITT population
11 being the critical population, that if two trials were
12 done, it was anticipated by some members of the panel
13 that the microbiological population of interest might
14 be too small in each study and that thus the studies
15 would be combined to a single to provide a large enough
16 population for analysis for the microbiological
17 intention to treat analysis.

18 It's in the documents that the FDA provided,
19 there is concerns that there's sufficient heterogeneity
20 across these two studies to do so and we've touched on
21 that, but what I'm wondering, I guess, is that whether
22 the -- if one corrects or adjusts for the differences

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1 in baseline variables amongst the patients, different
2 rates of renal dysfunction, different amounts of
3 diabetes, has it been touched on, do we see similar
4 treatment effects across the two studies and does that
5 then, from a statistical perspective, and I'll call on
6 my colleagues on the panel to address this more fully,
7 as well, provide a justification for combining those
8 subpopulations?

9 My take on what the FDA has presented thus
10 far is that there's a little bit of discrepancy on the
11 effect of congestive heart failure amongst the two
12 populations but otherwise the effects of the baseline
13 variables seem to be the same which suggests to me as a
14 non-statistician that one might combine those
15 populations, but I think that's a critical issue for us
16 all to understand.

17 DR. FOLLMAN: Could I take a shot at that?

18 DR. MOORE: Yes, please. Dr. Follman.

19 DR. FOLLMAN: So I think, you know, you make
20 some very good points about one study or two studies
21 and combining. I think there are two issues that I'd
22 like to talk about.

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1 One is two studies we often do because that
2 gives us greater assurance that, in fact, the result we
3 see is reliable if it's done in ideally somewhat
4 different studies.

5 Now these two studies had identical protocols
6 and so on but they seem to be done differentially in
7 the U.S. versus other countries and also we do see
8 these imbalances in important risk factors. So I think
9 these are two studies and sort of the standard view
10 about how you interpret them holds here that we want to
11 see, you know, a win on both basically, and I think the
12 combining issue really is, as you suggest, it's a good
13 thing to do sort of as a confirmatory -- well, as a
14 supportive kind of analysis for subgroups, like the
15 MITT, or maybe other groups where you don't have a lot
16 of patients and it's understood you won't at the start
17 of the study. So that's more where it's combining.

18 The regression analysis that you propose is
19 an excellent way to try and sort of level the playing
20 fields and take into account that the baseline
21 characteristics differ between the two groups and it's
22 a very straightforward kind of way, I think, to address

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1 the issue and I think it would be good to do those
2 kinds of analyses.

3 I haven't seen them in any of the reports.
4 It's a very good suggestion to do, I think, to do
5 regression modeling for the MITT and other subgroups
6 for which you have small numbers to try and level the
7 playing fields and combine the study, but still for the
8 overall effect, I'm looking at the two studies really.

9 DR. MOORE: Thank you. Dr. Parise, you had a
10 follow-up question.

11 CAPT PARISE: I didn't quite get my second
12 question answered before, but after this discussion, I
13 mean, I guess I'm still struggling with these two
14 studies. I mean, that was 274 sites in 38 countries
15 and so with the exact same protocol. I mean, you could
16 have cut it a different way had you divided it
17 differently.

18 So, I guess, has the FDA -- it seems to me
19 that there was two studies here just made because there
20 had to be two studies. I mean, has the FDA dealt with
21 this before where, you know, the requirement is two
22 studies and this happens and, you know, how -- is there

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1 any other experience with that before?

2 DR. COX: So you're correct. At the time the
3 studies were being planned, in essence, we were always
4 asking for two studies in nosocomial pneumonia. So, in
5 fact, that's what drove the decision, in essence, to
6 have the two studies.

7 You can see that there was, you know, some,
8 you know, plan ahead of time to look at the MRSA
9 population across the two studies because of the
10 numbers issue. So, you know, that was the plan and
11 that's the reason for the two studies.

12 Now help me a little bit more with the rest
13 of your question. You're wanting to know?

14 CAPT PARISE: I guess it seems to me an
15 artificial, to me an artificial division, and have you
16 all faced this in other approvals that you've done
17 where you've had, you know, two studies done with the
18 exact same protocol and, you know, is the typical way
19 that you look at it in two different studies?

20 DR. COX: And I think what you're asking is
21 have we ever seen two studies before where there's been
22 some differences in one study than the other, even

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1 though the protocol was identical, and then how did we
2 deal with the can you combine it issue?

3 I mean, I think that, in essence, is the
4 question that we're -- you know, the question the
5 committee's, you know, here to talk about a little bit
6 today. I mean, we talked about, you know, some of the
7 findings from the two studies.

8 You know, we've heard the idea of a
9 regression analysis to try and, you know, look across
10 the two studies as a good idea and so, yeah, I mean,
11 we're looking for your input on this very issue to see
12 what folks think.

13 How do we deal with the results of the two
14 trials and, you know, advice on that very issue?

15 I see Dr. Barriere standing up. I'm not sure
16 if you all have regression analyses that you all have
17 performed.

18 DR. MOORE: Dr. LaVange? Actually, let me
19 have Dr. LaVange from the FDA speak for just a moment.

20 DR. LaVANGE: I just wanted to add a couple
21 of comments before you spoke. I think I know what
22 you're going to show us.

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1 So, you know, we like two studies for the
2 reasons that Dr. Follman mentioned. The replication
3 gives you assurance that what you've seen is not
4 spurious. You see it twice. There's two sets of
5 investigators. There's two protocols. There's two
6 steering committees. Just being able to go through the
7 very hard process of running a successful study twice
8 is very good.

9 We often ask for the two studies to be pooled
10 to look at subgroups that don't have enough power to
11 see differences on their own and the problem with
12 replication and non-inferiority studies is if you have
13 a study that's positive and another study that's not
14 and you put them together, then you are moving towards
15 no difference and if it's a superiority study that is
16 conservative, if it's a non-inferiority study, it's
17 anti-conservative, and so that's why we might seem a
18 little nervous about the pooling.

19 If you knew ahead of time you were going to
20 pool and you could pre-specify some important risk
21 factors that you knew were related to outcome and that
22 you could say we will adjust for these in case there

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1 are differences between the two studies and you had
2 that all set up a priori, then we would be very
3 comfortable with it.

4 The problem here, which is unfortunate for
5 the sponsor, is the mortality endpoint was post-hoc,
6 you know, pooling the studies and adjusting for factors
7 was post-hoc, and so we don't have the luxury of being
8 that comfortable because of that reason.

9 And then my final comment would be that we
10 did in the agency look at the differences between the
11 studies in the all-treated and we looked again at the
12 differences between the studies in the Gram-positive
13 and Dr. Komo can back me up. I'm not sure it's in the
14 Briefing Document, but there was a little bit less
15 heterogeneity between the two studies and the Gram-
16 positive. So we were a little more comfortable with
17 that pooling than with the all- treated but I can't
18 remember if it's in the background.

19 DR. MOORE: Dr. Komo?

20 DR. KOMO: It was not in the background, but
21 that is true.

22 DR. MOORE: Okay. Last comment we'll take

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1 from Dr. Barriere.

2 MR. BARRIERE: Thank you. This referred to
3 the comments from Dr. Goetz and then confirmed by Dr.
4 Follman about the use of regression analysis, although
5 the points that Dr. LaVange made are, of course, well
6 taken, but to address her comments, I think not now but
7 after lunch perhaps Dr. Gary Koch can talk about those
8 kinds of issues.

9 But we did do a regression analysis exactly
10 as Dr. Follman had described and that's what Dr. Mammen
11 described very briefly in his presentation and we'd be
12 happy to go into more detail of that in the methodology
13 again after lunch.

14 DR. MOORE: That'd be fine. All right. So
15 let's break now for lunch. We'll resume discussions
16 here at 1 o'clock with the Open Public Hearing. Please
17 take any personal belongings you may want with you at
18 this time. The room will be secured by FDA staff
19 during the lunch break. You may not be allowed back
20 into the room until we reconvene.

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

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1 lunch amongst yourselves or with any member of the
2 audience.

3 Thank you.

4 (Whereupon, at 12:14 p.m., the meeting was
5 recessed for lunch, to reconvene this same
6 day at 1 o'clock p.m.)

7 AFTERNOON SESSION

8 (1:03 p.m.)

9 Open Public Hearing Session

10 DR. MOORE: All right. We'll commence with
11 the Open Public Hearing at this point.

12 Both the Food and Drug Administration and the
13 public believe in a transparent process for
14 information- gathering and decision-making. To ensure
15 such transparency of the Open Public Hearing Session of
16 the advisory committee meeting today, the FDA believes
17 that it is important to understand the context of an
18 individual's presentation.

19 For this reason, the FDA encourages you, the
20 Open Public Hearing speaker, at the beginning of your
21 written or oral statement to advise the committee of
22 any financial relationship that you may have with the

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1 sponsor, its product, and, if known, its direct
2 competitors.

3 For example, this financial information may
4 include the sponsor's payment of your travel, lodging,
5 or other expenses in connection with your attendance at
6 the meeting.

7 Likewise, the FDA encourages you at the
8 beginning of your statement to advise the committee if
9 you do not have any such financial relationships.

10 If you choose not to address this issue of
11 financial relationships at the beginning of your
12 statement, it will not preclude you from speaking.

13 The FDA and this committee place great
14 importance on the Open Public Hearing process. The
15 insights and comments provided can help the agency and
16 this committee in their consideration of the issues
17 before them.

18 That said, in many instances and for many
19 topics, there will be a variety of opinions. One of
20 our goals today is for this Open Public Hearing to be
21 conducted in a fair and open way where every
22 participant is listened to carefully and treated with

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1 dignity, courtesy, and respect. Therefore, please
2 speak only when recognized by the Chair.

3 Thank you for your cooperation.

4 Will Speaker Number 1 step up to the podium
5 and introduce yourself? It's Dr. Yttri, I think,
6 right?

7 DR. YTTRI: That is correct. My name is Dr.
8 Jennifer Yttri, and I have a Ph.D. in Immunology from
9 Washington University in St. Louis.

10 I thank you for the opportunity to speak
11 today on behalf of National Research Center for Women
12 and Families.

13 Our organization is a nonprofit research
14 center that does not accept funding from pharmaceutical
15 companies and therefore I have no conflicts of
16 interest.

17 The FDA has denied approval for Vibativ for
18 treatment of nosocomial pneumonia on two separate
19 occasions. After reviewing the required additional
20 data, there is not sufficient evidence to support
21 Telavancin as a safe and effective treatment for
22 nosocomial pneumonia.

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1 Instead, the new data raise more questions
2 about a high mortality rate associated with Telavancin,
3 especially in the intent-to-treat population.

4 Differences in mortality cannot simply be
5 explained by pre-existing conditions. In each of the
6 randomized trials, Telavancin and Vancomycin groups are
7 similar in pre-existing medical conditions. Without
8 additional trials, it cannot be determined if the day
9 28 mortality is associated with the drug alone or with
10 the combination of Telavancin and pre-existing renal
11 impairment.

12 It would be completely inappropriate to
13 combine the two randomized trials to mask any mortality
14 difference.

15 There is no way to determine if Telavancin is
16 non-inferior given the lack of clarity in study design,
17 especially the outcomes chosen by the sponsor. We
18 agree with the FDA reviewers who diplomatically stated
19 that the interpretation of results, based on clinical
20 response, is limited.

21 To be more blunt, clinical response is a
22 poorly- defined endpoint that does not reliably measure

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1 patient benefit.

2 Consider the large number of patients who
3 were considered clinical cures at the test-of-cure
4 assessment but subsequently died by day 28. Using the
5 company's definition of clinical response, which is an
6 unclear combination of laboratory tests and clinician
7 judgment, there is no way to evaluate any actual
8 benefit or comparison with other antibiotics.

9 When looking at the data for the microbial-
10 relevant population, every parameter tested trends in
11 favor of Vancomycin over Telavancin. If pneumonia
12 wasn't a serious life-threatening and contagious
13 disease, a slightly lower effectiveness might be
14 acceptable for a drug with better safety profile, but
15 Telavancin has numerous adverse side effects, including
16 nephrotoxicity, complications with renal insufficiency
17 in pregnancy, and a potentially higher mortality rate.
18 Any loss of effectiveness does not balance this risk.

19 Your job is to review the science, not reward
20 the company for perseverance in their efforts to get
21 this drug approved.

22 Based on the data, Vibativ must be denied

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1 approval for treatment of pneumonia.

2 Doctors like to have choices when they select
3 treatments for patients but we do patients and their
4 doctors no favors by approving new drugs that are less
5 safe and no more effective than drugs already
6 available.

7 If this drug is more effective for some
8 population, then the drug should be studied in and used
9 only in that patient population.

10 Today's study uses a non-inferiority trial
11 with patients that may or may not have pneumonia.
12 Benefits of the drug should not be assumed for groups
13 that have not been studied. To provide solid evidence
14 supporting Telavancin as a safe and effective drug, the
15 FDA should require superiority studies using the 28-day
16 mortality endpoint.

17 The study must be conducted in the
18 appropriate patient population that will have limited
19 treatment options already, not patients who have safer
20 and more effective options. Not only would such a
21 study require fewer patients, it will provide clear
22 data to address the benefits of Telavancin given the

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1 documented adverse effects.

2 Unfortunately, warnings on labels are also
3 not adequate to protect patients. The only way to help
4 doctors save their patients is by keeping this drug off
5 the market.

6 Thank you.

7 DR. MOORE: Thank you. The Open Public
8 Hearing portion of this meeting is now concluded and we
9 will no longer take comments from the audience.

10 The committee will now turn its attention to
11 address the task at hand.

12 Actually, before we do that -- excuse me --
13 I'm sticking to the script, Dr. Laessig, you had some
14 comments you wanted to make?

15 DR. LAESSIG: Yes, I do, actually. On behalf
16 of the FDA, I'd like to take a couple minutes to
17 acknowledge committee members who are rotating off the
18 advisory committee as of tomorrow.

19 So Dr. Kaplan, Moore, and Chatterjee, we
20 thank you for your dedication to this process, for
21 taking time out of your busy schedules to participate,
22 and for your always thoughtful and sage advice. You

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1 always manage to think of issues that we haven't and
2 for that we are extremely grateful, and as no good deed
3 goes unpunished, we'll probably be inviting you back,
4 and despite our limited budget, we were able to
5 scrounge up some funds to give you an appropriate token
6 of our appreciation and we have a plaque for each of
7 you instead of me writing a thanks out on a pile of
8 napkins.

9 So with that, I'll say thanks again and until
10 next time.

11 (Applause.)

12 DR. MOORE: Wow! That was completely
13 unanticipated and I don't know what to say. Thank you
14 very much. I don't know what to say next. I'm very
15 flattered and, yeah, thank you again.

16 It's an honor to serve. I'm speaking for Dr.
17 Kaplan and Dr. Chatterjee, I'm sure, but it's really a
18 pleasure and an honor to serve on this committee.

19 Let's move on. I'm being told I need to move
20 on and, yes, we will. But before we do, before we go
21 on to the Charge to the Committee, we had to cut off
22 discussion regarding questions of the sponsor earlier.

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1 So we'd like to ask if anybody has any
2 questions of the sponsor that were not able to be
3 asked.

4 Yes, Dr. Calhoun?

5 DR. CALHOUN: Thanks. So one of the safety
6 signals that actually does concern me is the apparent
7 consistent evidence of an increased mortality risk for
8 those people who have congestive heart failure and so
9 I'm interested in hearing a little bit about how that
10 diagnosis is made because I think it might have
11 something to do with labeling should this drug be used
12 in that context.

13 So either the FDA, from the standpoint of the
14 safety database that was polled to get that
15 information, or perhaps from the sponsor or perhaps
16 both, I'd really like to hear how the diagnosis of
17 congestive heart failure was made.

18 DR. MOORE: Dr. Barriere?

19 MR. BARRIERE: Thank you. The diagnosis was
20 made by the investigators. Unfortunately, we didn't
21 collect any additional information about whether it was
22 New York Card Class 1 through whatever. So it was

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1 congestive heart failure on the case report form and
2 then we also did a thorough search of the medical
3 history to find other patients and other evidence of
4 congestive heart failure, looking for various medical
5 history terms. So that was the collective population of
6 patients who had congestive heart failure.

7 I'd like to ask Dr. Mammen to perhaps do a
8 little bit further explanation of our analysis of the
9 risk of congestive heart failure.

10 DR. MAMMEN: We evaluated the impact of
11 congestive heart failure on mortality, both as an
12 individual factor and as part of the larger
13 multivariate analysis we've done.

14 ON-5 up, please. ON-5 up. So the top line
15 here shows that, both in Study 15 and 19 and the
16 combined study, congestive heart failure on its own is
17 indeed associated with increased mortality. However,
18 the second line or third line shows that there is no
19 significant interaction with treatment in either study
20 or in the combined population.

21 Furthermore, we've done a fairly exhaustive
22 examination of cardiac safety in the safety population

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1 and see no evidence of a signal relative to Vancomycin.

2 If anything, there are signals in the other direction.

3 DR. MOORE: Thank you. Dr. Alston?

4 DR. ALSTON: I was just hoping to make a

5 quick comment, not a question.

6 Part of the proposed indication is for
7 pneumococcal pneumonia and we haven't talked about that
8 and we think of that traditionally as a community-
9 acquired pathogen. It's not a traditional nosocomial
10 pathogen, and I think, if I interpreted the data
11 correctly, I think it only showed up in seven percent.
12 I think it was 29 Telavancin patients were coded as
13 having pneumococcus and I suspect some of those just
14 reflected pharyngeal flora that they came in from the
15 community with.

16 There's not an urgent need for a drug to
17 treat pneumococcus as a nosocomial pathogen and I think
18 a third of the patients got drugs, namely Piptaso and
19 Imipenem, that have activity against pneumococcus. So
20 even that small number got muddled even further and I
21 think as problematic as this approval is, I think we
22 should focus on the utility of Telavancin as an

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1 alternative agent for MRSA hospital-acquired pneumonia
2 in people who are having problems with Vancomycin or
3 Linezolid and not confuse the issue with a community
4 pathogen for which there's really no data to support
5 the approval.

6 DR. MOORE: Thank you. Mr. Mullins?

7 MR. MULLINS: Yes. One of the questions I
8 have for the sponsor is I'd like to see more
9 information from a public health perspective. I'm
10 concerned that because we aggregate the data, that we
11 lost a lot of the delineation on certain
12 subpopulations.

13 For instance, one of the areas where I'd like
14 greater detail and specificity is in the area of
15 patients with COPD. We know that Telavancin, we know
16 that it has adverse event of dyspnea, so the shortness
17 of breath, and then we see in CS-22 that one of the
18 causes of mortality is respiratory failure.

19 So my concern is the correlation, direct
20 correlation between dyspnea and respiratory failure and
21 how that affects that subpopulation of COPD patients
22 within the U.S. and throughout North America.

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1 So could you comment on that area because
2 that's my concern is that through this aggregation of
3 data, that we have lost greater detail in understanding
4 of subpopulations? So we are making false assumptions
5 about the general population based on this aggregate
6 data.

7 So I'd like for the sponsor to speak to that,
8 to those issues.

9 MR. BARRIERE: Two parts to that. One would
10 be to address your direct question which had to do with
11 COPD and the association with dyspnea and the
12 mortalities associated with respiratory failure and we
13 haven't looked at that. We haven't done the
14 association to see whether or not there is dyspnea.

15 There would, of course, be dyspnea in
16 patients with COPD, so that would be expected. We
17 haven't looked to see if there was dyspnea in non-COPD
18 patients. For example, we've not simply looked at
19 that.

20 But to address your question or comment about
21 subgroups and the ability to detect signals in
22 patients, particularly safety signals in populations,

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1 such as this, I'd like to ask Dr. Gary Koch to make a
2 comment about the appropriateness of aggregating the
3 data in order to find signals.

4 DR. KOCH: So slide up for CE-7. So the
5 program had a way of studying a large number of
6 patients, 1,500 patients or so, very diversely
7 recruited from 274 sites in 38 countries. So it has a
8 very diverse population and it needed to do that to get
9 enough patients with MRSA and other special pathogens
10 in order to do assessments of those for the combined
11 studies, recognizing that the patients would have a
12 diversity of other morbidities.

13 The assessment of safety is also more
14 informed when it looks at the totality of the data,
15 recognizing the diversity that the patients will have
16 in terms of co- morbidities, which could include COPD,
17 could include diabetes, could include heart failure and
18 other things, and when you look at the totality of the
19 data, you get the most information with respect to the
20 assessment of safety, identification of safety signals,
21 and then you can also do regression models as were
22 previously specified, where you identify all of the

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1 factors that are prognostic for mortality and the
2 sponsor did that and among those that they had
3 identified as prognostic only creatinine clearance was
4 the one that seemed to have effect modification,
5 meaning that the difference between treatments varied
6 according to whether the creatinine clearance was less
7 than 30 or not.

8 I did forget to mention that I am Gary Koch.
9 I am with the University of North Carolina
10 Biostatistics Department. My only financial
11 affiliation with the sponsor is through a cooperative
12 agreement that is directly to my university and that
13 agreement does provide funds for salary support as well
14 as travel.

15 MR. MULLINS: Do you know the demographic
16 breakdown of the study group?

17 DR. KOCH: I think the sponsor can show the
18 demographic background for both studies and may have
19 done that to some extent in the core.

20 MS. COLEMAN: We can. I will make an added
21 comment that I forgot to mention before, is that you
22 mentioned the dyspnea was an adverse event, but it was

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1 no more frequent. It was very low and it was no more
2 frequent in the Telavancin group than the Vancomycin
3 group.

4 But we do have the studies broken down by the
5 geographic regions. You would want geographic region
6 or U.S./non-U.S. or?

7 (Off-microphone response.)

8 MR. BARRIERE: So you want to see how
9 patients - - where they were derived from?

10 MR. MULLINS: Yes, sir.

11 MR. BARRIERE: So by country. Bear with us a
12 moment.

13 (Pause.)

14 MR. BARRIERE: GP-27 up, please. So here are
15 the countries that were enrolled in each of the
16 studies. As you can see, there were a wide variety from
17 all over the world where patients were enrolled. There
18 were some countries where both studies were conducted,
19 never in the same site, and some studies were only in
20 one of the studies was conducted.

21 MR. MULLINS: This doesn't tell me --

22 DR. MOORE: Mr. Mullins, please use your

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1 microphone.

2 MR. MULLINS: Yes. Could you give me greater
3 specifics on percentiles and percentages of subjects
4 that came from particular countries because this
5 doesn't really give me an understanding of the subject
6 base?

7 MR. BARRIERE: Yes, we have that. GP-29.
8 This is not necessarily percentages but it gives you
9 numbers by country in each of the studies. It also
10 shows you which countries were enrolled in both studies
11 and it shows numbers of patients and, of course, the
12 country with the largest number of patients that was
13 enrolled in either of the studies was the United
14 States.

15 MR. MULLINS: Is there any rationale in
16 selection or percentages, greater percentages from
17 particular countries of enrollment, rate of enrollment?
18 Is there any explanation for that?

19 MR. BARRIERE: The studies enrolled the
20 patients as they come. These studies are incredibly
21 difficult to do, finding patients who meet the criteria
22 and who -- the inclusion criteria and who have the

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1 pathogens that we're interested in and have the
2 characteristics that we're interested in. It's very,
3 very hard to do. So we allow the country -- pretty
4 much allowed the countries to enroll as many as they
5 possibly could without really any restrictions or caps.

6 DR. MOORE: Thank you. Dr. Barriere, you had
7 said before the lunch break you were going to show some
8 regression analysis.

9 MR. BARRIERE: Yes. I'd like Dr. Hopkins to
10 address that and if you would allow, after he finishes,
11 I'd just like to make a brief statement.

12 DR. MOORE: Sure.

13 DR. HOPKINS: So this is just a follow-up
14 from this morning.

15 I wanted to talk about the regression process
16 that we used and the advantages that we had from, I
17 think, doing the regression analysis. We've run
18 extensive regression analyses, analysis using Cox
19 Proportional Hazards Regression Models.

20 This is a methodology that's applicable to
21 censored survival data and compares treatment effects
22 as a hazard ratio or the ratio of mortality rates

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1 within the treatment groups.

2 We carefully screened a large number of
3 patients -- screened a large number of variables and
4 there were 18 variables that we found which were
5 strongly correlated with mortality.

6 It was the regression analysis that we did
7 that identified the treatment interaction with
8 creatinine clearance less than 30 as a treatment effect
9 modifier which means that the mortality rate must be
10 conditioned on the degree of renal impairment.

11 So if I could have Slide BI-14 up? The
12 independent risk factors that we ended up identifying
13 in our final model for mortality at day 28 were
14 geographic region, baseline vasopressor use, APACHE II
15 score, age, cardiovascular disease, baseline
16 bacteremia, multi- pneumonia, MRSA infection at
17 baseline, and acute renal failure.

18 So one of the lessons we learned, I think, is
19 that the co-morbidities of the patients is an important
20 thing to consider when doing any subgroup analysis and
21 those sorts of things.

22 We did a complete submission with using the

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1 regression model in our first submission but we've kind
2 of moved on from that and I don't have any particular
3 models to show today because it's something we've done
4 in the past, but I think the lesson here is that you
5 can get something out of doing these regression
6 analyses and adjusting for patient co-morbid
7 conditions.

8 MR. BARRIERE: So the only other thing I'd
9 like to add is just a reminder really that the pooling
10 issues really have to do with the subgroups, the
11 microbiologic subgroups where there's insufficient
12 power to determine whether or not there's a statistical
13 meaningfulness, but in the overall population,
14 particularly the ATS IDSA all- treated population,
15 which matches the criteria in the new FDA guidance for
16 how you would do studies, and this is exactly how we
17 would do studies in the future, that using those
18 criteria to select out the patients, that non-
19 inferiority was demonstrated in each study in the
20 population of interest.

21 DR. MOORE: Thank you. Dr. Goetz, did you
22 have something you wanted to say about the last

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1 comment?

2 DR. GOETZ: I was going to actually ask Dean
3 Follman to comment because of the dialogue we had
4 before lunch in the meeting as to regards to whether
5 how one might then answer the question with the data
6 that have been provided.

7 I guess what I'm struggling with -- let me
8 start over again -- is that what I was hoping that we
9 would find is an adjusted analysis that might provide a
10 basis, a stronger basis for contemplating merger of the
11 datasets to look to see whether a satisfactory --
12 whether the studies satisfied the non-inferiority
13 criteria for the subpopulations of particular interest,
14 being the microbiological intention to treat analysis
15 because if the treatment effect were uniform across the
16 studies after adjusting for differences in the baseline
17 variables, it would provide a plausible, at least to me
18 as the non-statistician, rationale for so doing.

19 But what we see here, I think, is just what
20 the model is and not what the model supports. So I'm
21 left feeling a little bit dissatisfied because, unless
22 Dean Follman, Yu Shyr, or other statisticians or people

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1 with wisdom that I don't have can provide a basis for
2 combining them, I'm left with the position we were
3 before we saw this last slide.

4 DR. MOORE: Dr. Barriere, you had a comment?

5 MR. BARRIERE: Yes. Thank you. Actually, in
6 the microbiologic subgroups of interest that we were
7 talking about before, including the FDA's MA2 Gram-
8 positive, as Dr. LaVange mentioned and confirmed by Dr.
9 Komo, that there is much less heterogeneity in the MAT
10 Gram-positive population or our microbiologic
11 subgroups, much less heterogeneity, allowing for, and
12 as Dr. LaVange said, more comfortable with combining
13 those populations and when you do, as we showed you,
14 when you combine the subgroups, those microbiologic
15 subgroups, we can demonstrate non-inferiority.

16 DR. MOORE: Dr. Follman?

17 DR. FOLLMAN: Yes. So you just mentioned
18 like when you combine the subgroups, you can
19 demonstrate non-inferiority. So that is -- to me, the
20 -- so there's a lot of issues going on here, like the
21 design and how we would evaluate -- the studies changed
22 over time. It was originally a cure endpoint. It

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1 changed to mortality and so on.

2 For me, the main measure of efficacy is the
3 traditional one of whether it meets non-inferiority for
4 the two studies separately and so that's one question I
5 think of when I'm trying to understand whether it's
6 really efficacious or not, and, you know, I think that
7 the evidence is really mixed there in terms of meeting
8 the bar for the two studies.

9 The issue of combining is, you know, to me a
10 kind of secondary analysis where you want to focus in
11 on specific questions and so on, but it's sort of an
12 analysis you do after you answer the first one about
13 whether it's passed the bar, the traditional bar for
14 efficacy.

15 MR. BARRIERE: Well, thank you for making the
16 reminder that the studies were not designed for
17 mortality endpoint in the first place. They were
18 designed for clinical response and, as we showed you in
19 the core presentation, perhaps we could have that slide
20 up, please, the endpoints of clinical response met non-
21 inferiority, although with the caveats that it's not
22 possible necessarily to determine what a true -- the

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1 real non-inferiority margin ought to be.

2 But in both of the studies and in both -- CE-
3 22 up, please. But in both of the studies and in both
4 of the -- can we free up the Slide CE-22? Thank you.

5

6

7 So in both of the studies and in both of the
8 co- primary endpoints, for clinical response, there
9 actually was very tight margins and the lower bound of
10 the 95- percent confidence interval was much less than
11 10 percent, assuming that that would be a valid margin.

12 DR. MOORE: Yes, Dr. Voynow?

13 DR. VOYNOW: I guess this is a question maybe
14 also for you, Dr. Follman, and perhaps also for the
15 sponsor. Sponsor Slide CE-33, which is the all-
16 treatment survival, those Kaplan-Meier plots.

17 When the two studies were separated out, then
18 is my understanding correct that that would be non-
19 inferiority for survival at 28 days, is that correct?

20 MR. BARRIERE: Sorry.

21 DR. VOYNOW: I'm sorry.

22 DR. FOLLMAN: Yeah. So, right, so you can

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1 read the margin there as the margin was minus 10. It's
2 minus 9.7. This is for a particular population, the
3 ATS IDSA AT population.

4 As we may recall, we've seen maybe five or
5 eight different kind of study groups that have been
6 analyzed and it's a little hard to keep track of them
7 all actually and so what I'd go back to is what were
8 the originally- intended populations which were the AT
9 all-treated population and the, I think, clinically-
10 evaluable population.

11 So if you look at the AT population here, not
12 the AT ATS IDSA, the margin is not met for that
13 particular analysis group which, in my mind, is closest
14 to what the original intent was.

15 In some ways, you know, we're kind of -- it's
16 a terrible situation here when you, you know, change
17 the rules because, I mean, it's a great example of why
18 we have statistical analysis plan because then there's
19 no ambiguity about should I prefer this analysis to
20 that analysis and we're in the situation, I think now,
21 that, you know, the rules were changed part of the way
22 through and I think for good reasons, but it's just a

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1 lot of different ways of looking at this data gives you
2 different conclusions.

3 DR. MOORE: Dr. Voynow?

4 DR. VOYNOW: Forgive me because I'm new to
5 this field and so I'm trying to read about this to try
6 to understand why the FDA changed to create the 28-day
7 survival because I read the Sorbello review and I did
8 not review the meeting notes here.

9 But if you could just -- because I guess I'm
10 concerned, and also I think it was in maybe Dr.
11 Lorenz's presentation, that there is some ambiguity
12 about choosing the 28-day survival as a primary
13 endpoint, that date, and if there may be co-morbidities
14 involved.

15 DR. FOLLMAN: I think the -- I mean, the FDA
16 can comment on this, as well, but I think the main
17 reason that the rules were changed, if we can put it
18 that way, is because there was not evidence that the
19 comparator within this study is Vancomycin would have
20 beaten a placebo had such a study been done.

21 So there's, I guess, not evidence of
22 Vancomycin versus no therapy or placebo and, as such,

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1 we don't really know that Vancomycin is an effective
2 therapy. There's no evidence. We might believe that
3 there is but we have no direct evidence and because of
4 that, we have no rational evidence-based way of setting
5 a margin and so that's the thinking that's been
6 percolating, I guess, over the last three-four years in
7 terms of non- inferiority trials.

8 You know, it's a definitely difficult
9 situation where you need a margin that's justified by
10 history and maybe there's no historical data but that
11 is the reason why the FDA changed the rules -- I keep
12 using that term - - part of the way through for good
13 reason.

14 You know, there's an analogy about moving the
15 goal posts. I thought of another analogy which is like
16 maybe you're a manufacturer of O rings and you've built
17 them for a long time, so they're the right size, and
18 now the requirement is that they, you know, perform
19 well in ice water and you might say, well, that's not
20 fair but yet maybe there's a legitimate reason for the
21 criteria to change and so that's sort of the spirit in
22 which I view this.

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1 It's unfortunate. It is what it is and I
2 think there's legitimate reasons. They have moved on.
3 I also, you know, beyond that, I guess personally, I
4 have questions about the use of cure as an endpoint
5 when you have people who died shortly after they've
6 been cured, so to speak. So there's some issues, you
7 know, concerns about the cure endpoint, as well, beyond
8 this issue of there's no margin, so we can't proceed.

9 DR. MOORE: Dr. Cox?

10 DR. COX: Yes. So as Dr. Follman's
11 summarized, when you do a non-inferiority trial, you're
12 comparing a test drug to an active drug and, you know,
13 part of that assessment is that you know in fact what
14 the effect of the active control drug is because if you
15 want to show that a test drug is performing about the
16 same as an active control drug, in order for that to be
17 a sensitive assessment, you need to know what the
18 effect of the active control drug is.

19 Take, for example, if the active control drug
20 has a very large effect, then you're pretty comfortable
21 if your test drug is performing about the same as an
22 active control drug that has a very large effect.

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1 Take sort of the opposite situation and these
2 are just sort of extreme examples to illustrate the
3 points. Suppose the active control drug has very, very
4 little effect on the condition and showing that the
5 test drug is doing about the same as another drug that
6 has very little effect. It's not a sensitive way to
7 evaluate the effect of the drug.

8 So that's sort of the basic, you know, issue
9 and one of the great challenges in a non-inferiority
10 trial is how do you know what the active control, you
11 know, the standard control, how do you know what the
12 effect of that drug is on a particular endpoint, a
13 particular point in time, and a particular patient
14 population, and as Dr. Follman's mentioned, finding
15 that sort of data can be particularly challenging and
16 difficult.

17 You know, antibiotics discovered many years
18 ago and had a very large effect in medicine and adopted
19 very widely in a number of different conditions. So,
20 you know, the data that we have and we turn to are
21 oftentimes less than, you know, ideal information to
22 assess the effect of a drug in a particular condition

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1 and, as was presented, you know, some of the work that
2 went into trying to figure out quantitatively for the
3 purposes of a clinical trial what the effect of an
4 active control drug is in nosocomial pneumonia were
5 summarized by Dr. Komo and presented.

6 It's also in the Appendix of the Guidance
7 Document on HAP/VAP Nosocomial Pneumonia, but this
8 truly is one of the challenges that we face. It's the
9 limits of the available information, where we have
10 information to assess treatment effect, where we don't,
11 and then, you know, how we work through, you know, the
12 challenges of non-inferiority trial designs. So I hope
13 that helps some.

14 DR. MOORE: Dr. Barriere?

15 MR. BARRIERE: Dr. Koch would like to make a
16 comment.

17 DR. MOORE: Please.

18 MR. BARRIERE: Also, I'd like to ask Dr.
19 Shorr to address the issue of death after cure.

20 DR. KOCH: So if we could look at the CE-22
21 again, there are sort of our two different ways that
22 you might develop more comfort with the clinical

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1 response criterion.

2 The down side, as you've heard, is there's no
3 prior data. On the other hand, if, because clinical
4 response is related to what is going on with the
5 pathogen that one is trying to address, if one is
6 willing to make the argument that the effect size for
7 clinical response would be at least as large as the
8 effect size for mortality, then you could then reason
9 that a margin that worked for mortality could work for
10 clinical response and that would be the 10 percent and
11 all of these confidence intervals address that.

12 The other way to look at it is that you can
13 look at the response rates for each of the groups
14 separately. So if we look at the all-treated
15 population, they're in the vicinity of 60 percent. The
16 measure of variability that goes with that 60 percent,
17 a standard error, is in the vicinity of five or six
18 percent. So if we subtract six percent from 60
19 percent, we get about 54 percent.

20 If you think that in this particular response
21 for these patients, placebo could have a response rate
22 that approached 50 percent, that would then make

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1 clinical response less interpretable. It would also
2 make a placebo-controlled trial much more ethical.

3 If you believe the response rates for a
4 placebo would be well below 40 percent, then the lower
5 confidence limits that each of the groups is showing
6 separately are sufficiently above the best case for
7 placebo to support both assay sensitivity for
8 Vancomycin as well as efficacy for Telavancin.

9 Those are some ways that you can try to think
10 about in terms of trying to understand what you can
11 make of the clinical response data.

12 DR. SHORR: So I'd like to address the
13 conundrum that I think you all face here at the table
14 and that I face daily at the bedside as not only an
15 academic intensivist but someone who's the Director for
16 the Medical ICU that's five miles from this hospital.

17 I take care of a number of patients whom die
18 with their nosocomial infection but don't die of it. If
19 you look historically at the literature for nosocomial
20 infection, whether it be pneumonia or bloodstream
21 infection, there's very little evidence to support that
22 there's an attributable mortality.

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1 Again, people die with this, they don't die
2 of it, and I would illustrate that conversely as
3 another point with an analogy or a case study of
4 someone that I took care of about a week ago.

5 A woman with advanced lung cancer was
6 admitted to the hospital and as a complication of her
7 care developed respiratory failure requiring mechanical
8 ventilation. She developed VAP. We treated her
9 successfully because we had appropriate agents for her
10 Gram-negative infection. We were able to liberate her
11 from the ventilator. Despite her being liberated from
12 the ventilator, she went home to hospice and died 10
13 days later.

14 Liberating her from the ventilator was a
15 valuable thing to accomplish for that patient. It was
16 an important thing to accomplish for that patient and
17 it's one of the reasons why I go to work in the morning
18 and I think we all need these kinds of anti-infectives.

19 Did she die of her lung cancer? Absolutely.
20 Antibiotics don't treat lung cancer.

21 In the same way in one of the slides that was
22 shown earlier in the FDA presentation, there was a

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1 death that was labeled due to brain metastasis
2 subsequent from the adjudication of cure, and I don't
3 remember if it was in the Telavancin or Vancomycin arm,
4 but there's no biological reason to believe that an
5 anti-infective would have affected the natural history
6 of death from brain metastasis and so it's certainly a
7 conundrum I face sometimes when I try to figure out
8 whether I'm doing good or not in the hospital but it's
9 the real world of this disease and it's the nature of
10 all nosocomial processes.

11 DR. MOORE: Dr. Parise, you had a question?

12 CAPT PARISE: I don't.

13 DR. MOORE: Okay. Are there any other
14 questions of the sponsor? Dr. Shyr?

15 DR. SHYR: So I want to make sure the sponsor
16 and FDA are on the same page which is we heard both
17 sides comment about for the Gram-plus, for those subset
18 of patients, both side agree to pull the data together
19 is what the sponsor just mentioned that and how about
20 FDA, have any -- for that particular subgroup, is that
21 baseline covariates is homogeneous enough? Do you
22 agree to pull those two together?

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1 DR. MOORE: Dr. LaVange?

2 DR. LaVANGE: Well, I guess I introduced
3 that, so I have to defend it.

4 So in the all-treated population, we found
5 several significant differences between the two studies
6 and we looked at differences that were significant
7 because these are not differences between randomized
8 groups. These are differences between studies and we
9 had a table, I think, in the presentation, age,
10 diabetes, renal disease, several baseline factors, and
11 there was also, I believe, significant study by -- was
12 it study by treatment interaction?

13 There was a significant study by treatment
14 interaction in the all-treated and then we did an
15 analysis with the Gram-positive, the NE Gram-positive,
16 and the interaction became non-significant which was
17 how we were using to test whether there was less
18 heterogeneity between the studies.

19 There were still some differences between the
20 two studies. It just looked better. There was no
21 agreement to pool between us and the sponsor but that
22 was just an analysis that we did.

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1 Scott, is there anything else?

2 DR. MOORE: Dr. Komo?

3 DR. KOMO: No. You covered everything.

4 DR. SHYR: So jut FDA also feels that less is
5 less heterogeneous, whatever is close, but there is no
6 agreement there. Okay.

7 My follow-up question is can we go back to
8 the CE-34 again? So is this CE-34, this PP population,
9 like FDA presentation, FDA, Scott, your slide is 19, is
10 this the same slide? This is the sponsor CE-34?

11 MR. BARRIERE: Yes.

12 DR. SHYR: Dr. Komo, your presentation, is
13 that the same as your Slide 19? Is that the same? This
14 is Gram-plus. This is the PP.

15 MR. BARRIERE: It's the same population,
16 except it's modified --

17 DR. SHYR: It's the same population.

18 MR. BARRIERE: -- for ATS IDSA.

19 DR. KOMO: The difference is, I think, --

20 DR. MOORE: I'm sorry. Dr. Komo?

21 DR. KOMO: I'm sorry. This is the population
22 -- I think this is the patients who had a Gram-positive

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1 pathogen isolated at baseline but also met the ATS IDSA
2 criteria, whereas mine --

3 DR. SHYR: So that's a little bit different.

4 DR. KOMO: That's the difference.

5 DR. SHYR: Okay. All right. So do we -- so
6 I also asked to see these separated by two groups, 0015
7 and 19. Can you show that slide one more time?

8 MR. BARRIERE: Sure.

9 DR. SHYR: Okay. If you -- do you have an
10 analysis exclude the baseline creatinine clearance less
11 than 30?

12 MR. BARRIERE: I'm sorry?

13 DR. SHYR: Do you have any subgroup analysis,
14 the analysis based on each independent study exclude
15 the creatinine clearance less than 30? You still show
16 the survival curve. Do you have that?

17 MR. BARRIERE: So the survival curves --
18 first of all, EM-88 up, please. So this is what you
19 first asked for, which is by the by study and that ATS
20 IDSA PP population, okay, and the sample sizes are
21 small enough so that the margins are wide enough and I
22 believe we do have this by -- broken out by less than

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1 30 and greater than 30. It might take us a second to
2 find it, please. Almost. Doesn't matter. It's going
3 to be very close.

4 So we'll show you EM-43 because of
5 expeditiousness. So this is the PP without ATS IDSA
6 modifications. So this is identical to the FDA's MAT
7 Gram-positive population and then we can also show you
8 EM-96, please, and this is the ATS IDSA PP population.
9 It shows the same thing for the patients less than 30,
10 although the numbers are quite small, and with the
11 greater than 30 where the curves are super-imposable.

12 DR. SHYR: Do you have 19?

13 DR. MOORE: I'm sorry. Dr. Shyr, what did
14 you say?

15 DR. SHYR: I'm sorry. Do you have 19? That's
16 combined.

17 MR. BARRIERE: Yes, those were combined.

18 DR. SHYR: Those are combined.

19 MR. BARRIERE: That's very similar in the
20 two, yes.

21 DR. SHYR: Okay. Thank you.

22 DR. MOORE: Thank you. Mr. Mullins?

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1 MR. MULLINS: Yes. In Slide CS-22, how many
2 of the respiratory-related deaths had pre-existing
3 conditions of COPD or other respiratory illnesses?

4 MR. BARRIERE: We don't know that offhand.
5 I'm sorry. We can certainly go back and look at the
6 individual cases, but I don't have that information
7 right at hand.

8 MR. MULLINS: Okay. Then my one other
9 question was how was, in the conduct of the clinical
10 trials, how was the cause of death adjudicated? I'm
11 trying to understand the objectivity of that.

12 MR. BARRIERE: So the cause of death that was
13 reported on the case report form or in the death report
14 was the investigator's assessment of what the patient
15 died of. We went back and did, during the monitoring
16 and re-monitoring of as many sites as possible, to
17 verify the information in the case report form against
18 the medical record, so that we made sure that what was
19 reported to us was in fact reflected in the medical
20 record of the patient that was the cause of death. So
21 that was the adjudication that was done.

22 MR. MULLINS: Okay. And did you do any

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1 neurological analysis on the effects of Telavancin?

2 MR. BARRIERE: Any neurological?

3 MR. MULLINS: Telavancin. Yeah. The
4 neurologic impact on the brain because there have been
5 -- I was looking at some of the information on the
6 impact of some of the subjects on their -- on -- as far
7 as mental fogginess and things like that. So I wanted
8 to know if there was any neurological implications.

9 MR. BARRIERE: No, there's no evidence of the
10 brain or the central nervous system as a target of
11 toxicity at all.

12 DR. MOORE: Thank you. Dr. Kaplan?

13 DR. KAPLAN: I wanted to ask Dr. Komo if FDA
14 had a chance to look at the outcome based on Vancomycin
15 MICs. We saw from the sponsor some breakdown,
16 especially MIC, less than one, greater than one.

17 DR. KOMO: I'm sorry. I don't have those
18 analyses right now.

19 Could I make one --

20 DR. MOORE: Yes, Dr. Komo.

21 DR. KOMO: I do have the analyses that Dr.
22 Shyr had asked for.

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1 DR. MOORE: Yes.

2 DR. KOMO: The ones he asked for prior to
3 lunch. So this is in the population for the patients
4 who had a greater -- at least one Gram-positive
5 pathogen isolated at baseline.

6 So in Study 15, for patients with creatinine
7 clearance less than 50 for Telavancin, the mortality
8 rate is 41.8 percent and the Vancomycin mortality rate
9 is 35.4 percent, so the treatment difference is 6.3
10 percent with a 95-percent confidence interval of minus
11 10.4 to 23.1 percent.

12 In the patients who had greater than or equal
13 to 50mls per minute at baseline, the Telavancin
14 mortality rate was 22 percent, the Vancomycin mortality
15 rate was 17.6 percent, with a treatment difference of
16 4.4 percent, and a 95-percent CI of minus 5.8 to 14.7
17 percent. That was in Study 15.

18 For Study 19, for patients with a creatinine
19 clearance less than 50mls per minute, the Telavancin
20 mortality rate was 42.8 percent and the Vancomycin
21 mortality rate was 29.6 percent with a treatment
22 difference of 13.2 percent and the confidence interval

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1 of minus 4.8 to 31.2 percent.

2 For patients with the creatinine clearance
3 greater than or equal to 50mls per minute, the
4 Telavancin mortality rate was 18.7 percent and the
5 Vancomycin mortality rate was 19.4 percent. So for a
6 treatment difference of negative 0.7 percent and a 95-
7 percent confidence interval of minus 9.4 to 8.1
8 percent.

9 DR. SHYR: Thank you.

10 DR. KOMO: Sure.

11 DR. MOORE: Dr. Kaplan? Dr. Goetz? Sorry.

12 DR. GOETZ: Yes. Before lunch, we talked
13 about the rates of multi-organ failure in the study
14 groups and I believe the sponsor indicated that that
15 information would be available after lunch.

16 MR. BARRIERE: That would have been
17 insufficient time to gather that information.

18 DR. GOETZ: Okay.

19 MR. BARRIERE: I'm sorry.

20 DR. MOORE: Dr. Barriere?

21 MR. BARRIERE: One more comment. I'd like
22 Dr. Mammen to address the issue of the mortality in the

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1 patients with creatinine clearances between 30 and 50
2 because this appears to be the difference between what
3 we're proposing versus what the FDA is proposing.

4 DR. MOORE: Yes.

5 DR. MAMMEN: Similar to the table that Dr.
6 Barriere just showed you, SA-19, we have again compiled
7 investigator-assessed causes of death for all patients
8 that died with the 293 patients that began therapy with
9 baseline creatinine clearance between 30 and 50 and the
10 first thing to note here is that this is a very mixed
11 etiology, typical etiology of death, typical of
12 nosocomial pneumonia trials, and the other point to
13 note is the renal-related deaths which again we pay
14 close attention to.

15 There's one in each of Telavancin and
16 Vancomycin.

17 DR. MOORE: You have an additional comment,
18 Dr. Barriere?

19 MR. BARRIERE: No.

20 DR. MOORE: Okay. All right. Before we go
21 to the Charge to the Committee, were there any
22 outstanding questions of the FDA that were not asked?

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1 Yes, Dr. Chatterjee?

2 DR. CHATTERJEE: So I had a question for Dr.
3 Scott Komo.

4 When you talked about the deaths, this was on
5 Slide 6 and 7 on your presentation, I believe, being
6 close as far as the test of cure and the time of death,
7 in really both arms, of the studies, the test of cure,
8 if I'm not mistaken, is seven to 14 days after the
9 antibiotic is completed.

10 So what I've been struggling with is how
11 could this death be from the nosocomial pneumonia when
12 it's happening one or two weeks or more than that
13 actually after the antibiotic's been completed?

14 I would expect that in these very sick
15 patients who have a nosocomial pneumonia, if you stop
16 the antibiotic and you've not treated the infection,
17 they would die much sooner than that if the death was
18 from the nosocomial pneumonia.

19 DR. KOMO: So I think what you're getting at
20 is possibly with other -- one of the issues was that
21 the possibility that maybe the actual window we're
22 using to capture deaths may not be appropriate, whether

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1 to -- because we want to choose a window that maximizes
2 the number of nosocomial pneumonia-related deaths and
3 minimizes the number of non-infection-related deaths.

4 So that was one of the issues that was
5 brought up there as one of the possibilities that's
6 causing this phenomenon.

7 DR. CHATTERJEE: It's the same problem with
8 the Vancomycin group which is the next slide and,
9 clinically, I don't get the -- I don't understand why
10 you think that the deaths were related or could have
11 been related to the pneumonia more than a week after
12 the antibiotics have been stopped.

13 DR. MOORE: Well, I guess, if I may, I guess
14 the question is, is death related to sepsis which --
15 septic shock, which is even though the infection has
16 been treated, resulted in multi-organ failure. Is this
17 the attribution that the FDA is saying?

18 Dr. Cox?

19 DR. COX: Yeah. We've talked about this
20 slide and I think there's a lot of complicated issues
21 here because if you can think about it, too, I mean,
22 you know, one of the questions is related to the window

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1 issue because if your, you know, window is 14 days and
2 you had a death at day 16, then it wouldn't be part of
3 the window, too.

4 So there's a lot of complicated things here
5 that I think, you know, come into this analyses and
6 what conclusions you can draw from it. You know, is
7 the clinical response evidence of, you know, response
8 to antibacterial drug therapy? Is the patient
9 succumbing to other causes? It's impossible to know.

10 I think that's what makes, you know, these
11 slides very difficult to interpret.

12 DR. MOORE: Thank you. Charge to the
13 Committee

14 DR. MOORE: Let's proceed with the Charge to
15 the Committee.

16 DR. LAESSIG: Okay. So moving to the Charge
17 and the Questions, I'd like to thank all the speakers
18 from Theravance and Drs. Lorenz and Komo for their very
19 thorough presentations. Also thank the committee for
20 their insightful questions and valuable discussion and
21 Dr. Yttri for her perspective, as well.

22 With respect to the questions, as with any

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1 application that is discussed at an advisory committee,
2 we ask that when you respond, you consider the totality
3 of the evidence regarding the safety and efficacy of
4 the product, Telavancin for nosocomial pneumonia, that
5 you have heard today as well as read in the Briefing
6 Documents. Questions to the Committee/Committee
7 Discussion

8 DR. LAESSIG: So we'll go on to Question 1
9 and for the record, Question 1 is considering the
10 totality of the data presented, including the analyses
11 of clinical cure and 28-day all-cause mortality, do the
12 results provide substantial evidence of the safety and
13 effectiveness of Telavancin for the treatment of
14 nosocomial pneumonia?

15 So if you vote yes, please provide any
16 recommendations concerning the label and if you vote
17 no, please provide what suggestions you have regarding
18 additional studies and analyses.

19 DR. MOORE: Yes, Dr. Alston?

20 DR. ALSTON: Do we have a chance now to talk
21 about this question before we vote on it?

22 DR. MOORE: Absolutely.

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1 DR. ALSTON: If I could just clarify with the
2 FDA, you know, it's always semantics, but as it's
3 written now, it just says nosocomial pneumonia, which
4 would mean all causes of nosocomial pneumonia, and this
5 was a study of Gram-positive nosocomial pneumonia.

6 In fact, people with only Gram-negatives on
7 smear or culture were excluded, and I would hate for
8 this to have a blanket approval for nosocomial
9 pneumonia and then all those people with Gram-negatives
10 and anaerobes would be treated with Telavancin alone
11 and wouldn't do well.

12 So I don't see how anyone could vote yes to
13 Number 1 as written. We would have to change the
14 wording a little bit to say either Gram-positive or
15 proven or suspected MRSA nosocomial pneumonia.

16 DR. LAESSIG: Okay. How about we say do the
17 results provide substantial evidence of the safety and
18 effectiveness of Telavancin for the treatment of
19 nosocomial pneumonia or for the requested indication of
20 nosocomial pneumonia caused by susceptible Gram-
21 positive designated organisms, Staphylococcus aureus,
22 methicillin- sensitive and -resistant and Strep pneumo?

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1 DR. MOORE: So that would include then Strep
2 pneumo? That was the issue we're discussing.

3 DR. ALSTON: Same question.

4 DR. MOORE: Right. Okay. I have to say that
5 I'm not sure that -- thank you for the clarification,
6 but I have to say I'm not sure that it changes the
7 intended - - from my standpoint, I'm not going to tell
8 you how I'm going to vote, but it's -- yeah. Well,
9 never mind. I'll move on.

10 Dr. Goetz?

11 DR. GOETZ: Yeah. My question is -- well,
12 again, it's a question about the question. So we're
13 combining -- a vote on this, as it's written then, is
14 on the combined safety and effectiveness which is
15 perhaps complicated, at least in my mind and maybe
16 someone else's mind, because whether death is a safety
17 issue or whether death is an effectiveness issue, it's
18 an issue one way or the other, but it plays out a
19 little bit differently, depending on how one looks at
20 that, and then the other thing is, as it's written,
21 it's straight up and down question and even if we parse
22 out the safety and effectiveness, there are concerns

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1 that people may have regarding the roles of underlying
2 conditions where the medication might or might not be
3 safe or effective, renal function being the clear
4 example that's been discussed extensively.

5 So, again, it makes it problematic because
6 some consideration might be given to voting yes in one
7 circumstance and no in the other circumstance,
8 depending on what the baseline factors are of the
9 patients.

10 I'm wondering what guidance the FDA might
11 provide in that regard or considerations of rewriting
12 the question yet further.

13 DR. LAESSIG: Well, I don't know that we want
14 to go on to rewrite the question any further. You
15 know, certainly in your response, you can address those
16 type of issues, but I would also refer you to Question
17 2 where we're basically asking you would you approve it
18 with a more limited indication and, if so, you know,
19 describe what kind of limited indication you might
20 approve it for or you would recommend approval for.

21 Does that help?

22 DR. MOORE: That helps.

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1 DR. GOETZ: That is helpful. Thank you.

2 DR. MOORE: All right. If there are no
3 further clarifications about the question or discussion
4 about the question, we can -- no? Sorry? I'm sorry.
5 I'm being signaled.

6 (Pause.)

7 DR. MOORE: All right. So we're going to
8 wait for the question to be reworded and put on the
9 slide and then we'll proceed with the vote.

10 While we're waiting for that, I'll just read
11 this. We'll be using an electronic voting system for
12 this meeting. Once we begin the vote, the buttons will
13 start flashing and will continue to flash even after
14 you have entered your vote. Please press the button
15 firmly that corresponds to your vote. If you are
16 unsure of your vote or you wish to change your vote,
17 you may press the corresponding button until the vote
18 is closed.

19 After everyone has completed their vote, the
20 vote will be locked in. The vote will then be
21 displayed on the screen. The DFO will read the vote
22 from the screen into the record.

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1 From there, we'll go around the room and each
2 individual who voted will state their name and vote
3 into the record. You can also state the reason why you
4 voted as you did, if you want to, and, in fact, I would
5 encourage that. We will continue in the same manner
6 until all the questions have been answered or
7 discussed.

8 (Pause.)

9 DR. MOORE: Are there any other points to
10 discuss before we -- anybody wants to discuss before we
11 go to the vote?

12 (No response.)

13 (Pause.)

14 DR. MOORE: Okay. Can everybody see -- well,
15 hang on a second. The answer would be no. Can
16 everyone read the -- see the question from where
17 they're sitting? There you go. I shall do that. I'll
18 read this into the record.

19 Question Number 1. Considering the totality
20 of data presented, including the analyses of clinical
21 cure and 28-day all-cause mortality, the voting
22 question is the following: do the results provide

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1 substantial evidence of the safety and effectiveness of
2 Telavancin for the requested indication of
3 treatment of nosocomial pneumonia, including
4 ventilator-associated pneumonia, caused by susceptible
5 isolates of the following Gram- positive
6 microorganisms: Staphylococcus aureus, both MSSA and
7 MRSA, and Streptococcus pneumonia?

8 All right. Okay. We'll proceed. If there
9 are no further discussion, we'll begin the voting
10 process. Please press the button on your microphone
11 that corresponds to your vote. You'll have
12 approximately 20 seconds to vote. Please press the
13 button firmly. After you've made your selection, the
14 light may continue to flash. If you're unsure of your
15 vote or you wish to change your vote, please press the
16 corresponding button again before the vote is closed.

17 A little bit more editing before we move on.
18 So we have a time filler. I don't have any amusing
19 anecdotes to tell in the meantime.

20 Okay. All right. So let's reread it into
21 the record.

22 All right. So the question put before the

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1 committee is the following: considering the totality
2 of data presented, including the analyses of clinical
3 cure and 28-day all-cause mortality, do the results
4 provide substantial evidence of the safety and
5 effectiveness of

6 Telavancin for the requested indication of
7 treatment of nosocomial pneumonia, including
8 ventilator-associated pneumonia, caused by susceptible
9 isolates of the following Gram-positive microorganisms:
10 Staphylococcus aureus, both MSSA and MRSA, and
11 Streptococcus pneumonia?

12 If there's no further -- all right. So vote
13 now, please. Let's put this question out of its
14 misery.

15 Okay. Everyone has voted. The vote is now
16 complete. The DFO will read the vote into the record
17 from the screen when it is in.

18 MS. GOYETTE: The vote on Question 1, yes-
19 six, no-nine, abstain-zero, no voting-zero.

20 DR. MOORE: Okay. We'll now go around the
21 room and everyone will state how they voted and ideally
22 why.

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1 Dr. Cappelletty, can we start with you,
2 please?

3 MS. CAPPELLETY: Yeah. This was not an easy
4 one. Dr. Cappelletty. I voted no on the question.

5 The clinical cure, you know, some of the data
6 is there using the 28-day all-cause mortality and
7 looking at the larger patient group as opposed to the
8 subgroups, the non-inferiority just wasn't demonstrated
9 there for me.

10 Looking at the MRSA, it wasn't bad in that
11 arena but subpopulation just wasn't there power-wise or
12 sample size-wise for me to really support that, and as
13 far as the addition then of the Strep pneumo into the
14 database, we really don't need another drug for Strep
15 pneumo. I think it was sort of a throw-in in here to
16 be able to broaden out its use and indication and the
17 utility for that just isn't there.

18 The renal information, the low renal function
19 being tied in with this, as well, was just something I
20 wasn't comfortable with, given the difficulties of
21 identifying true renal function in these patients and
22 the ability to have somebody with lower renal function

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1 or be at the border of it and go over quite quickly
2 with a higher mortality rate there does not clearly
3 answer for me. I voted no.

4 DR. MOORE: Thank you. Dr. Voynow?

5 DR. VOYNOW: I voted yes but with the caveat
6 that it should be indicated for Staph methicillin-
7 sensitive and methicillin-resistant but not Strep, and
8 I also agreed with the limitation that it should not be
9 used in patients who are in renal failure or have a
10 creatinine clearance less than the 30 threshold.

11 The reason for this for me was I, as a
12 clinician, the major concern about another effective
13 agent for MRSA and I felt that their test of cure data,
14 which we really didn't discuss very much, I thought
15 that that met the non-inferiority comparison with
16 Vancomycin.

17 Also, when I look at the data from the FDA on
18 the test of cure and then those patients who died at
19 day 28 and looked at that comparison, I'm not convinced
20 that the cause of death at day 28 was related to the
21 pneumonia. So these are very sick patients. The
22 mortality rates are high, but I felt that under the

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1 right circumstances this may be a useful drug for this
2 population and so that's my vote.

3 DR. MOORE: Thank you. Mr. Mullins?

4 MR. MULLINS: Yes. I voted no because of the
5 safety signals and I had particular concerns about
6 aspects of the general population and I was concerned
7 about subjects that had a predisposition to
8 cardiovascular disease and subjects and subpopulations
9 that had a predisposition to renal failure which leads
10 me to the geriatric population, seniors.

11 I feel like they have a predisposition. They
12 are vulnerable populations from a public health
13 standpoint and I think that needs to be considered and
14 I think that they would have a predisposition for renal
15 failure and renal impairment, and I felt like there was
16 - - I was very concerned about the fact there was very
17 little research done on the issue with developmental
18 toxicity.

19 I felt like that information was marginalized
20 from a public health standpoint and it was very
21 graphic. I mean, the impact on the pregnant animals
22 during the gestation period, they had mutations. There

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1 was severe effects and I wanted to see more so I could
2 make some assumptions with humans because that was --
3 to me, those were serious implications.

4 I was also concerned about the effectiveness.
5 It seems like the effectiveness of Telavancin decreased
6 as renal impairment increased. So those issues helped
7 me make my determination.

8 Thank you.

9 DR. MOORE: Dr. Goetz?

10 DR. GOETZ: Yes. I'm Dr. Goetz. I did vote
11 no, primarily because of the overarching nature of the
12 question that didn't distinguish between clinical
13 subgroups and looked at both safety and effectiveness.

14 I think that in that regard, my particular
15 concerns are the signal of increased mortality in
16 people certainly with creatinine clearances less than
17 30 but also in the creatinine clearance range of 30 to
18 50 as was presented in the data shown to us after
19 lunch.

20 I'll go back to my statement before. As a
21 clinician, I cannot predict whose creatinine clearance
22 will decrease over time. I recognize, of course, there

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1 are many nuances that need to be brought to bear to the
2 decisions that we make in treating patients but
3 clinicians need that guidance as to what the baseline
4 is and what the outcomes are. So I regard the data for
5 creatinine clearance of 30 to 50 as also being very
6 important.

7 I think the clinical cure data do have a lot
8 of merit and the point made that, no, I don't believe
9 that placebo has a 40-percent effectiveness rate in the
10 treatment of MRSA pneumonia, clearly don't believe
11 that, and there are issues that could be raised as to
12 exactly what the lower bound of the non-inferiority
13 margins should be and is the clinical cure data in the
14 context of all other information sufficient perhaps but
15 not as a blanket statement looking across all patient
16 subpopulations with the clear mortality signal which is
17 seen.

18 DR. MOORE: Thank you. Dr. Katona?

19 DR. KATONA: I voted no. You know, I was
20 struck by the fact that when asked why did you do two
21 studies, well, we were told to do two studies, and what
22 if they had been told to do one study, would we have

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1 been having this discussion today? Maybe, but maybe
2 not.

3 So I'm kind of struck by that and the fact
4 that when the rules are changed, does the sponsor have
5 a chance to also change the rules, getting back as a
6 response to that.

7 You know, so all of these things made it very
8 difficult for me to come to a decision here and I
9 certainly could have gone either way, but I did vote
10 the way I did because I feel very strongly that when
11 you start a study and you have pre-designated
12 endpoints, you really don't want to deviate from that
13 if you can at all help it.

14 You know, once you open the window to deviate
15 from what you originally intended to do, it kind of
16 opens up a Pandora's box of things that may not serve
17 us well maybe in this case and maybe for future cases.

18 Certainly the baseline characteristics being
19 different between the two groups was another factor,
20 but that to me was an overriding thing and when I came
21 to this meeting this morning, I was under the
22 assumption that the toxicity issues wouldn't be much

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1 different from what we had discussed when we approved
2 this drug for complicated skin and soft tissue
3 infections, but I am struck by this creatinine
4 clearance of less than 50 being of some importance,
5 especially since that's a large number of the patients
6 we will see with this condition and how important that
7 is, as well as the patients who died close to the
8 clinical cure date. Those were rather important.

9 Finally, I do have a question of the
10 effectiveness of Vancomycin and that we're comparing
11 this to something that we really don't understand. I
12 don't know how effective Vancomycin is. We all use it
13 because that's what we've been kind of taught to do,
14 but I wish we had the information to be able to
15 determine that a lot better.

16 DR. MOORE: Thank you. Dr. Shyr?

17 DR. SHYR: Yu Shyr. I voted yes, but with
18 the conditional yes. That means this drug can only be
19 used for creatinine clearance of about 50. That's this
20 condition because the statistical tells that.

21 Let me tell you why I voted yes. As I said,
22 I only looked at the data. The data is confidence

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1 interval. We know that 10-percent threshold as
2 everybody agreed from FDA. So when we look at the
3 data, I asked the question this morning, if we have
4 sufficient power with enough sample size because this
5 would be unfair to the sponsors because this was not
6 their primary endpoint. So they did not power that
7 reasonably to the so-called 28 mortality, 20 days
8 mortality rate.

9 So if we give them enough power, suppose they
10 have enough power for at least one Gram plus, for that
11 confidence interval, if we have calculated the
12 confidence at exactly less than 10 percent, now if you
13 combine the two studies, that's why I asked sponsor and
14 FDA, does FDA feel now that the trials should be
15 combined this for the Gram plus population, if we
16 combine them, add all this together, so the evidence,
17 the upper bound of that is slightly lower than 10
18 percent, either you combine or you look at them in
19 separate model -- separate study which is sufficient
20 power. That's why I vote yes, but, however, there is
21 clearly evidence that for the creatinine clearance less
22 than 50, that it's not a group that should -- the

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1 patient should use this drug.

2 DR. MOORE: Thank you. Dr. Parise?

3 CAPT PARISE: I voted yes. I thought, you
4 know, if we -- so we have two studies. The one study
5 did show non-inferiority with a mortality endpoint and
6 the other - - and to me, the totality of the rest of
7 the evidence was enough evidence for me to vote yes.

8 I think the -- I have the same comments as
9 others related to the labeling for Staphylococcus only
10 and for some of the renal considerations that have been
11 mentioned.

12 DR. MOORE: Thank you. Dr. Alston?

13 DR. ALSTON: I voted yes, because I didn't
14 want to delay the whole thing again. That was with the
15 caveat obviously that pneumococcus wouldn't be part of
16 that and I thought that was a minor thing but it's
17 still important.

18 Of all these applications I've listened to
19 over the years, I think this one ended up the most
20 muddled but I don't think that's necessarily the fault
21 of Telavancin. It speaks to it's a very heterogeneous,
22 very difficult diagnosis to make. It's very hard to

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1 assess a cure and the sponsor said that those people
2 who died shortly after being proclaimed cures were
3 actually low in number, but I think that's not the
4 point.

5 The point is it speaks to the fact that if
6 you can't tell they're going to die, you also can't
7 tell if they're cured from hospital-acquired pneumonia
8 and I think it's just very hard remembering that by
9 definition the people didn't have this infection when
10 they got admitted. So they had all kinds of other
11 problems to land them in the hospital and it's very
12 hard to attribute mortality and to know when someone is
13 cured of that.

14 The endpoint's changed. It wasn't designed
15 for mortality and that was no fault of the sponsor. The
16 trials looked different, even though they were the same
17 trial, which I still don't understand. A third got
18 concurrent drugs for anaerobes and Gram-positives. Over
19 50 percent were treated more than 24 hours prior to
20 diagnosis. Over 25 percent had Gram-negatives isolated
21 and they said, and I don't know how this could happen
22 in the context of a clinical trial that's being

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1 micromanaged, that 40 percent of those never got
2 adequate treatment for their Gram-negative.

3 So I put all this together and I can't
4 imagine how it wouldn't look non-inferior. I mean,
5 this was the perfect set-up for a non-inferiority but
6 as I -- and I came into this thinking I was going to
7 vote no, but the more I thought about it, the more I
8 decided that all of that is the fault of trial design
9 surrounding nosocomial pneumonia and not the fault of
10 Telavancin and in my heart of hearts, I think
11 Telavancin would probably cure MRSA pneumonia at least
12 as well as Vancomycin and that the problems we're
13 encountering have to do with the unknowns surrounding
14 how do you do trials for nosocomial pneumonia, not the
15 drug itself.

16 DR. MOORE: Thank you. Dr. Calhoun?

17 DR. CALHOUN: Calhoun. I voted no. I was,
18 as many of us have articulated, extremely conflicted
19 about this vote because, as Dr. Alston just mentioned,
20 I think Telavancin probably does work pretty well
21 against MRSA and MSSA.

22 I'm also philosophically attuned to giving

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1 doctors choices because physicians need choices. We
2 need more opportunities to ameliorate illness and cure
3 patients, but that wasn't actually what the question
4 was.

5 The question was is there evidence of safety
6 and effectiveness and so from the standpoint of the
7 clinical cure data, although those were reasonably
8 solid from a statistical standpoint, I think there is
9 some question about whether that's a sharp tool and in
10 this regard, it's an important point because adult tool
11 means that it's more likely that you'll find non-
12 inferiority and so this is a bias toward the finding of
13 a non-inferiority and so I'm a little uncomfortable
14 using the clinical cure data.

15 Even though it's a clinically-relevant and I
16 think probably valid measurement, it just doesn't have
17 enough oomph for me to -- for efficacy.

18 Then from the mortality standpoint, the 28-
19 day mortality, and again it wasn't the sponsor's fault
20 that their study wasn't powered for it, but the fact of
21 the matter is that numerically one of the studies
22 didn't meet the 10-percent non-inferiority and so there

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1 aren't in fact two replicating studies that demonstrate
2 efficacy against the mortality endpoint and so without
3 efficacy, then I had to vote no on this question.

4 I'm actually not concerned about the safety
5 issues. Docs deal with drugs that are much, much more
6 toxic than this. I think we have to be aware of the
7 issue of renal damage. I think we have to be aware of
8 those people who've got existing renal dysfunction but
9 that doesn't bother me. A competent clinician can take
10 that into consideration as they're doing the
11 management.

12 I was surprised at the number of times that
13 when questions for clarification were asked of the
14 sponsor, that the answer was we haven't done that
15 analysis yet. This is a four-year-old dataset. So one
16 might think, given the fact that it's been back to this
17 table a number of times, these questions presumably
18 have arisen before, that those sorts of analyses
19 haven't been done. I just thought that was surprising.

20 In any case, I think with the absence of the
21 solid efficacy signal, I had to vote no.

22 DR. MOORE: Thank you. Dr. Chatterjee?

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1 DR. CHATTERJEE: So I voted yes, and I have
2 to say that as a pediatrician, I do not care for this
3 category of patients. So I had to really look at it
4 from sort of the perspective of how my colleagues on
5 the adult side would look at it, and the thing that
6 struck me about this was this is a condition for which
7 -- and I'm referring specifically to the MRSA pneumonia
8 really here.

9 We have very limited options. It's a killer
10 disease and having another option in my mind outweighs
11 some of the concerns that have been raised. So that
12 was a major thing for me.

13 We were asked to advise regarding labeling
14 and one of the things that's been said before, I would
15 take out pneumococcus from there for sure and then put
16 in the caveat about the creatinine clearance, but
17 weighing the totality of evidence, as we were asked to
18 do, I believe that this is a safe drug.

19 As you mentioned, Dr. Calhoun, we use a lot
20 of drugs and I don't think Vancomycin is that safe a
21 drug, frankly, which is our other option to use. So
22 this is a safe drug to use and it gives us an option

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1 for a condition for which we have very few options.

2 That's the reason I voted yes.

3 DR. MOORE: Thank you. This is Dr. Moore. I
4 voted no, but for the same reasons that Dr. Alston
5 offered for his vote for yes.

6 I was very conflicted and I really wanted to
7 vote yes on this question for the simple reason that I
8 think the data did show that the drug was efficacious,
9 is efficacious for the indications stated in the
10 question.

11 The issue really for me was a blanket
12 statement of safety. The drug appears to be safe,
13 except for in the individuals who have lowered
14 creatinine clearance, and that seems substantial enough
15 to me to warrant a no vote strictly as the question was
16 worded.

17 But I can't emphasize strongly enough that I
18 think drugs like this, despite their blemishes, need to
19 be available in the armamentarium of physicians who are
20 caring for patients in the ICU who are critically ill
21 for which perhaps no other option is available.

22 The analogy there being Gentamycin or

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1 Tobramycin in the case of drugs which I think I would
2 face a very hard road for approval if they were
3 submitted as NDAs today. Nevertheless, we use them and
4 they are effective, despite known toxicities.

5 So as I say, because of the overall blanket
6 statement, I had to vote no, but I do think that
7 ultimately the drug ought to be approved, at least
8 available for use in special situations which we'll
9 hopefully address in the next question or two.

10 Dr. Kaplan?

11 DR. KAPLAN: Sheldon Kaplan. I voted no, but
12 I had a terrible time with this, too. I wish I could
13 have voted maybe.

14 I only voted no because of the strict
15 requirement for non-inferiority in two studies and
16 hopefully, you know, with the next question, there will
17 be some other issues.

18 DR. MOORE: Mr. Mikita?

19 MR. MIKITA: Well, I really struggled with
20 this issue from the outset. But I'm not only a patient
21 but I'm an attorney and I understand the vote. I
22 understand what substantial evidence is. I believe

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1 that the burden was made and I'm going to hold
2 jealously to my gold purse analogy and not give way to
3 the O rings and I believe, like Dr. Alston said much
4 more eloquently than I, that if there is a fault here,
5 it's the way the clinical trials are set up for
6 patients and clinicians who are searching for drugs in
7 very dire life-threatening situations and the
8 clinicians that spoke today, I think, got to the heart
9 of the matter.

10 Their patients are very sick and I've been
11 one of those patients and I've been ventilated and I
12 had to make choices in consultation with my doctor by
13 blinking my eyes for a yes or a no and it's the most
14 terrifying experience to live through those ordeals and
15 to try to communicate to others what you want and what
16 you need and what options there are for you to get
17 better and to feel better and to get off those
18 ventilators and I applaud all of you for your words and
19 your sensitivity. I applaud both the FDA and also the
20 sponsor, but in the final analysis, I believe the
21 patients who are this sick and the very, very talented
22 clinicians who treat them have enough information to

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1 make the effective and right choices for their
2 individual patients and that's why I voted in favor of
3 this indication.

4 Thank you very much.

5 DR. MOORE: Thank you. Dr. Stevenson?

6 DR. STEVENSON: Yeah. Kurt Stevenson. I
7 voted no, and I think mostly because of the broad
8 sweeping implications of the first question. It
9 doesn't mean that I don't think there's a role for the
10 drug, which I think we'll probably be talking about,
11 but I think the concerns I had was around the
12 differences in the two study populations. I think the
13 FDA's raised appropriate concerns.

14 There are statistically-significant
15 differences in baseline characteristics between the two
16 groups which bothered me in terms of the combination of
17 the data and based on the FDA's selected population,
18 the 0015 trial did not meet the non-inferiority
19 requirement.

20 Having said that, I do recognize that using
21 the sponsor's selected population, there is
22 demonstration of efficacy of the drug and I think the

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1 concern I had was a broad approval for general
2 ventilator-associated pneumonia.

3 I spend a lot of my time in antimicrobial
4 stewardship and sometimes clinicians look at the newest
5 drug as the best drug and I think that there's concerns
6 about this being used outside of selected patient
7 populations, particularly in the ICU where there's a
8 high percentage of people who are going to have renal
9 dysfunction and that.

10 So I think that the drug will have a role
11 with some clear-cut parameters and restrictions that
12 can be applied to it, but I did not feel that the
13 evidence supported it for a broad use for all
14 ventilator- associated pneumonia as outlined in the
15 question.

16 DR. MOORE: Thank you. Dr. Follman?

17 DR. FOLLMAN: I voted no. I think I'd like
18 to explain my reasoning a little.

19 First, setting aside the issue of the safety
20 signal with creatinine clearance, so let's suppose that
21 wasn't an issue, I would have been inclined to look at
22 the cure endpoint modified like the FDA suggested where

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1 death shortly after cure counted as failures, and if
2 you use that endpoint, I believe you get -- both
3 studies meet their margin and so the only remaining
4 concern is there is evidence that Vancomycin is better
5 than placebo. It's not in the history. So we might
6 look within the study itself for such evidence.

7 A priori specified subgroup was to look at
8 superiority in the MRSA patients who had MRSA. So if
9 there were no mortality concern and if we had shown
10 superiority in the MRSA subgroup, I might have been
11 inclined probably to vote for approval on that
12 endpoint, but neither of those happened. We didn't
13 show superiority on MRSA and we have this mortality
14 issue. So, anyway, that deals with the cure endpoint.

15 So I move on to the mortality endpoint. In
16 one of the studies, the non-inferiority margin wasn't
17 met. It was -- and you could look at this two ways. One
18 way, in that it's close to the margin, the other way,
19 that it's close to showing harm, but, ultimately, I
20 really didn't struggle about those issues, as well.

21 For me, the overarching concern in this study
22 was the interaction between treatment and creatinine

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1 clearance and when I looked at this originally, to me,
2 I broke the creatinine clearance at 80 and looked at
3 whether there was a differential effect above and below
4 80. Above 80, Telavancin is superior. Below 80,
5 Telavancin is inferior.

6 So there's a very strong what we call
7 qualitative interaction where, on the basis of a
8 baseline variable, treatment goes from being actually
9 good to actually bad. So this is very uncommon and it
10 made me think that there's basically an elephant in the
11 room. I can't ignore this. I don't really have strong
12 evidence that there's a benefit for this.

13 I understand, you know, Dr. Calhoun's point
14 earlier about, gee, if we look at things enough ways,
15 we'll maybe be misled and raise concerns that aren't
16 really there, but I think this is a substantial effect
17 on creatinine clearance and about the cutting at 80,
18 the sponsor talked about cutting at 30, FDA talked
19 about cutting at 50. I, you know, thought of cutting
20 at 80.

21 There's a great ambiguity, I think, about
22 precisely where to draw it and so with that

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1 uncertainty, even if we wanted to carve out, you know,
2 a subgroup that we would think would be successful, in
3 my mind, we don't have a lot of evidence about where to
4 draw that now.

5 DR. MOORE: Thank you. Dr. Robinson, you had
6 a comment?

7 DR. ROBINSON: Yeah. If I could, I've been
8 listening to all of the struggles with the various
9 endpoints and interpretation, subgroups and so forth,
10 and I've been impressed by the idea of the recognized
11 validated endpoint of death actually seems to me to be
12 at least as problematic an interpretation as does the
13 clinical response endpoint.

14 Now I have to agree with Dr. Goetz. It's
15 hard for me to believe that a placebo in MRSA infection
16 would be as effective as 40 percent. What the
17 committee is being asked for is evidence of efficacy
18 and safety but evidence of efficacy. It is not
19 evidence of efficacy specifically compared to
20 Vancomycin.

21 Vancomycin was to have been the marker but
22 the evidence of efficacy would be related back to

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1 whatever data might be available for placebo if placebo
2 could have been ethically used in this situation.

3 So I think there needs to be some way, some
4 way to bring into play this more practical usable
5 endpoint of clinical response.

6 We've just seen the largest nosocomial
7 infection program ever. If this is insufficient, then
8 we are really in difficult situation if we move into
9 some less- frequent nosocomial infection situations,
10 such as individual Gram-negatives. So I certainly
11 understand the difficulty in interpreting the data in
12 the absence of some historical landmark.

13 But I think there has to be taken into
14 account some level of judgment and certainly part of
15 that judgment would be what we would project placebo
16 might to do in this situation.

17 DR. MOORE: Thank you for those comments.
18 Let's proceed now with the second question.

19 Dr. Laessig?

20 DR. LAESSIG: Okay. So as we discussed, the
21 intent of this question was primarily should the answer
22 to Number 1 be no, would a limited, more limited

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1 indication be appropriate?

2 So the question reads considering the
3 totality of the data presented, including the analyses
4 of clinical cure in 28-day all-cause mortality, do the
5 results provide substantial evidence of safety and
6 effectiveness of Telavancin for the treatment of
7 nosocomial pneumonia when other alternatives are not
8 suitable, and Part A is, if yes, please provide
9 recommendations concerning the labeling, particularly
10 labeling concerning the use in patients with renal
11 dysfunction, and, if not, what additional studies or
12 analyses are needed.

13 So the intent was to leave this fairly open-
14 ended. So we would appreciate whatever you have to say
15 in terms of a more limited indication.

16 DR. MOORE: Dr. Laessig, may we change this
17 question, as well, to reflect the first question in
18 that I would propose that we change the nosocomial
19 pneumonia reading to MRSA, MSSA, or --

20 DR. LAESSIG: Well, I think because we don't
21 know what you're going to say, I mean, some people may
22 say all Staph aureus, some people may say only MRSA,

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1 that's why I don't know if we necessarily want to start
2 putting the organisms up there.

3 DR. MOORE: That's fine. You just didn't
4 want to get up here and type the question again.

5 All right. Does anybody have any -- will
6 there -- is there any discussion about the question?

7 (No response.)

8 DR. MOORE: All right. Well, if there's no
9 further discussion on this particular question, we'll
10 now begin the voting process. Please press the button
11 on your microphone that corresponds to your vote and
12 you'll have approximately 20 seconds to vote. Please
13 press the button firmly. After you've made your
14 selection, the light may continue to flash. If you're
15 unsure of your vote or you wish to change your vote,
16 please press the corresponding button again before the
17 vote is closed.

18 All right. The vote is -- everyone has voted
19 and the vote is now complete. The DFO will read the
20 vote into the record from the screen.

21 MS. GOYETTE: The vote on Question 2 is yes-
22 13, no-two, abstain-zero, no voting-zero.

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1 DR. MOORE: All right. So we'll go around
2 the table again. Let's reverse it this way.

3 Dr. Follman, let's start off with you.

4 DR. FOLLMAN: So I voted no. The major
5 reason I voted for no is sort of a matter of principle,
6 I guess.

7 Overall, I don't think there's evidence of
8 safety and efficacy when we look at the totality of
9 evidence over the two trials and so that's a red light
10 to me.

11 I'm very uncomfortable, like taking an
12 overall null study and saying, oh, but here, there is a
13 benefit and here there's not a benefit and here there's
14 harm, on and on, just because there's so many ways we
15 can cut and look at the data, that I don't have a lot
16 of confidence we're doing it properly.

17 So one of the subgroups we thought, you know,
18 going in, there would be benefit in the MRSA. We
19 didn't show superiority, even though there was a priori
20 defined endpoint and so I think I'm just uncomfortable
21 trying to make something more out of this kind of shaky
22 evidence that we have.

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1 DR. MOORE: Thank you. Dr. Stevenson?

2 DR. STEVENSON: Kurt Stevenson. I recognize
3 the argument that Dr. Follman just made. I voted yes
4 for the reason I think that there is, again depending
5 on the population to look at, there is enough
6 supportive data in my mind that this drug has a role
7 for treatment and I think in the context of this
8 question, it allows us to stipulate specifically and so
9 what I would -- I voted yes with the idea that the
10 restriction be that this be approved for MRSA only, not
11 for MSSA. We have other drugs that are -- we have a
12 lot of drugs available for treating MSSA and the same
13 with Strep pneumo, and that it be only in the setting
14 when there's no other alternatives and that there be,
15 you know, data or statements regarding the concern
16 about the renal -- the creatinine clearance and the
17 renal failure issues, and also that there be a
18 requirement that there be aggressive post-marketing
19 data collection in terms of safety and efficacy.

20 Interesting thing. I looked and I don't know
21 if this is -- I found on the Web from the National
22 Electronic Library of Medicine in the U.K. announcing

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1 the approval of this drug in Europe and which said
2 specifically that this is for treatment of nosocomial
3 pneumonia caused by MRSA when other alternatives are
4 not suitable which I think is some information we
5 didn't -- wasn't presented to us in exactly that way
6 when we first were looking at that.

7 So I think this gives us an opportunity to
8 very specifically define how this drug could be used
9 and take advantage of the efficacy that the trials have
10 demonstrated it may have.

11 DR. MOORE: Thank you. Mr. Mikita?

12 MR. MIKITA: Just very briefly, I voted yes
13 for my previous dissenting -- for all the reasons in my
14 previous dissenting vote on the first and I believe
15 that there's, you know, again every reason to show that
16 this drug for certain subpopulations is effective and
17 it's safe to the extent that the doctor and patient are
18 informed through labeling, through other guidelines and
19 directions from the FDA and from their respective
20 professional standards of care.

21 So I believe absolutely it's a yes vote on
22 this, as well.

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1 Thank you.

2 DR. MOORE: Thank you. Dr. Kaplan?

3 DR. KAPLAN: I voted yes. I agree with Dr.

4 Stevenson's comments and the comments before about

5 options and focusing this for MRSA.

6 I was, I think, most impressed with the

7 Vancomycin MIC data. It looked to me like the biggest

8 difference between the groups when you do put them

9 together is with isolates with MICs to Vancomycin over

10 one mcg per ml and that's using micro-broth dilutions

11 which typically actually give you a lower MIC than the

12 E test.

13 So I think that it does have a role

14 specifically in that setting.

15 DR. MOORE: Thank you. This is Dr. Moore.

16 For reasons which we've already stated, I voted yes,

17 primarily because, as I said, I think the drug does

18 have a role in the armamentarium of physicians treating

19 critically-ill patients with MRSA pneumonia and it

20 needs to be available when other options are not

21 available and the only concern I have, of course, would

22 be labeling with regard to creatinine clearance less

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1 than 30 where you'd have to again state that the
2 benefit -- should be used if the benefit outweighs the
3 risk.

4 Dr. Chatterjee?

5 DR. CHATTERJEE: I voted yes on this
6 question, and the reasoning was exactly the same that I
7 had before, which is this is a deadly condition for
8 which we have very few options and this is an option
9 that should be available to patients and physicians to
10 use.

11 DR. MOORE: Thank you. Dr. Calhoun?

12 DR. CALHOUN: Calhoun. So I'm one of those
13 who switched my vote from negative to affirmative and
14 with credit to Dr. Follman.

15 You are absolutely right but the difference
16 in this question for me as a clinician is the context;
17 that is, when other alternatives are not available and
18 so as Dr. Stevenson pointed out, if other alternatives,
19 Vancomycin or Linezolid, aren't available, then we
20 don't have anything else and so in that context, I'm
21 willing to look at the test of cure data with a little
22 more liberal eye, a little more open mind, and so, as

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1 has been pointed out down the table several times, it's
2 unlikely that placebo would have a 40-percent benefit
3 on test of cure in MRSA. That's a bad disease and
4 people die from it.

5 So it seems to me that taking those data as
6 being positive now in the setting where other
7 alternatives are not proper and, as I've previously
8 said, I'm actually not at all concerned about the
9 potential toxicity. It's not that people who get this
10 drug with a creatinine clearance less than 30 die. It's
11 just that they die a little more frequently than those
12 who get Vancomycin.

13 So I'm not all that concerned about the
14 toxicity side of the equation and I think in this
15 setting where there isn't anything else there, as Dr.
16 Stevenson pointed out, I think his modification to the
17 language is just about perfect.

18 DR. MOORE: Thank you. Dr. Alston?

19 DR. ALSTON: I voted yes, and I voted yes
20 before. So nothing to add there.

21 DR. MOORE: Thank you. Dr. Parise?

22 CAPT PARISE: I voted yes before, so not much

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1 to say, other than I agree this should be used for
2 MRSA, not sensitive Staph.

3 DR. MOORE: Thank you. Dr. Shyr?

4 DR. SHYR: I voted yes before. I don't have
5 anything to add.

6 DR. MOORE: Thank you. Dr. Katona?

7 DR. KATONA: I voted yes, and, you know, my
8 response to Question Number 1 may have had something to
9 do with the fact that Question Number 2 was actually on
10 the docket. So I had no problem voting yes on this. I
11 had a lot of problems voting no on the first question.

12 As a clinician, I'd certainly like to have
13 this in my armamentarium, especially if there's some
14 contraindications to only two other drugs that are
15 clearly indicated here.

16 One point about the MICs. My understanding
17 was all of the patients that had been studied by the
18 sponsor had MICs of one or less. So the indication to
19 use this drug for higher than one MICs may be good in
20 the theoretical literature but we don't have, I mean,
21 really good data to substantiate that.

22 My last comment is that, going back to

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1 Question 1, I think it's very interesting that the two
2 biostatisticians voted differently and the two
3 pediatricians voted differently. It shows you how much
4 of a controversy this is and it goes back to what Dr.
5 Cox has told us that we're more interested in our
6 reasoning than actually what our vote is. So I think
7 this is a good example of that.

8 DR. MOORE: Thank you. Dr. Goetz?

9 DR. GOETZ: Yes. I also changed my vote from
10 the original one because of the context of the
11 question, having Question Number 2 matters, and I hope
12 my vote matters, too, as well as my commentary.

13 So in regards to the commentary, I think that
14 the -- I see a creatinine clearance of 50 as being the
15 important cut point here, based upon the mortality data
16 that we saw presented after lunch and refer back to
17 that again where there was a definite difference in
18 mortality in the patients with the creatinine clearance
19 at 30 to 50, as I recollect the data being presented. I
20 think the point estimate was minus eight percent in the
21 people receiving Telavancin.

22 In terms of the -- but the clinical -- I come

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1 back to the clinical cure data and the people with
2 creatinine clearances over 50. I think it's a
3 reasonable -- although data mining is dangerous
4 certainly, there was prior evidence of this medication
5 having a lesser effect in people with creatinine
6 clearances than 50 which came out of the complicated
7 skin/soft tissue infections. So this is not just a
8 criteria that's drawn out of thin air and I'm looking
9 at the package insert from 2009 which maybe has been
10 modified since then which says that patients with a
11 creatinine clearance less than 50 also had lower
12 clinical cure rates and I think that that point has
13 been made before.

14 So I think that we have some justification
15 for looking at the medication in that regard and not
16 just saying that we're sifting the data to find
17 something that supports a point of view that we want to
18 come to.

19 In terms of labeling, certainly MRSA, but
20 when it comes to the MSSA issue, I'm going to differ
21 with some of my colleagues here and say we have
22 adequate drugs for MSSA. There are some interesting

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1 analyses that have been published in the last couple of
2 years that would suggest that methicillin-susceptible
3 Staph aureus with higher Vancomycin MICs also do less
4 well, regardless of whether -- and so I think we don't
5 know specifically this will hold true with Telavancin,
6 but they've showed data that the medication is
7 effective in MSSA and looking at their slides and the
8 data presented, looking at clinical cure rates, the
9 point estimate certainly favor Telavancin, people with
10 MSSA, as the point estimates, not necessarily a full
11 confidence interval, favored Telavancin in people with
12 MRSA.

13 So I'd certainly say MSSA and MRSA, and Strep
14 pneumo doesn't trouble me one way or the other, but
15 clearly we're not talking about this drug for
16 community- acquired Strep pneumo disease. If Strep
17 pneumo happens to be the pathogen that someone has with
18 nosocomial pneumonia, they may not need Telavancin but
19 I think there are very few clinicians that are going to
20 continue it specifically to treat pure Strep pneumonia
21 infection in people with hospital-associated pneumonia.

22 Oh, and finally, I think that there are other

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1 studies that the sponsor should certainly be looking
2 into. If the medication's been used in a 125,000
3 people in Europe and it has this indication for use
4 when other medications aren't suitable for use, I would
5 wager that there are ecological studies that can be
6 done and certainly non-prospective studies are limited.
7 With the right propensity analyses, we may get some
8 indications as to its safety and efficacy in people
9 with lower creatinine clearances and also other data
10 that bolster our confidence in the clinical community
11 in using it in patients with higher creatinine
12 clearances.

13 DR. MOORE: Thank you. Mr. Mullins?

14 MR. MULLINS: Yes. I tried to think about, in
15 answering this question, I tried to think about
16 something my mother always told me to be consistent. So
17 I said no the first time, so I'm saying no again. But
18 there was a lot more deliberation than that and much
19 more -- I went through many more mental gyrations to
20 come to my conclusion and it was a tough one for me
21 because I thought about from the aspect as I travel
22 around the nation and deal with public health sectors

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1 and I deal with people who don't have the acumen of my
2 august peers here, they don't have the navigational
3 aptitude to understand and speak in this health and
4 statistical vernacular.

5 They just want to know is this therapy safe
6 and when I ask myself that question, I found myself
7 challenged because I said if I give them this
8 parachute, if I say, yes, it has some holes in it but
9 here's your parachute but it has a few holes in it, I
10 wonder how they would feel and that was the stress that
11 I went under making this decision.

12 I didn't feel good about it because there
13 were several instances when analyzing the data where I
14 felt like the treatment differentials were close and I
15 felt like the safety, my safety concerns eclipsed any
16 benefits of the therapy, that I had concerns about
17 toxicity, I had concerns about the conduct of the trial
18 that really caused me to vote no, and I voted no based
19 on the terms that I felt like there were concerns about
20 efficacy, the treatment differential between Telavancin
21 and Vancomycin, and I felt like the treatment of cure
22 rate, the cure differential was very small in some

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1 instances.

2 But I did vote no because I had concerns
3 about safety primarily and that was my rationale.

4 Thank you.

5 DR. MOORE: Thank you. Dr. Voynow?

6 DR. VOYNOW: I voted yes before and so I felt
7 that I'm being consistent with my last vote.

8 DR. MOORE: Thank you. Dr. Cappelletty?

9 MS. CAPPELLETY: Yes. I voted yes, and
10 again I think, like many of the people around the
11 table, it was easier to sort of say no maybe to the
12 first question. It was more global over-arching
13 knowing that the second question was here.

14 I agree with the MRSA Staph indication. I
15 was also looking at MSSA with respect to severe beta-
16 lactam allergy, anaphylaxis for an MSSA-type of
17 patient.

18 As far as the renal issue goes, the data was
19 there for 50. The data was there for 30 or 33. I'm
20 not sure that I'm the person to say where to draw that
21 line at, other than in a good number of ICU patients,
22 you draw the line at 50, there's going to be a good

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1 chance that it's not going to be used, depending on
2 what that statement reads at.

3 So I would not look at a contraindication
4 below a particular creatinine clearance but maybe just
5 indicating caution values as renal function declines.

6 DR. MOORE: Thank you. We're scheduled for a
7 break at 3:15, but I think we can probably squeeze in
8 the last question, unless everybody objects. Do you
9 want a break and then discuss or you want to move
10 ahead? Any objections if we move ahead, if we move
11 ahead to the third discussion question? Are we okay?
12 Okay. Fair enough.

13 All right. So why don't we proceed then to
14 the third question?

15 Dr. Laessig?

16 DR. LAESSIG: Okay. Last one. So this is
17 just a discussion question for you and you probably
18 touched on some of this already.

19 So the nephrotoxicity of Telavancin has been
20 established based on experience with treatment of
21 complicated skin and skin structure infections. For
22 the treatment of nosocomial pneumonia, are there any

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1 additional comments or further recommendations,
2 particularly concerning the use in patients with
3 baseline renal dysfunction, and, if so, what are these
4 recommendations?

5 DR. MOORE: Thank you. So we'll go around
6 the table and -- well, I guess before we do that, let's
7 just open up to discussion, if anybody has any
8 particular points about this that have not already
9 spoken to the matter?

10 Yes. Dr. Calhoun?

11 DR. CALHOUN: So I'm going to come back to my
12 concern about congestive failure which I actually don't
13 think has been well addressed by the sponsor.

14 I think that what we saw in some of the
15 mortality data was actually an increase in the rate of
16 multi-organ failure in Telavancin-treated patients
17 compared to the Vancomycin-treated patients and whether
18 that simply reflects when kidneys go bad, other organs
19 tend to follow or whether there's something more to it
20 than that, but I think that's probably something that
21 could be clarified a bit with some focused data-mining.

22 So I think the recommendation on caution

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1 clearly needs to be there for 30 or 50 creatinine
2 clearance, whatever the agency thinks is the proper
3 cut-off, but I do think that we need to know more about
4 other organs that fail because that was actually the
5 more concerning mortality signal that I saw that was
6 associated with multi-organ failure.

7 When multiple organs fail, then mortality
8 really skyrockets and so.

9 DR. MOORE: I had one comment and that's,
10 technically speaking, patients who have complete renal
11 failure and go on continuous hyper-filtration would be
12 considered to have creatinine clearance of certainly
13 less than 30, but when they go on continuous hyper-
14 filtration, they tend to have a creatinine clearance on
15 the machine of about 40.

16 My question is -- and I don't know whether
17 these data are available, but it would be interesting
18 to see if the mortality information holds up on or if
19 the mortality information is available for individuals
20 who are put on CVH, continuous venous hyper-filtration,
21 as I say, because the machine, if you will, provides
22 them with an estimated creatinine clearance of

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1 approximately 40 or higher, depending on the situation.

2 It would just be interesting to have that
3 data, particularly in light of the data that's been
4 shown, that everybody who has creatinine clearance of
5 less than 30 has a significantly higher rate of
6 mortality.

7 Any other points about this discussion?

8 Yes. Dr. Chatterjee?

9 DR. CHATTERJEE: As one of the two
10 pediatricians on this committee, over the last four
11 years, I have pleaded many times with sponsors for
12 pediatric formulations and pediatric studies on new
13 agents and I will continue with that today, to say that
14 in the pediatric population, we see MRSA pneumonia,
15 too. It's not necessarily nosocomial pneumonia but we
16 have community-acquired pneumonia with MRSA and it
17 really isn't very different in terms of how it looks.

18 It is a deadly disease and we do not have
19 very many options to treat our patients with either. So
20 I would encourage the sponsor, if they're not already
21 doing that, to consider developing this drug for that
22 use.

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1 Pediatric patients have much better renal
2 functions. We don't have the same kinds of problems
3 with you all see on the adult side and so it may
4 actually be a very good drug that could be used in that
5 patient population.

6 DR. MOORE: Thank you. Dr. Alston?

7 DR. ALSTON: Just to point out that
8 Vancomycin's probably more nephrotoxic now than when
9 this study was done five years ago because we're
10 pushing the levels because we don't trust its efficacy
11 anymore and I can tell you anecdotally that I see much
12 more renal injury now with Vancomycin than I do because
13 we've gone from trough levels less than 10 to 10 to 15
14 and now 15 to 20 and I wonder if currently the
15 comparable nephrotoxicity is closer and, as others have
16 echoed, you know, we get creatinines every day. We can
17 objectively measure creatinine. We can't measure
18 headache but we can measure creatinine clearance.

19 So if this was some insidious irreversible
20 hard- to-measure toxicity, then that would be a big
21 problem but I think this is something that we can
22 easily deal with, physicians are used to dealing with

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1 it, and we can give creatinine clearance guidance.

2 DR. MOORE: Dr. Voynow?

3 DR. VOYNOW: I would also like to encourage
4 the FDA to work with the sponsor to have a plan for
5 post- market follow-up for this because I'm pressed
6 with the concerns of safety that may already be in
7 place for the indication for skin infections, but it's
8 going to be, I think, particularly important for this
9 indication in, as we've discussed, such a complicated
10 population.

11 So I'm not sure in what form that would be
12 most effective to follow safety in those patients, but
13 I think it's a very important question.

14 DR. MOORE: Are there any -- I'm sorry. Dr.
15 Goetz, did you have a comment?

16 DR. GOETZ: So I'm a little bit uncertain
17 which way we're going to go around the table. I guess
18 we're going to be commenting just sort of globally at
19 this point.

20 DR. MOORE: Well, my apologies. I've been
21 derelict in my duties as chair to provide clear
22 direction, speaking with both sides of my mouth. I

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1 opened it up for discussion and then said we'd be going
2 around the table. So why don't we just do that?

3 For those of you who have additional comments
4 to make or haven't made a comment yet, why don't we go
5 around the table and provide some input to the
6 discussion.

7 Dr. Cappelletty, we'll start again with you.

8 MS. CAPPELLETY: Yes. With regard to the
9 renal, as I said earlier, it does appear that there is
10 something there. It is something that I would continue
11 to monitor and get post-marketing data on. It is not
12 anything that I would list as any sort of
13 contraindication in the labeling. It would solely be
14 cautionary statements and, as I said earlier, I'm not
15 quite sure where to draw the line. I think there needs
16 to be a little bit more discussion between the sponsor
17 and the FDA with whether the 30 is the appropriate
18 number or 50 or somewhere in between that.

19 DR. MOORE: Thank you. Dr. Voynow, anything
20 else? Okay. Thank you.

21 Mr. Mullins, anything?

22 MR. MULLINS: I think my concern is that we

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1 develop a profile of the subject or potential patient
2 that has a greater level of vulnerability when it comes
3 to nephrotoxicity. So what's the profile of that
4 patient or subject that should receive some type of
5 special exclusion from this therapy? That's one thing
6 that I think should be emphasized.

7 Thank you.

8 DR. GOETZ: This is Dr. Goetz. I think that
9 in terms of further recommendations regarding the use
10 in patients with baseline renal dysfunction, I think it
11 will be important to provide the mortality data and I
12 would break it down 30, 50, and less than 30 because
13 those distinctions make sense to me as a clinician who
14 makes decisions as to when to use a medication and when
15 not.

16 I agree with the sponsor, remembering that
17 this drug, 33ml creatinine clearance permitted is the
18 breakpoint would be not wise because people would not
19 be able to operationalize that.

20 It would be useful -- there may be more
21 analyses that can be done to look at what models and
22 predicts mortality, in addition to renal function, but

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1 I leave that to the agency to decide.

2 I think I agree with the agency the
3 nephrotoxicity has been well established before.

4 Looking again at the package insert, it's almost
5 identical findings that 15 percent versus seven percent
6 of patients had an increase of creatinine 1.5 times
7 baseline in skin and soft tissue infections studied.

8 DR. MOORE: Thank you. Dr. Katona?

9 DR. KATONA: I'd reiterate I'm concerned
10 about the creatinine clearances less than 50 as much as
11 I am about 30 and I'd like to see clinically-available
12 drug levels if we were going to use this drug.

13 DR. MOORE: Thank you. Dr. Shyr?

14 DR. SHYR: I do agree that post-market
15 surveillance trial is necessary to closely monitor,
16 especially when we already have a lot of data right
17 now. So I think that we should be monitoring for the
18 renal function, especially find out the cut point 30,
19 50, or whatever other numbers, but clearly this is a
20 baseline risk factor associated with the outcome. I do
21 think we should pay a lot of attention on this.

22 DR. MOORE: Thank you. Dr. Parise? No?

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1 Okay.

2 CAPT PARISE: No additional comments.

3 DR. MOORE: Dr. Alston?

4 DR. ALSTON: Nothing to add.

5 DR. MOORE: Dr. Calhoun?

6 DR. CALHOUN: The only thing to add is to
7 follow on what Dr. Alston mentioned a few minutes ago.

8 This is a manageable toxicity and it would be
9 really interesting to do a little data mining from the
10 dataset both in skin and soft tissue infections and in
11 the clinical trial database to see to what extent the
12 kinetic of return of renal function might differ,
13 depending on what baseline renal function was.

14 That is, if you see a little bump in renal
15 function and the baseline creatinine clearance is 50
16 and then it's 40, that might well clear up. By doing
17 that, one could actually provide an objective algorithm
18 for a clinician. You have a patient on this drug and
19 the creatinine clearance changes in this direction or
20 to this degree, here's what you should do.

21 In some cases, it might just be fine to
22 continue the drug if it's clinically indicated. It

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1 might be fine just to continue the drug and watch renal
2 function very carefully, but it might be possible to
3 data mine the safety dataset and look at serial
4 creatinines that have been drawn to get some sense of
5 that.

6 DR. MOORE: Thank you. Dr. Chatterjee?

7 DR. CHATTERJEE: Just a follow-up comment to
8 what you said, Dr. Calhoun.

9 It might also be possible to reduce the dose
10 and still use the drug.

11 DR. MOORE: This is Dr. Moore. I have
12 nothing further to add.

13 Dr. Kaplan?

14 DR. KAPLAN: Same.

15 DR. MOORE: Mr. Mikita?

16 MR. MIKITA: Nothing.

17 DR. MOORE: Dr. Stevenson?

18 DR. STEVENSON: I just have a question. In
19 the FDA Briefing Document, it refers to the labeling of
20 the complicated skin and soft tissue infections and
21 listed as a warning precaution informing prescribers
22 about creatinine clearance less than 50.

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1 So I don't know what the requirements are as
2 far as doing more, anything more aggressive than just
3 put a warning in the label, you know, what constitutes
4 a stronger statement than that, you know, like a black
5 box warning or whatever. So I'm just asking that
6 question, but at least there should be at least a
7 comparable warning as there is in the skin and soft --
8 the indication for the skin infections.

9 DR. MOORE: Thank you. Dr. Follman?

10 DR. FOLLMAN: I guess I would just say, I
11 think the major concern is with mortality, not
12 nephrotoxicity, for people with poor creatinine
13 clearance, and, you know, that is a premise I wonder
14 how useful the experience in CSSI is for these patients
15 with nosocomial pneumonia and a much higher mortality
16 rate.

17 DR. MOORE: All right. I'm going to give the
18 last word to Dr. Robinson.

19 DR. ROBINSON: I think this has been a
20 fascinating discussion. Everything has been said, as
21 far as I'm concerned, and I appreciate the opportunity
22 to participate.

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1 DR. MOORE: Thank you. If there's no further
2 discussion, then I'll call the meeting adjourned.

3 I'll now adjourn the meeting. I want to
4 thank everybody for putting up with my -- I'm sorry.
5 What? Sorry. Before -- sorry.

6 Dr. Laessig?

7 DR. LAESSIG: Yes. Just to thank you all for
8 a job very well done. We recognize how difficult this
9 was and clearly you can see how difficult it's been for
10 us. So thanks very much and safe travels home.

11 DR. MOORE: One more thing. I need just to
12 summarize briefly for the record the Question Number 3.
13 That is, everyone had concerns about nephrotoxicity and
14 labeling with regard to creatinine clearance less than
15 30 or even less than 50 and other concerns addressed
16 were whether -- sorry -- mentioned were whether to have
17 a fuller understanding or fuller explanation of the
18 labeling that goes into the CSSI labeling for this
19 particular drug and discussions about concerns about
20 mortality.

21 I apologize for the vague summary but the
22 devil's in the details and I think that should suffice.

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1 Sorry.

2 Anyway, thank you, everybody, for putting up
3 with my arbitrary and capricious chairmanship. It's
4 been a pleasure.

5 So we'll now adjourn the meeting and please
6 remember to drop off your name badge at the
7 Registration Table on your way out so they may be
8 recycled.

9 I want to thank the FDA and the sponsor for
10 putting together superb presentations and thank the
11 panel members for their service.

12 (Whereupon, at 3:12 p.m., the meeting was
13 adjourned.)

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2 I, Natalia Thomas, the officer before whom the
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21 My commission expires: 12/21/2015

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