DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH

Anti-Infective Drugs Advisory Committee

Wednesday, July 16, 2008

8:00 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane, Room 1066
Rockville, MD

C O N T E N T S

C O N T E N T S (Continued)

P A R T I C I P A N T S

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Designated Federal Official

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Katherine Laessig, M.D.
Thomas Smith, M.D.
Alfred Sorbello, M.D., MPH
Scott Komo,, Dr.P.H.

P R O C E E D I N G S

LCDR MOSADDEGH: Good morning. This is the July 16, 2008 meeting of the Anti-Infective Drug Advisory Committee to discuss doripenem by Johnson & Johnson. The Chair for this Committee is Dr. Townsend and I will turn the meeting over to Dr. Townsend.

Call to Order and Opening Remarks

DR. TOWNSEND: Good morning, everybody. Introductions--I will introduce myself and then we will get started. I am Greg Townsend. I am the Acting Chairman for this Committee in the Division of Infectious Diseases at the University of Virginia. That's it. Dr. Cox?

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

DR. LAESSIG: Katie Laessig, Deputy Director, Division of Anti-Infective and Ophthalmology Products.

DR. SMITH: Tom Smith, Medical Team Leader, Division of Anti-Infective and Ophthalmology Products.

DR. SORBELLO: Alfred Sorbello, Medical Officer, Division of Anti-Infective and Ophthalmology Product.

DR. KOMO: Good morning. Scott Komo, Division of Biometrics IV.

DR. REHM: Susan Rehm. I am an adult infectious-disease practitioner at the Cleveland Clinic.

LCDR MOSADDEGH: Sohail Mosaddegh, Exec Sec for Anti-Infective Drugs Advisory Committee.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. EDWARDS: Jack Edwards, Adult Infectious Diseases, Harbor, UCLA.

DR. HILTON: Joan Hilton, Division of Biostatistics, UCSF.

DR. BRANTLY: Mark Brantly, University of Florida, Pulmonary Diseases.

DR. STOLLER: Jamie Stoller, Pulmonary Critical Care, Cleveland Clinic.

DR. LEGGETT: Jim Leggett, Adult Infectious Diseases, OHSU.

DR. M. SMITH: Margo Smith, Adult Infectious Diseases, Washington Hospital Center.

DR. DOWELL: Scott Dowell with CDC.

DR. BENNETT: I am Jack Bennett from NIAID at HIH.

DR. OHL: Chris Ohl, Wake Forest University, Adult Infectious Diseases.

DR. CALHOUN: Good morning. I am Bill Calhoun, Adult Pulmonary Critical Care Medicine from the University of Texas.

DR. REX: And, finally, John Rex. I am formerly with Adult and Critical Care, Internal Medicine and Infectious Diseases, University of Texas Medical School at Houston. I am currently the V.P. for Clinical Infection at AstraZeneca Pharmaceuticals. My role on the committee today is that of the non-voting Industry Rep.

In addition, I will note that potentially relevant today is the fact that I am the Vice Chair of the Area Committee on Microbiology for the Clinical Laboratory Standards Institute, an international consensus organization that develops methods for testing and interpretation of microbiology results. To the extent that it becomes relevant. I will comment from that perspective as well.

DR. TOWNSEND: Thank you very much, everybody.

I have a statement to read. For topics such as those being discussed at today's meeting, there are often a variety of opinions some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals

can express their views without interruption.

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

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

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

Thank you.

LCDR MOSADDEGH: Good morning. The Food and drug Administration is convening today's meeting of the Anti-Infective Drugs Advisory Committee undre the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the Committee are special

government employees or regular federal employees from other agencies and are subject to federal conflict-of-interest laws and regulations.

The following information on the status of the Committee's compliance with federal ethics and conflict-of-interest laws covered by, but not limited to, those found 18 USC, Section 208, and Section 712 of the Federal Food, Drug And Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the Committee are in compliance with Federal Ethics and Conflict of Interest Laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts, when necessary, to afford the committee essential expertise.

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

Today's agenda involves discussion of doripenem powder, Doribax, for reconstitution and intravenous administration, sponsored by Johnson & Johnson Pharmaceutical Research and Development LLC, a Johnson & Johnson company, proposed for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia.

This is a particular matter meeting during which specific matters related to Doribax will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflicts of interest waivers have been issued in connection with this meeting.

With respect to FDA=s invited industry

representative, we would like to disclose that Dr. John Rex, M.D. is participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. Dr. Rex' role at this meeting is to represent industry in general and not any particular company. Dr. Rex is an employee of AstraZeneca.

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

Thank you. Dr. Townsend?

DR. TOWNSEND: Thank you very much. Actually, I think, Dr. Laessig, if you are ready?

Welcome and Meeting Overview

[Slide]

DR. LAESSIG: On behalf of the Division, I would like to welcome members and guests of the committee,

colleagues from Johnson & Johnson and the audience to our meeting today.

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Our objectives today are two-fold. The first is to discuss New Drug Application 22-171 for doripenem. The applicant, as you have heard, is Johnson & Johnson. The formulation is 500 mg for intravenous injection, and the proposed indication is adults with nosocomial pneumonia, including ventilator-associated pneumonia. The second objective is to discuss clinical trial design for future studies of nosocomial pneumonia.

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So, what are nosocomial and ventilator-associated pneumonia? Well, definitions may vary slightly but, for our purposes, nosocomial pneumonia occurs 48 hours or more after hospital admission and is generally not incubating at the time of admission. Ventilator-associated pneumonia is a subset of nosocomial pneumonia and arises more than 48-72 hours after endotracheal intubation.

These are important illnesses and nosocomial pneumonia is the third most common cause of healthcare-associated infections. It is also the leading cause of

death among these infections and, as noted by Klevans et al., in 2002, it resulted in approximately 36,000 deaths.

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Doripenem was initially approved in October of 2007. It is a carbapenem antibacterial that is indicated in the treatment of adults with complicated intra-abdominal infections or complicated urinary tract infections, including pyelonephritis. Of note, there are also three other approved carbapenems; imipenem, meropenem and ertapenem.

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The antibacterial armamentarium for nosocomial pneumonia consists of only four approved products; ciprofloxacin, levofloxacin, linezolid and piperacillin/tazobactam. Note that there are actually no approved antibacterials for nosocomial pneumonia that include the specific subset of ventilator-associated pneumonia. Now, there is a related indication called lower respiratory tract infection which is an indication for which there are other products approved, but not specifically nosocomial pneumonia.

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The development program for doripenem nosocomial pneumonia consisted of 2 Phase 3 non-inferiority studies. DORI-09 was an open-label, randomized, multi-center, active controlled study that compared doripenem to piperacillin/ tazobactam in non-ventilated subjects with nosocomial pneumonia and early onset, less than 5 days of ventilator-associated pneumonia.

DORI-10 was also an open-label, randomized, multi-center, active controlled study that compared doripenem to imipenem in subjects with either early or late-onset VAP.

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After the applicant's presentations the FDA presentation will consist of the justification for the non-inferiority margin for the clinical studies.

First, Dr. Sorbello will review the historical data to establish the treatment effects of antibacterials for this indication, and Dr. Komo will elaborate on the methodology used to determine the margin. Dr. Smith and Sorbello will go over the clinical efficacy and safety of doripenem and will specifically review issues with the Phase 3 study designs and discuss adverse events and deaths. Finally, Dr. Coderre will discuss the microbial resistance

of doripenem that is based on the in vitro and clinical susceptibility data.

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Related to these presentations are issues for the committee=s discussion, specifically, the adequacy of the information to support and select an appropriate non-inferiority margin; the adequacy of the data to demonstrate the efficacy and the safety of doripenem for this proposed indication, whether the committee has any concerns with the microbial resistance information and, lastly, input on future trial designs, specifically study population, diagnostic criteria, endpoints and analysis populations, appropriate use of concomitant antibacterials and switch to oral antibacterials.

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Last, but not least, I would like to acknowledge the hard work of the review team whose names are listed here. With that, I will turn it over to the first presenter from Johnson & Johnson, Alysia Baldwin-Ferro.

Applicant Presentations

Introduction

MS. BALDWIN-FERRO: Thank you.

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Good morning. I am Alysia Baldwin-Ferro, from the Regulatory Affairs Department of Johnson & Johnson Pharmaceutical Research and Development.

On behalf of J&J PRD and the doripenem team, I would like to thank the review committee and the advisory committee and the FDA for taking the time today to discuss doripenem for the treatment of nosocomial pneumonia and ventilator-associated pneumonia.

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This morning I will begin with a brief presentation. It will then be followed by Dr. Wunderink who will discuss his thoughts on nosocomial pneumonia. Dr. Flamm will discuss the microbiology of doripenem. Dr. Friedland will review the study design and efficacy of doripenem, and Dr. Redman will discuss the safety and overall benefit/risk of doripenem and then end with concluding remarks.

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Doripenem was initially developed by Shionogi in Japan. Shionogi ultimately received approval of doripenem, under the trade name Finibax in July of 2005 for the

treatment of multiple indications. J&J acquired development rights of doripenem for the Americas and Europe and continued the clinical development.

Doripenem, as noted, was submitted to the FDA in December of 2006 for the treatment of complicated intra-abdominal infection and complicated urinary tract infection. From a clinical perspective, the NDA contained 2 trials for each indication. In total, 2,117 patients were studied; 1,276 were treated with doripenem. The dosing regimen for the doripenem-treated patients was 500 mg every 8 hours over a 1-hour infusion.

These 4 studies showed that doripenem was safe and efficacious in this patient population, and this led to the approval and subsequent launch of doripenem under the trade name Doribax, in October of 2007.

A second NDA for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia, was submitted in June of 2007. This file contained information from 2 clinical studies, with a total patient population of 979, 485 treated with doripenem. Recently, in Europe doripenem received a positive opinion by the Committee of Medicinal Products for Human Use for all 3 indications.

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With that as background today, we are here to discuss doripenem for the treatment of nosocomial pneumonia and ventilator-associated pneumonia. The 2 studies that were conducted to support this indication were complementary in design. Although they have similar designs, they have different patient populations but, when taken together, encompass the full range of nosocomial pneumonia patients generally seen in clinical practice. Dr. Friedland will discuss these trials in detail during his presentation. The data from these studies support the efficacy and safety for the treatment of patients with nosocomial pneumonia and ventilator-associated pneumonia.

With that, I would like to turn the podium over to Dr. Wunderink, who will discuss his thoughts on nosocomial pneumonia. Thank you.

Management of Nosocomial Pneumonia

DR. WUNDERINK: Thank you. It is my privilege to address the agency and the advisory committee, and my goal here is to try and put these 2 trials in the context of the usual clinical practice in the management of nosocomial pneumonia.

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The driving issue for us in clinical practice is this issue of inappropriate initial antibiotic therapy compared to appropriate therapy. There are multiple studies. I have just selected a few to show you here that show that if you start with inappropriate initial empirical antibiotic therapy there is a higher associated mortality that occurs because of that.

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If you look at gram-negatives which have multi-drug resistanceB-here showing data from the time of admission but we know that this has been occurring for a long time in the hospital itselfB-we see occasionally some fairly rapid increases in resistance rates. The important thing about this is that these patients who harbor these multi-drug resistant pathogens are very likely to receive inappropriate initial antibiotic therapy, and in this particular study two-thirds of them did.

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We also have seen that if you start with an initial empiric antibiotic regimen and have to escalate, either by adding antibiotics or using a broader-spectrum

antibiotic regimen than what the initial is, there seems to be a mortality associated with that. So, the importance is to get the correct antibiotic up front. Conversely, if you de-escalate, go to fewer antibiotics or narrower spectrum, there is no mortality worsening, and potentially some benefit there.

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That is the driving idea behind the recent ATS/IDSA guidelines for patients who are at risk for multi-drug resistant pathogens. They are specifically Pseudomonas, Acinetobacter, MRSA and gram-negatives, particularly those that harbor an ESBL.

So, the recommended therapy empirically to start with is a 3-drug regimen with a beta-lactam and multiple choices there, a second agent to cover gram-negatives, specifically immunoclygocides or fluoroquinolines, and then some gram-positive coverage.

Now, there is a fairly broad spectrum of beta-lactams here, and the choice there depends on the local ecology. So, if you have institutions that have a lot of Nitobacter or have a lot of ESBLs or particular resistance problems with Pseudomonas there has been a tendency to need

to use the carbapenems as the initial up-front therapy.

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So, gram-negative bacilli are an important cause of severe hospital-acquired pneumonia. Carbapenems are an important class of agents for the appropriate empiric therapy and initial empirical combination therapy is the norm, and that is what we have been emphasizing.

Now, what I want to point out is that combination therapy is based on increasing the probability of at least 1 initially appropriate antibiotic, and it is not necessarily that there is increased efficacy of the combination therapy once you actually know what the pathogen is.

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That is illustrated by the next slide, which is one of several meta-analyses that have looked at the need for combination antibiotic therapy for ventilator-associated pneumonia. The relative risk of the summary statistic here clearly crosses 1 so there is no documented benefit for combination therapy, at least with the immunoclygocides, by these meta-analyses. So, it is not based on efficacy; it is appropriateness of initial therapy.

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Now, the problem with the clinical management of pneumonia that is clearly reflected in clinical trials of nosocomial pneumonia is the difficulty in the diagnosis. There are 2 main keys to the diagnosis. One is the radiology. Both in clinical practice and in clinical trials the clinician seeing the patient is sometimes pitted against the radiologist as far as interpretation of chest x-rays.

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We actually looked at this. If you look at the graph on your right, we gave 3 expert radiologists, chest radiologists, films to look at on the day that we did bronchoscopy and, therefore, used a quantitative culture bronchoscopy as the gold standard to say that they had pneumonia or not. In that setting, the radiologists' accuracy, if you look at the area under the ROC curve, with 0.5 being essentially a coin toss, their accuracy was not very good, only 0.57.

Now, that is not how radiologists practice and, in all fairness to them, they are usually comparing 2 x-rays side by side and seeing is there a change and does this change look like pneumonia. When we actually gave them that comparison x-ray their accuracy went down. Then we made the

mistake of giving them clinical information and their accuracy was even worse, such that if they said it was pneumonia it was likely to not be pneumonia.

There was significant inter-observer variability there between the 3 radiologists. There were also significant differences when you asked them to look at very specific signsB-is there an air bronchogram, are the? Alveolar infiltrates? Does this look like atelectasis with volume loss? They disagreed on those specific signs in a significant number of cases, including things like atelectasis where, if the radiologist said it was atelectasis, it was actually highly predictive that the patient had pneumonia.

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The other important issue is not only if you feel that you have a diagnosis of pneumonia, the other issue is the microbiologic etiology. We depend on gram stain and respiratory cultures here. Most of the research has been done on ventilator-associated pneumonia. For hospital-acquired pneumonia non-intubated patients we are back to depending on expectorated sputum, similar to what we have to do with community-acquired pneumonia.

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In the ATS/IDSA guidelines we concluded that a quantitative culture strategy or the clinical strategy, which is basically use of non-quantitative tracheal aspirates, were equally valid as long as you use these same important principles of broad-spectrum coverage and de-escalation.

There has been a gradual increase in the quantitative culture strategy in the U.S., especially in the last few years with the advent of non-bronchoscopic BAL catheters, but the norm is still really the clinical diagnosis based on endotracheal aspirates done in a non-quantitative way. We have no data on the use of quantitative cultures in non-intubated patients.

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That is illustrated by a couple of recent studies. This is a landmark study published in the New England Journal by the Canadian Critical Care Trials Group. What you see on the graph is the actual number of cultures or the number of patients and their culture results. With tracheal aspirates you have a yes/no whether there is a positive culture. With quantitative cultures you have the

intermediate of a positive culture but growth below.

What I want to point out is two things. One is that the final diagnosis in this important study was made by an expert review panel, similar to what was done in DORI-09. The other thing that they did is that they asked the clinician before they did the diagnostic testing what is the probability of pneumonia. Is it low, moderate or very high? In the patients with low or moderate pre-test probability of pneumonia who had subsequent negative cultures antibiotics were still continued in a high percentage of those patients, 85 percent with tracheal aspirates and slightly lower with quantitative cultures.

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This is another recent study looking at the usual standard of practice, surveying in a prospective observational way almost 400 patients in 20 different medical centers. There were a few patients in whom no culture was sent but, most importantly, in 50 percent of the patients, the cultures were negative.

If you look at the graph, if the patients had positive cultures, it was helpful both in that they could de-escalate and also escalate. But, if they had negative

cultures, most clinicians continued the therapy that they had actually started them on in an overwhelming majority. If you started with 3 drugs, they were a little bit more likely to de-escalate than if they had started with 2 drugs.

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The last point I will make is regarding sputum gram stains. This has been a key in trying to make an early diagnosis, and it has been very poorly studied, especially in nosocomial pneumonia. This is one study that looked at 50 samples from 5 hospitals. They basically had their technicians do each sample 3 different times, 3 different technicians, 3 different interpretations. Our usual standard for appropriateness of this specimen as far as the etiology is to see if it is contaminated by squamous epithelial cells.

Overall, 43 percent of them failed that screening. But if you look at whether all 3 samples failed the screen, that occurred in 18. But if 1 failed the screen or 2 failed the screen it was actually more and more. So, there was significant variability in that. There is even variability in the gram stain morphology. So, in 50 percent of the specimens they had a change of at least 1 morphotype.

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So, our clinical practice is very similar to clinical trials and it also varies from clinical trials. We have a lot of difficulty in identifying patients with multi-drug resistant pathogens at the time of diagnosis, and specifically we have difficulty distinguishing between the different MDR pathogens. So, the risk factors for MRSA are very similar to the risk factors fox Pseudomonas. So, it necessitates the use of multi-drug empirical regimens.

We also have vulnerable patient populations that we need to deal with but that oftentimes don't get enrolled in clinical trials because of the time course of the informed consent process, very severely ill patients, or patients with multiple confounding medical conditions.

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In summary, early appropriate empirical therapy is necessary for improved outcome in hospital-acquired pneumonia. That has been the emphasis of the ATS/IDSA. High resistance rates make carbapenems the most reliable beta-lactam, especially for ventilator-associated pneumonia, and definitive diagnosis of etiologic pathogen is difficult, especially in the un-intubated patient. Thank you.

Microbiology

PK/PD

DR. FLAMM: Good morning.

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I am Bob Flamm, from microbiology research at Johnson & Johnson Pharmaceutical Research and Development.

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Doripenem is a broad-spectrum carbapenem with activity against gram-positive and gram-negative bacteria. Comparative activity from a North American surveillance program demonstrates that for the Enterobacteriaceae, including ESBL-producing isolates, doripenem and meropenem have similar activity, with imipenem being 4- to 8-fold less potent. Again, for Pseudomonas aeruginosa doripenem is the most potent carbapenem and for Acinetobacter imipenem is the most potent carbapenem.

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An evaluation of longitudinal data from North American surveillance for the years 2003 through 2005 show that for the MIC90 for Pseudomonas aeruginosa increased 2-fold from 2003 to 2004 for doripenem, imipenem and piperacillin/tazobactam, and 4-fold for meropenem. The

MIC90 values were unchanged in 2005. Further data, which has not yet been submitted to the FDA, from the JAI surveillance program for the year 2006 show that the MIC90s have remained unchanged. These increases occurred before doripenem was approved for use in the United States in 2007.

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An overview of activity against gram-positive organisms shows that carbapenems are potent against methicillin-susceptible Staph. aureus, with MIC90 values less than or equal to 0.12 mcg/mL. They are inactive against methicillin-resistant Staph. aureus and for the Pneumococci carbapenem MICs increase as penicillin MICs increase. However, the MIC90 values are less than equal to 1 mcg/mL.

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As resistance development for all antibiotics is a concern, studies have evaluated potential resistance mechanisms to doripenem. Doripenem is stable to most beta-lactamases, including ESBL and AmpC cephalosporinases. It is, however, unstable to carbapenemases such as metallo-beta-lactamases and the emergent serine carbapenem such as KPC. Of note, no organism producing a KPC enzyme was found

in the nosocomial pneumonia studies.

Cell permeability and efflux changes in gram-negatives lead to resistance and in vitro studies have shown that there is a low potential for selection of resistance in Pseudomonas aeruginosa. Doripenem MIC values greater than 8 mcg/mL are associated with at least 2 independent mutations, whereas imipenem MIC values up to 32 mcg/mL can be associated with a single mutation resulting in loss of OprD.

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A study to evaluate in vitro single step resistance development was conducted in Dr. David Livermore's laboratory. Resistance selection for doripenem and other agents was evaluated for individual P. aeruginosa isolates for their ability to produce colonies on agar plates containing various multiples of the MIC. The number of Pseudomonas aeruginosa strains that produced resistant mutants upon selection with doripenem was lower than the other carbapenems, other beta-lactams, representative fluoroquinoline, representative aminoclycoside across a range of concentrations.

Imipenem is known to select for resistance in Pseudomonas aeruginosa. Although not shown on this slide,

both imipenem and meropenem selected for resistant mutants in a concentration of 8 times the MIC whereas doripenem did not.

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In an effort to force resistance selection, 1 Pseudomonas aeruginosa strain was passaged separately with doripenem, imipenem and meropenem. Resistance developed during the multiple passages. Resistant isolates were cross-resistant to the other carbapenems under passage with each of the antibiotics. The imipenem MICs increased to 16 mcg/mL. The doripenem MIC increased to 4 mcg/mL and the meropenem MIC increased to 8 mcg/mL during passage with meropenem.

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Now turning to pharmacokinetics/pharmacodynamics--

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--doripenem pharmacokinetics are similar to other carbapenems. The half-life is approximately 1 hour. There is no tissue or plasma accumulation with repeat dosing, and there is an approximate dose proportional increase in the AUC with increasing concentrations over the range of 250-1,000 mg.

Doripenem is rapidly distributed in the extracellular fluid volume. Protein biding is low and approximately 8 percent. There is no cytochrome P450 induction or inhibition, and it is stable to renal dehydropeptidase. Thus, there is no need to co-administer dehydropeptidase inhibitor.

There is one major non-active metabolite in open ring form. Excretion is through the renal route and approximately 85 percent of the parent and primary metabolites are recovered in the urine in 24 hours. A dose adjustment is required in renal insufficiency and there is minimal biliary excretion.

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Pharmacodynamics have been studied in the mouse neutropenic thigh model and have shown that, as other carbapenems, the time above MIC is the definitive pharmacodynamic index. Mean time above MIC for stasis to a 1 log-10 kill for the Enterobacteriaceae ranged from 30-37 percent, and for Pseudomonas aeruginosa 23 and 28 percent respectively.

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A comparison of plasma concentrations over time,

for a 1-hour infusion in yellow and a 4-hour infusion in orange for a 500 mg dose, show that for the 1-hour infusion the peak is higher, whereas in the 4-hour infusion there is a more gradual peak.

If one is targeting pathogens with MICs less than or 1 mcg/mL both dosing regimens will achieve time above MIC targets for most of the dosing interval, and it is not expected that the 2 dosing regimens would be different against these pathogens. However, if one is targeting pathogens with MICs in the range of 2-4 mcg/mL it is the 4-hour infusion which will achieve concentrations above that range for a longer period than a 1-hour infusion. This is the basis for our studying a 4-hour infusion where organisms with higher MICs are suspected.

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Monte Carlo simulations based on human pharmacokinetic data in healthy human volunteers and clinical trials have been done to evaluate the effect of extending the infusion time on target attainment.

For the 500 mg 1-hour infusion, evaluating the target thresholds of 24-35 percent, the probability of attaining those thresholds ranged from 74-90 percent for

organisms with an MIC of 2 or less. The MIC distribution of isolates that occurred during both the nosocomial pneumonia trials are shown as bars at the bottom of this figure, and it should be noted that, due to the potency of doripenem, there were few organisms from nosocomial pneumonia studies that had MICs greater than 2.

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With the 4-hour infusion we now see a shift to the right, where now the probability of attaining the target thresholds of 25-35 percent is greater than 90 percent for organisms with an MIC of 4 or less, thus providing better coverage for organisms with higher MICs such as Pseudomonas aeruginosa, shown as the yellow bars on this graph, an important nosocomial pathogen.

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In summary, doripenem has a broad spectrum of activity against many gram-positive and gram-negative bacteria, including resistant organisms producing ESBLs and common beta-lactamases.

It exhibits in vitro a low potential to select for resistant mutants to Pseudomonas aeruginosa, and high target attainment is achieved with a 500 mg dose of doripenem. The

4-hour infusion further increases target attainment for organisms with higher MICs.

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Now I would like to introduce Dr. Ian Friedland who will present the clinical aspects of doripenem

Clinical Study Design and Clinical Efficacy

DR. FRIEDLAND: Good morning. I am going to present the clinical study design and efficacy results.

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We know that with nosocomial pneumonia there is a medical need for additional therapies, especially for infections caused by pathogens that could be resistant to other treatment regimens.

We have shown that doripenem has broad spectrum in vitro activity, including against some more difficult to treat pathogens, such as Pseudomonas, Acinetobacter and ESBL producing Enterobacteriaceae. Based on the need in nosocomial pneumonia, 2 clinical studies were conducted and these were designed utilizing PK/PD principles previously described.

The stability of doripenem in solution allows us to use doripenem as a more extended infusion. In addition,

in terms of safety, preclinical studies have demonstrated a favorable safety profile, with a lower propensity of doripenem to cause seizures compared with other carbapenems.

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In nosocomial pneumonia 2 large, multi-national Phase 3 non-inferiority trials were conducted. These were complementary in that many aspects of the designs were similar but the patient populations differed in some respects.

In the first study, DORI-09, the target population were patients outside the ICU who were not on ventilators. But we also included patients with early onset ventilator-associated pneumonia--i.e., those ventilated for less than 5 days. The patient population in DORI-09 was anticipated to have pathogens with MICs less than or equal to 2, and for this reason the 500 mg 1-hour infusion of doripenem was chosen.

The second study, DORI-10, was conducted exclusively in patients with ventilator-associated pneumonia, both early and late onset. Here, because of the greater risk of less susceptible Pseudomonas in particular, a 4-hour infusion of doripenem was used.

The non-inferiority margin defined in the protocol was 20 percent. The results of the 2 studies taken together support the efficacy of doripenem in a broad nosocomial pneumonia population.

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These studies were conducted as open-label trials and, although it was carefully considered to conduct them blinded, there were a number of reasons why it was not clinically feasible to conduct blinded trials. These included the fact that the comparators had dosing frequencies different from doripenem. For example, piperacillin/tazobactam is given 6 hourly compared with 8 hourly for doripenem and we allowed 2 independent dosing regimens, which would not have been possible to blind.

There was also a potential for fluid overload that could have occurred with use of placebo infusions, which is an important considerations in critically ill patients. We wanted to allow for differential adjunctive therapy use between the 2 treatment arms, and this would not have been possible in a blinded study. Also, we wanted to evaluate the utility of doripenem for pathogens resistant to the comparators, and this would not have been possible in a

blinded study.

[Slide]

Two types of potential bias need to be considered in open-label studies. Selection bias in the doripenem studies was unlikely because the decision to enroll a patient was made before randomization and before treatment assignment was known. Randomization was done centrally, and randomized blocks were grouped by region and not by study site, reducing the likelihood of predicting treatment assignment.

Assessment bias was reduced by ensuring company study staff were blinded, by use of an external blinded evaluation committee and by ensuring objective outcome assessments were collected to support the clinical outcomes. The external blinded evaluation committee consisted of 10 outside experts who evaluated the available clinical data in order to assess patient outcomes which were then used in the outcome analyses.

[Slide]

Shown here are the time and events of both nosocomial pneumonia studies. During the screening period a lower respiratory tract specimen was obtained in all

patients. Patients were then randomized to study therapy and treated for 7-14 days.

A test of cure where the primary outcome assessment was made was conducted 6-20 days following therapy. In addition, there was a late follow-up visit conducted 28-35 days following all therapy. And, safety was assessed throughout the entire study period.

[Slide]

Because nosocomial pneumonia can be caused by a wider variety of pathogens, including those resistant to the study drug, adjunctive or combination therapy was allowed where potentially resistant organisms were suspected.

In DORI-09, because the piperacillin/tazobactam package insert recommends combination with an aminoglycoside, this was recommended in this trial. In DORI-10 the use of aminoglycosides was optional. Addition of vancomycin was allowed in each study if resistant Staph. aureus was suspected.

In DORI-09 there was an optional oral switch. The oral switch agent here was levofloxacin 750 mg once a day after patients had received a minimum of 3 days of intravenous therapy and after meeting stringent criteria

showing improvement. In DORI-10 there was no oral switch.

[Slide]

This slide summarizes important inclusion and exclusion criteria in the 2 studies. Both studies required evidence of nosocomial pneumonia based on the presence of a new or progressive infiltrate on chest x-ray, and patients had to have fever or an elevated white cell count.

The presence of respiratory signs and symptoms of pneumonia were required in DORI-09 but, because of the difficulty in assessing such signs and symptoms in patients on ventilators, these were not specifically described in the inclusion criteria in DORI-10. However, patients in DORI-10 had to meet the diagnostic criteria for ventilator-associated pneumonia.

In addition to traditional criteria, there was incorporated a minimal clinical pulmonary infection score, or CPIS. This score has been used to improve the accuracy of the diagnosis of pneumonia in intubated patients. Important exclusion criteria are also shown here.

[Slide]

I am going to say a few words about the CPIS in the doripenem studies. The FDA briefing book stated that a

fair proportion of patients had scores less or equal to 6, which was stated to indicate a low likelihood of them having ventilator-associated pneumonia. However, it is important to note that there are different CPIS systems that have been described and we used the simplified system of Luna et al.

The Luna system is scored out of 10 and does not include microbiological findings which are usually not available at study entry. Other retrospectively derived systems use a 12-point scale that include gram staining and culture results. In the 12-point scale scores less than or equal to 6 have been stated to predict a low likelihood of VAP. However, patients in the doripenem studies had to have positive cultures to be included in the clinically evaluable population and almost all patients had positive gram stains. Thus, almost all patients in the doripenem studies would have scores greater than or equal to 7 if a 12-point scale were used.

Of note, the mean CPI scores in the doripenem studies were very similar to that in the Luna study in which patients were confirmed to have VAP based on quantitative BAL cultures. Thus, the CPI scores in the doripenem studies provide confidence that patients enrolled did have VAP.

[Slide]

These are the study populations used in the analyses that we will be referring to and the percentages in each population in each study. The intent-to-treat population included patients who received any study drug and this population was used in the safety analyses.

The clinical modified intent-to-treat population were those patients who received any study drug and had evidence of pneumonia.

The clinically evaluable population, also known as the per protocol evaluable population, were those patients who followed the protocol definitions and procedures, had a test of cure in the allowed time window and did not have confounding events of antibiotic therapy during the conduct of the trial.

The microbiological modified intent-to-treat population was a subgroup of the clinical MITT and included those patients in whom a baseline pathogen was identified. Likewise, the microbiologically evaluable patient population included clinically evaluable patients with a baseline pathogen identified.

[Slide]

Clinical outcomes were defined as follows: Clinical cure required resolution of signs and symptoms of pneumonia or return to baseline and improvement or lack of progression in chest x-ray findings. Failure assessment was based on persistence or worsening of the clinical picture, or progression of pneumonia on chest x-ray, or death related to pneumonia.

Of note, patients who received additional antibiotic therapy for ongoing symptoms were assessed as failures. Patients who died or had treatment changes in the first 48 hours were considered non-evaluable and were excluded from the clinically evaluable population.

[Slide]

This slide summarizes the reasons why patients were not included in the primary analysis population, which was the clinically evaluable population. The most common reasons were having only a resistant pathogen or patients who received confounding non-study antibiotic therapy. Another common reason was either missing a test of cure assessment or having the assessment done outside the allowed window.

[Slide]

The baseline demographics of the CE population, shown here, were similar to those in the randomized population. The mean age was just under 60 years and the majority of patients were male, which is typical in this indication.

In DORI-09 the majority of patients were enrolled outside of North America. Most patients had non-VAP, although over 20 percent had early onset VAP--i.e., onset less than 5 days after start of ventilation. About one-quarter of patients had APACHE II scores greater than 15. The rate of bacteremia at baseline was higher in the piperacillin/tazobactam arm. However, the most common single blood isolate was coagulase negative Staphylococcus and, therefore it is not anticipated that this imbalance affected the overall comparison.

Of particular note was the high rate of abnormal renal function at baseline, and this is an indicator of how sick this population was and that many patients had multi-organ failure at the time of enrollment.

[Slide]

This is a summary of the most common baseline pathogens isolated in both treatment groups and their

resistance to the study drugs. The most common pathogens were Staph. aureus and Pseudomonas aeruginosa. Of particular note was the extremely high resistance rate to piperacillin/tazobactam in Klebsiella pneumoniae where 44 percent of strains were resistant to that agent. This was generally the result of the presence of extending the spectrum of beta-lactamases in these strains. In contrast, none of these was resistant to doripenem.

Among the non-fermenters, higher resistance rates to piperacillin/tazobactam and to doripenem were observed in Pseudomonas aeruginosa. High resistance rates to Acinetobacter were observed particularly to piperacillin/ tazobactam. Among Staph. aureus, 32 percent were methicillin resistant and were regarded as resistant to both doripenem and pip/tazo.

Of note, pathogens resistant to study drug received were generally not included in the primary CE population analyses. For example, patients in the comparator arm with pip/tazo resistant pathogens, such as those resistant Klebsiellas I showed you, were excluded from the CE population. But patients with similar ESBL producing organisms were included in the doripenem arm as they were

susceptible to doripenem.

[Slide]

The median duration of study drug in DORI-09 was 11 days, and this included both the IV and oral portion of therapy. However, 54 percent of patients received IV study drug only and the median duration in these patients was 10 days. Less than 50 percent of patients switched to oral therapy. Of those who switched, oral therapy was given for a median of 5 days after receiving a median of 7 days of intravenous therapy before the switch. Therefore, although an oral switch was allowed in this trial, most of the therapy received was the intravenous study drug.

Because aminoglycoside therapy was recommended in these trials we can see high empiric usage rates of aminoglycoside in both treatment arms. Empiric vancomycin was used for suspected methicillin-resistant Staph. aureus in approximately 16 percent of patients overall. Thus, in this study a relatively small proportion of patients received monotherapy.

[Slide]

Now let's turn to the primary efficacy results. The primary endpoint of the study was the clinical cure

rate. This was assessed in the cMITT and the clinically evaluable population which were considered co-primary endpoints. Similar cure rates in the cMITT and CE populations were observed in the 2 treatment arms. The 95 percent confidence interval around the difference between the treatments met the prespecified definition for non-inferiority of 20 percent and exceeded this by a large margin.

[Slide]

Cure rates in important subgroups are shown in the table. In the elderly similar high cure rates were achieved in the 2 treatment arms. Patients with ventilator-associated pneumonia had poorer outcomes than those who were not ventilated in both treatment arms. However, the outcome in the doripenem arm compared favorably to that of piperacillin/tazobactam.

[Slide]

Approximately 20 percent of patients in this study did not receive an aminoglycoside, and in these patients the cure rate with doripenem was 82.8 percent compared with 77.8 percent in the pip/tazo group.

In addition, among patients who did receive

adjunctive aminoglycoside therapy, there were 30 patients in the doripenem group and 32 patients in the pip/tazo group who received this therapy for less than or equal to 3 calendar days, which was generally less than 48 hours. The cure rates in patients who received adjunctive aminoglycoside therapy were similar to those in patients who did not. A definite conclusion regarding the added benefit of aminoglycoside therapy is difficult to draw from these data.

[Slide]

Following submission of the NDA, we were requested by the FDA to confirm that all the criteria defining pneumonia in the protocol had been met in the study populations. We confirmed that the vast majority of patients did have objective confirmation of protocol criteria, including the presence of pulmonary infiltrates confirmed independently in radiology reports.

The table shows the original analyses I have already shown you and a sensitivity analysis including only patients who met all protocol inclusion criteria for pneumonia, including independent radiological confirmation. The results in the sensitivity analyses were essentially

the same as those shown previously. If you look at the confidence intervals in the original analysis compared with those with the new definitions, you can see these are very similar.

[Slide]

This shows microbiological cure rates or eradication rates and demonstrates high microbiological cure rates for the most common baseline pathogens including methicillin-susceptible Staph. aureus or MSSA, the Enterobacteriaceae and Pseudomonas aeruginosa.

[Slide]

Now I will show you the results of the second study, DORI-10, which was conducted exclusively in patients with VAP. This slide summarizes the reasons why patients were not included in the primary analysis population, which was the clinically evaluable population. Like DORI-09, the most common reasons were either missing a test of cure assessment or having the assessment done outside the allowed window confounding non-study antibiotic therapy.

[Slide]

Patients with only a resistant pathogen at baseline were also excluded from this population. But, in

addition, patients with a negative lower respiratory tract culture who were not receiving antibiotic therapy were excluded.

Patients in DORI-10 were on average slightly younger than in DORI-09 and, again, the majority were male. You can see that the majority of patients enrolled in this trial had late onset VAP. In this study more than 40 percent of patients were enrolled in North America. A large proportion of patients had high APACHE II scores, again evidence of how sick this population was. There was a lower rate of abnormal renal function in this study compared with DORI-09 because a larger proportion of young trauma patients with normal renal function were enrolled in DORI-10.

[Slide]

Here are the common baseline pathogens for both treatment arms and, again, Staphylococcus aureus and Pseudomonas were common pathogens. Among the Enterobacteriaceae no carbapenem-resistant strains were isolated. In Pseudomonas aeruginosa none of the strains was considered resistant to doripenem compared to 13 percent resistant to imipenem, with similar resistance to the 2 carbapenems in Acinetobacter baumannii. Twenty-four percent

of the Staph. aureus were methicillin resistant.

[Slide]

The median duration of study drug therapy was 8-9 days. Because aminoglycoside usage was optional this was used only in 21-25 percent of patients. Vancomycin was used in approximately 30 percent of patients. Therefore, in this study we see a large proportion of patients who received monotherapy with study drug.

[Slide]

This shows the primary efficacy results. As in DORI-09, the primary endpoint of clinical cure, was assessed in co-primary populations, which were the modified intent-to-treat population and the clinically evaluable population. One can see similar cure rates in the cMITT population, 59 percent on doripenem versus 58 percent on imipenem.

In the clinically evaluable population cure rates were 68 percent versus 65 percent. The 95 percent confidence interval around these differences exceeded the prespecified lower bound of 20 percent by a large margin. These results indicate non-inferiority of doripenem to imipenem.

[Slide]

Here are the outcomes in important subgroups. One can see favorable comparative cure rates in the elderly, in patients with late onset of ventilator-associated pneumonia and patients with high APACHE II scores.

[Slide]

As with the evaluation shown previously for DORI-09, the protocol inclusion criteria relating to the diagnosis of pneumonia could be confirmed in the vast majority of patients in DORI-10. When analyses were rerun and patients were confirmed to have met all criteria, including independent radiological confirmation, the results were essentially the same as those previously described.

[Slide]

Shown here are the microbiological cure or eradication rates. Similar rates were observed in the 2 treatment groups for methicillin-susceptible Staph. aureus and the Enterobacteriaceae. For P. aeruginosa microbiological cure rates appeared higher for doripenem although sample sizes were small. The apparent lower microbiological eradication rates for P. aeruginosa compared to other pathogens reflect the difficulty in completely eradicating this pathogen from respiratory secretions in

intubated patients. However, clinical cure rates in patients with P. aeruginosa were 80 percent for doripenem and 43 percent for imipenem.

[Slide]

Aminoglycoside therapy is most likely to impact the outcome of gram-negative pathogens. This table shows microbiological cure rates in patients with gram-negative infections who received aminoglycoside therapy versus those who did not. Approximately 75 percent of patients with gram-negative infections did not receive adjunctive aminoglycoside therapy and the cure rates were similar whether they received aminoglycoside therapy or not. Similar to the results in DORI-09, these data appear to indicate no added benefit with aminoglycoside therapy.

[Slide]

The emergence of resistance or reduced susceptibility is a concern for all antibiotic therapy, particularly in organisms such as Pseudomonas aeruginosa which frequently develop resistance on exposure to antibiotic therapy. In DORI-10 this was actively evaluated and serial cultures were taken from tracheal aspirates in all patients in this trial regardless of clinical response.

This table summarizes the data shown in Table 5 in the FDA briefing book, but we have also included here the imipenem MIC. This table includes baseline and repeat isolates that had at least a 4-fold increase in the doripenem MIC and that were genetically related.

Points to note are that the imipenem MICs are generally 2- to 4-fold higher than doripenem MICs and that there were an additional 6 strains in the imipenem arm, shown in the last row, that were already non-susceptible to imipenem at baseline. Thus, in the doripenem arm there were only 3 strains that had increased MICs greater than or equal to 8 mcg/mL, whereas in the imipenem arm there were 16 strains that had either MICs greater than or equal to 8 at baseline or that occurred on therapy.

Furthermore, the 4-fold increased carbapenem MICs in the imipenem arm were associated with failures at the end of therapy in 6 patients compared to 0 in the doripenem arm. Resistance mechanisms were determined in the strains shown in the table.

In the imipenem group non-susceptibility was often found to be due to a single mechanism, usually reduction in the porin OprD, whereas in the doripenem group non-

susceptible strains often had 2 resistance mechanisms, OprD reduction, thus, increased MC production. The requirement for 2 mechanisms to cause doripenem non-susceptibility may explain the lower rates of non-susceptibility seen with doripenem therapy.

[Slide]

This slide summarizes the primary efficacy results from the 2 trials. The difference between the 2 treatment groups and the 95 percent confidence intervals in the clinically evaluable population and the co-primary modified intent-to-treat population are shown here. All these analyses make the original protocol specified 20 percent non-inferiority margin.

Although 20 percent was defined in the protocol as the NI margin, a post hoc justification following a request by the FDA supported an 18.5 percent margin versus imipenem and a 15.8 percent margin versus pip/tazo. Both these margins were exceeded. In addition, in the FDA briefing book a 10 percent margin was proposed and the results from both studies exceeded even this margin.

The FDA briefing book also mentioned a 6 percent non-inferiority margin for mortality. Although mortality

was not a primary endpoint in the doripenem studies and the individual studies were not sized for this endpoint, for the combined 28-day mortality the upper bound of the non-inferiority margin was less than 6 percent.

[Slide]

The microbiological cure rates in the combined studies are shown here. Patients with expectorated sputum specimens not deemed to be suitable based on gram stain criteria were excluded here. The results were generally similar between the treatment groups, although eradications were generally higher in gram-negative infections with doripenem therapy.

[Slide]

This becomes even more apparent when considering the subgroup of patients with VAP. For example, microbiological eradication rates were 79 percent for doripenem versus 43 percent for comparators against P. aeruginosa.

[Slide]

Although it was intended in DORI-10 to show that the 4-hour infusion would be effective against strains with high MICs, as it turned out very few strains with high MICs

were isolated in the trials and there is little direct clinical evidence of the added effectiveness of the 4-hour infusion from this study.

The table shows estimations of PD targets of time of MIC values of 25-35 percent using Monte Carlo simulations that included all the pathogens isolated during the nosocomial pneumonia clinical trials and population PK data.

One can see for both the 1-hour infusion and the 4-hour infusion for most pathogens extremely high target attainment would be anticipated. This, and the efficacy results in DORI-09, is the basis for the recommendation that for most infections the 1-hour infusion was anticipated to be adequate.

However, for Pseudomonas aeruginosa it is clear that there is a small but potentially important increase in target attainment with a 4-hour infusion. Thus, the 4-hour infusion is likely to produce an advantage for Pseudomonas aeruginosa, particularly when strains with lower susceptibility are suspected.

[Slide]

I will now hand over to Dr. Redman, who will discuss safety and the overall benefit/risk profile of

doripenem.

Clinical Safety

Benefit/Risk, Conclusions: Doripenem for NP

DR. REDMAN: Good morning.

The safety of doripenem has been evaluated in over 2,000 patients who have participated in 15 completed Phase 1, 2 and 3 studies. This presentation will focus on the safety data obtained from the 969 patients who received study drug in the 2 Phase 3 nosocomial pneumonia studies, of which 485 were exposed to doripenem.

[Slide]

A majority of patients had at least 1 adverse event. Within each study the number of adverse events, drug-related adverse events, serious adverse events, discontinuations due to adverse events and deaths were similar between the treatment groups.

Low all-cause mortality rates were seen in both trials and were similar to those in other recently published NP studies, indicating that therapy in these trials was appropriately effective. The greater number of deaths that occurred in both treatment arms of DORI-09 and 10 is believed to be related to the greater overall number of

elderly patients in DORI-09 with chronic comorbid conditions such as COPD and impaired renal function and those who were transferred from a chronic care facility.

[Slide]

As presented by Dr. Friedman, when a fixed interval of 28 days is applied all-cause mortality rates were comparable between treatment arms within each study and for both studies combined. However, patients in the ITT population were followed for variable periods of time as the last assessment visit occurred 4-5 weeks after administration of the last dose of study drug. When we evaluate all-cause mortality rates during the entire study period the total number of deaths increased, as would be expected, but remained comparable between the treatment arms.

[Slide]

Patients had many concurrent serious and life-threatening events ongoing prior to death, and attributing the cause or mortality would be difficult in the absence of an autopsy. Furthermore, there was variability among investigators regarding which events would be associated with a fatal outcome versus not resolved at the time of

death.

This slide presents the adverse events the investigators associated with a fatal outcome. For some patients more than one adverse event was associated with a fatal outcome. Most events in DORI-09 occurred in the system organ class of infections and infestations and then the respiratory, thoracic and mediastinal disorders.

The higher rate of infections and infestations in the doripenem arm of DORI-09 is a reflection of the higher rate of the adverse event termed pneumonia reported for this treatment group, and pneumonia will be discussed in the next slide. In DORI-10 similar numbers of patients in both treatment groups had fatal outcomes across the systems presented. No system organ class had a significantly greater number of events.

[Slide]

When we look at the specific term pneumonia in DORI-09 there appears to be an imbalance in this event between the treatment arms. However, a number of different terms could have been chosen to describe the same event such as pneumonia, respiratory failure, cardiopulmonary arrest. Therefore, we assessed events that were used tp describe

pneumonia and respiratory failure to determine whether similar rates of these events combined were reported as fatal outcomes.

When evaluated in this manner 14, or 6.3 percent, of the doripenem-treated patients and 11, or 5.0 percent, of the piperacillin/tazobactam-treated patients had a fatal pneumonia or respiratory failure event. This finding suggests a possible imbalance in reporting the specific term pneumonia with a fatal outcome between the treatment arms in DORI-09.

[Slide]

All patients with pneumonia events associated with a fatal outcome were assessed as clinical failures in our efficacy analyses. When we examined the 10 pneumonia events with a fatal outcome in the doripenem arm of DORI-09 we find that the patients were enrolled from 7 different sites, and 6 patients were enrolled from South America. Most were male. Most were elderly and the median age was 75. As expected, most had complex medical histories and most had significant chronic comorbid conditions such as COPD, emphysema, renal failure, prior CABG procedures, myocardial infarctions and cancer.

Three patients had a documented fungal infection at the time that they died. Two had candidemia and one had Aspergillus pneumonia. Most patients had confounding concurrent events, including candidemia, MRSA bacteremia, sepsis, renal failure, respiratory failure, all these likely contributing to the patient=s death. There was no common characteristic seen among these 10 patients that would distinguish them as having pneumonia reported as a fatal event.

[Slide]

The most common serious adverse events occurring in the doripenem-treated patients in both DORI-10 and DORI-09 combined are listed on this slide. Although this table presents the SAEs that occurred more commonly in the doripenem arms, within each study the rates of these events were generally comparable to the comparator arms. As expected, most common serious adverse events were pneumonia, respiratory failure, sepsis and septic shock. These events were frequently related to the progression of or complications of the infection under study.

[Slide]

The FDA mentions in their briefing book that of

the more than 600 adverse event terms that were reported in the NP studies, 3 events, oral candidiasis, increased hepatic enzymes and rash, occurred more commonly with the doripenem 4-hour infusions in DORI-10 than doripenem 1-hour infusions in DORI-09, and that this difference was statistically significant.

The agency also points out that this finding was not buttressed by statistically different differences in the rates of these events in the doripenem and the comparator arms within each study. The frequency of these 3 events are shown in this table.

In addition, results of an analysis of laboratory data evaluating increases in serum ALT and AST is presented. One doripenem-treated patient had a rash that was a serious event. This patient had a poorly described exanthem occurring on the fifth day of doripenem therapy that prolonged hospitalization. Both the investigator and the consulting dermatologist considered that this rash was not related to study drug.

The number of these events is small and it cannot be determined whether the higher frequency seen with the 4-hour infusion in DORI-10 is related to the infusion time or

the study population. All 3 events were seen in patients treated with doripenem 1-hour infusions in the prior cUTI and IAI trials, and some cases were considered plausibly related. Therefore, these events are currently listed as adverse drug reactions in the doripenem label.

[Slide]

Seizures are a well-known complication of carbapenem therapy, particularly with imipenem, and 0.8 percent of the patients in the doripenem arms of the 2 nosocomial pneumonia studies had seizures during the IV study drug period. This is compared to 0.5 percent in the piperacillin/tazobactam arm of DORI-09 and 2.3 percent in the imipenem arm of DORI-10. None of the seizures occurring in the doripenem treatment group were clearly related to doripenem.

In contrast, 2 imipenem-treated patients had no identified risk factors for seizures other than the imipenem therapy. These data are supported by preclinical studies that demonstrate that doripenem has a lower potential to induce seizures than either imipenem of meropenem.

[Slide]

In general, the safety profile of doripenem

appears to be similar to other carbapenems. No unexpected safety signals were found for doripenem compared to other carbapenems or the safety profile previously seen in cUTI and the IAI studies. Severe hypersensitivity reactions and C. difficile colitis have both been identified as risks in the doripenem UTI and IAI studies. Both of the events occurred in 1 percent or fewer of the patients treated with doripenem in nosocomial pneumonia trials.

Infections with emergent drug resistant bacteria are a risk for antibiotic therapy. However, there was a low incidence of such emergency in our clinical trials. However, in order to evaluate this the long term surveillance studies are ongoing.

The benefits of doripenem include proven efficacy in 2 large clinical trials where it has been shown to be non-inferior to 2 different ATS/IDSA-recommended comparator agents. Potent broad-spectrum activity has been developed, demonstrated in vitro, and high cure rates against a variety of pathogens were observed in clinical trials, including Pseudomonas aeruginosa.

In addition, the fact that doripenem is stable in solution allows the option for it to be administered as a

prolonged 4-hour infusion. This optimizes the PK/PD parameter of interest for beta-lactam antibiotics, allowing physicians to target less susceptible pathogens without increasing the dose.

Importantly, preclinical and clinical studies suggest that doripenem has a low propensity to induce seizures, which makes it attractive from a safety perspective for ICU patients who frequently have predisposing conditions increasing the risk for seizures.

[Slide]

The results of DORI-09 support the efficacy and safety of doripenem 500 mg 1-hour infusion in patients with nosocomial pneumonia, including ventilator-associated pneumonia. For doripenem 500 mg 1-hour infusions target attainment of 35 percent time above MIC is achieved for more than 90 percent of the pathogens usually found in patients with NP, a value customarily considered of relevance for in vivo efficacy.

The overall efficacy of doripenem 1-hour infusion was non-inferior to the comparator agent piperacillin/ tazobactam. In addition, the efficacy in patients with early onset was not inferior to piperacillin/tazobactam.

The safety profile of doripenem 1-hour infusions was similar to piperacillin/tazobactam.

[Slide]

For doripenem 500 mg 4-hour infusions, target attainment of 35 percent above MIC is achieved for more than 90 percent of the pathogens usually found in patients with VAP, including Pseudomonas aeruginosa. In DORI-10 the overall efficacy of doripenem 4-hour infusion was not inferior to the comparator agent imipenem. Although the numbers are small, higher microbiological cures for Pseudomonas aeruginosa were seen with doripenem compared with imipenem. The safety profile of doripenem 4-hour infusions was similar to imipenem, with a possible lower incidence of seizures with doripenem.

[Slide]

In conclusion, doripenem is the first antibiotic to be developed for the treatment of patients with nosocomial pneumonia with a trial dedicated to ventilator-associated pneumonia. Two independent studies have shown the efficacy of doripenem to be non-inferior to 2 different ATS/IDSA-recommended comparator agents. Our data show that doripenem is a potentially important alternative agent for

the treatment of patients with nosocomial pneumonia, including ventilator-associated pneumonia, and especially for patients at risk for infections resistant to other agents.

On behalf of Johnson & Johnson and the doripenem team, I thank you for your attention. We would be happy to answer your questions.

Questions Regarding Applicant=s Presentation

DR. TOWNSEND: Thank you very much. Are there questions from the committee for representatives from Johnson & Johnson? Dr. Edwards?

DR. EDWARDS: A question for Dr. Friedland. I was wondering if you might have a backup slideB-it would be around CC-68--that would visually show your reference to the less than 6 percent delta for all-cause mortality. I realize the study wasn't powered for that but I was just wondering if you could show us anything visually on that.

DR. FRIEDLAND: Could you clarify exactly in what kind of format you would like to see that?

DR. EDWARDS: Do you have any graphical representation of what the confidence intervals look like with those estimates you made?

DR. FRIEDLAND: The overall confidence interval is shown here on the slide for the combined study.

DR. EDWARDS: I am referring to the all-cause mortality analysis.

DR. FRIEDLAND: This is all-cause mortality.

DR. EDWARDS: I think that is your clinical cure rate.

DR. FRIEDLAND: In the bottom, in the blue, is the combined all-cause 28-day mortality for the 2 studies combined, and the difference is 1.4 with a confidence interval of minus 2 to 2.56.

DR. EDWARDS: Thank you. Then, could you estimate what your sample sizes might have been had you been using all-cause mortality if you had been powered for all-cause mortality?

DR. FRIEDLAND: As we mentioned, these studies were designed to look at clinical cure as the endpoint and we have not done calculations using mortality as an endpoint.

DR. EDWARDS: Thank you.

DR. DOWELL: This is another question for you. Could you tell us a little bit more about the primary endpoint and how that was determined, so this is clinical

cure at the test of cure visit? I was understanding that there was a blinded evaluation of that, but I am particularly interested in the data that went into that evaluation, who produced the data and were those people blinded to the treatment allocation? If they weren't blinded, were these primarily objective or subjective criteria that they were using?

DR. FRIEDLAND: The original outcome assessments were made by the investigators in both trials, and these were based on the definitions in the protocol, similar to what I showed you, which involved improvement in the clinical picture but also improvement in more objective measures such as temperature and white count. That was assessed at the test of cure which was approximately 1-3 weeks following the completion of therapy. Any prior failure was carried forward to that test of cure visit, whereas cure was only assessed at the test of cure visit.

That was partly based on subjective findings and partly on objective findings such as laboratory findings, chest x-ray findings. That was assessed by the investigator and was not blinded.

The evaluation committee then took all the

information available from the case report forms in a blinded manner and looked at all those data, and evaluated whether they agreed with the investigator or did not agree with the investigator based on the available data. When they did not agree with the investigator the outcome was changed to that of the evaluation committee, and that is what was shown in the analyses.

DR. DOWELL: Thanks. That is very helpful. I find it reassuring that the final evaluation was done by a committee that was blinded to the treatment allocation, and I was trying to get a sense of that committee.

You said some of the data were subjective and some were objective. Can you give us a sense whether that committee presumably has a protocol that they are going to apply to decide whether to overrule? Was the majority of that objective data like white count, temperature, and so forth? Or, is it heavily weighted towards subjective assessments by people who knew which drug the patients got?

DR. FRIEDLAND: The committee did have a chart on which to base their assessments, and their charge was to evaluate the patient=s outcome as described in the protocol. You know, they checked the outcome assessments that were

required at the test of cure and looked at those. So, they looked at the signs and symptoms described, the severity of those, white count, temperature and the course of the patients during the trial including at the end of therapy and other assessment times. They looked at the microbiology.

So, all the data that was available in the case report form they used, and the totality of those data is what they used to assess whether there was substantial evidence for cure of failure. They did have the option, if there was not sufficient information, to make the patient non-evaluable or indeterminate.

DR. TOWNSEND: You had a question, Dr. Bennett?

DR. BENNETT: Could you give us a little more detail about how the conflict was resolved between you and the agency about the interpretation of the x-ray? I think we all agree that the radiologic results are absolutely pivotal in the diagnosis and you had disagreement between the clinician and the radiologists, and Dr. Wunderink pointed out that that is not entirely uncommon.

But then the agency said that the results from the radiology also have statements suggesting that radiologists

hadn't compared prior films and part of the diagnosis, of course, requires increased or a new infiltrate. So, how did you go back and decide which radiology you could really document and which you couldn't?

DR. FRIEDLAND: During that process of the reevaluation we looked at two things. There was the radiology interpretation on the case report form, which was the clinician's interpretation of that x-ray taking into account the total picture of the patient. In addition to that, we had a printed radiology report from the radiology department independent of our study. These radiologists were not involved in our study.

In the vast majority of cases, and we can pull up that slide that shows the correlation between the investigator and the radiologistB-in the vast majority of cases they did agree. But the FDA pointed out one or two cases where there was a discrepancy between the radiology report and the investigator but that was in a very small percentage of cases. So, in well over 90 percent. I will give you an example. Slide up.

[Slide]

What we have here are two definitions for

pneumonia based on radiology reports. PS or strict definition is based only on what the radiologist said. The PC is based on the interpretation by the investigator on the case report form. In addition, both these definitions required all the other definitions of pneumonia to be met such as the white count, the temperature, signs and symptoms.

You can see here that for the strict definition in 98 percent of cases the radiologist did confirm what the investigator said. That is in the doripenem arm, and 97 percent in the pip/tazo arm.

[Slide]

If we look at DORI-10, if we look at the confirmation by the radiologists there was correlation between the radiologist and the investigator in 91 percent and 89 percent. These percentages also include cases where there was a missing radiology report, in which case we said there was not a correlation between them. So, 91 percent is where we have a radiology report and the radiology report correlates between the radiologist and the investigator.

DR. BENNETT: Just to clarify, this is the original radiology report, not a request back to the individual

investigator or study coordinator to get a re-reading or an expert? This is what you had documented when you submitted your case report form?

DR. FRIEDLAND: In the vast majority of cases, although there were a number of centers around the world where it was not routine to have radiology reports for ICU patients. Typically, in many European countries the radiologists dontt write reports for all the x-rays done in ICU. So, in those centers we actually requested that the forms be read by radiologists independent of our study and provide us with those reports.

DR. BENNETT: Could I ask one more question? I am a little confused about co-primaries. I am used to having one global endpoint instead of having two. So, when you calculated each one of the co-primaries did you act as though it was the only one, or did you adjust for the fact that you had two endpoints?

DR. FRIEDLAND: The sample sizes were calculated based on the clinically evaluable population. Even though it was calculated based on that, we were required to meet the non-inferiority margin for both populations.

DR. BENNETT: I am not talking about the sample

size. I am talking about the confidence intervals around the difference in the CE at the end of the study.

DR. FRIEDLAND: Could you rephrase your question? I am not sure.

DR. BENNETT: Well, perhaps we will return to this when the agency discusses the statistics of the study so I will table that question. Thanks.

DR. TOWNSEND: Dr. Stoller?

DR. STOLLER: A point of clarification, it is my understanding that in DORI-10 there was no blinded evaluation committee and, although there is text about that on page 51, I am wondering what the rationale for not having a blinded evaluation committee in DORI-10 would be in the context of having had one in DORI-09.

DR. FRIEDLAND: So, we did carefully consider doing one in DORI-10. However, as you can imagine, for ICU patients the amount of data that is collected during their stay can be quite substantial and it was a logistic challenge to collect all that data and have that evaluated by an evaluation committee. In discussions with the evaluation committee, their opinion was that the assessment was best made by the clinicians at the bedside taking into

account everything that was going on at that time. So, those were some of the reasons why.

In addition, in DORI-10 there were a number of objective measures that gave us some confidence that we could confirm the outcome assessment made by the investigators, such as ventilation status, oxygenation, these kinds of objective measures.

DR. STOLLER: So, just for clarification, would it be true that the assessment of outcomes, the clinical assessments, clinical evaluations, the test of cure were made exclusively by unblinded investigators in DORI-10. Is that correct?

DR. FRIEDLAND: That is correct.

DR. TOWNSEND: Dr. Hilton?

DR. HILTON: The protocol calls for 7-14 days of treatment, but I see that in DORI-09 43 percent of all patients were excluded from the CE population and in DORI-10 53 percent were excluded. One of the reasons for exclusion in both cases was insufficient study drug. So, I wonder what your threshold was for calling a patient=s treatment insufficient.

DR. FRIEDLAND: Yes, the rule we applied was 80

percent to 120 percent of specified durations and 5 days was the cutoff. Less than 5 days was considered inadequate.

DR. HILTON: And a second question is when you say that the studies were adequately powered, did you anticipate this proportion of patients not making it into the CE population?

DR. FRIEDLAND: Yes, based on previously published studies we had a fair idea of the evaluability, and the evaluability seen in this trial is actually very typical of comparative drug trials.

DR. FLEMING: Just to comment on this point, I think you presumed that the CE would be 60 percent but the CE in DORI-10 was only 47 percent. And, it is one thing to be excluding people based on not having the bug or based on some criteria before randomization, but you were excluding 14 percent of people because of inadequate study drug. You were excluding 27 percent of people because of concomitant treatment violations. You were excluding 23 percent because of test of cure being outside of windows. These are stunning levels of exclusion and actually exceed even the very generous high level exclusions that you had assumed.

DR. FRIEDLAND: Yes, all the exclusions were

described in detail in the statistical analysis plan prior to completion of the study and database lock. So, we did follow strict rules that were predetermined for making these exclusions.

DR. FLEMING: And it is apparent that in terms of quality of study conduct there were high levels of irregularities, which when you exclude those people from the CE analysis, you are really compromising the integrity of randomization, and when you include them in the MITT you are including a lot of people where there are significant irregularities. So, neither of these two analyses are getting around the high level of irregularity that you have.

DR. TOWNSEND: Dr. Leggett?

DR. LEGGETT: A point of clarification in CC-45. It was my understanding that most of this was based on the Luna and, yet, when you were talking about it you started shifting gears and moving to the Pugin. Could you elucidate?

[Slide]

DR. FRIEDLAND: So, the CPS was originally described based on retrospective analyses in which data such as culture results were available. That original

description had a 12-point scale including those culture results. Luna then described a system to try and evaluate prospectively patient treatment and, because the culture results and microbiology results were not available at the time of the study, they described a 10-point scale excluding the microbiology findings and that is the system we used. The cutoff of 6 or less, those determinations of a low lack of VAP are based on the 12-point scale.

So, what we are saying is if we had used the 12-point scale, used it retrospectively, and included all the microbiology data the scores of 5 that we saw in the trial would actually have been 7 in the new scale and scores above 7 indicate a high likelihood of having VAP.

DR. TOWNSEND: Dr. Fleming, you had another question?

DR. FLEMING: Well, there are many issues to be raised surrounding your justification of the non-inferiority margin and I am assuming we can discuss those throughout the day, including when the FDA is presenting.

The recent October, >07 FDA guidance on NI studies for antibacterial agents say that non-inferiority study designs may be appropriate when there is adequate evidence

of a defined effect size of the active control regimen so that a non-inferiority margin can, in fact, be supported. So, in essence applying that here, there has to be adequate evidence in the historical data for the effect of the active comparator piperacillin, for example or imipenem, on the endpoint of clinical efficacy.

Comprehensive synthesis of the evidence that supports the effect size of the active comparator and the proposed non-inferiority margin should be provided and sponsors should provide adequate evidence to support the proposed margin.

There are so many issues here when you actually look at the science of how you have proposed to defend this. I just want to highlight a few of these issues. So, essentially you went back and said for piperacillin the failure rate on the clinical efficacy outcome is 40 percent. So, what is the failure rate in the absence of those agents? That is, in essence, what we have to know.

As you noted, there isn't any literature for what you would get in the absence of giving piperacillin or imipenem. So, you went to mortality and you used a contrast of appropriate versus inappropriate therapy, and I will get

into that discussion later because the FDA will talk about this as well. There are significant biases when you do that in terms of overestimating what the actual effect of effective therapy would be on mortality.

But putting that aside, you, in essence, estimated there to be a 2.2-fold higher mortality rate. Then you made the incredibly strong assumption that if effective therapy decreases the mortality rate by 2.2, then it would decrease the clinical failure rate by a factorB-that the clinical failure rate would be a factor of 2.2 higher, saying, therefore, if it is 40 percent with imipenem or piperacillin it would be 85 percent. In fact, that formula doesn't work when the baseline rate is above 40 percent. So, I won't even ask you to defend that incredibly strong assumption. It is almost assuredly not true.

But then you go further and ignore the fact that historical data give you an exaggerated estimate of that 2.2-fold increase. You also ignore the fact that in the historical data people weren't getting amikacin, MRSA therapies, etc., etc. So, in essence, what we needed to know was what would be the effect of the active comparator in the context of the totality of the supportive regimens

that people were getting versus what you are estimating it to be, which was in the absence of those supportive agents.

In fact, on page 77 in your briefing document you say the results in the 09 trial showed much higher resistance rates to piperacillin than had been anticipated. In fact, on page 78 it looks like it is 31 of 110. So, there is a very high level of resistance. But you go on to say, defending the control regimen, but the adjunctive amikacin therapy was given and most are susceptible to amikacin so that patients did receive at least one appropriate antibacterial agent.

So, the logic to this is people are getting supportive care that you are saying is effective even when there is resistance to the active comparator. Yet, you are claiming that the active comparator is providing this 2.2-fold effect on the relative risk of mortality, which is completely illogical. All these issues have been ignored. It is entirely possible that the active comparator has relatively little effect on mortality, certainly much less than you are claiming it has from the historical data.

So, putting all this together, there is no justification, certainly there isn't justification you have

provided to the argument that the margin of 20 percent could be defended.

Let me just go with that for a minute. If you assumed the 20 percent margin were valid, essentially what you would be saying is a failure rate, if it is 40 percent on the active comparator, it could be as high as 60 percent before it mattered. If we use your exact relationship to mortality that would essentially be saying you could have an absolute increase of 15 percent in mortality before it mattered, which also isn't justifiable. How do you address these issues?

DR. FRIEDLAND: Those were a lot of issues. I am only going to make one comment, two comments. In the clinically evaluable population, which is the kind of population described in the previous clinical trials, resistant pathogens are excluded. So, in the clinically evaluable, those are only against susceptible pathogens.

DR. FLEMING: But in the MITT they are not excluded. It could be one of the reasons you get a little bit of--

DR. FRIEDLAND: Correct. I think it is important to consider in nosocomial pneumonia that there is not going

to be any one drug that is effective for all the pathogens all the time. What clinicians need are a variety of drugs that may be better in certain circumstances and may be better in other circumstances, and particularly drugs that may cover pathogens that they cannot treat with any other agents that may be clinically reasonable to allow a slightly larger risk of it being overall ineffective but actually adds a benefit for some more resistant pathogens.

DR. FLEMING: Then on average you will see that overall net effect. In essence, what we have here is a justification, your intended justification of what the effect of the active comparator is but, in fact, the active comparator in your trials was given in the context of substantial supportive care, amikacin, MSR therapy. In fact, people received antibiotics even prior to randomization, did they not? Did you, in fact, give access to antibiotics just prior to randomized?

DR. FRIEDLAND: They were allowed, yes.

DR. FLEMING: And I understand that, but the point is all of those supportive care interventions substantially contribute to the overall good outcome for patients, and our need here is to understand what did piperacillin add to all

of that. And, you are going back to historical data when all that supportive care wasn't there and you are getting an exaggerated estimate of what the effect of the active comparator or effective therapy would be.

So, the essence of this-Bthe reason this is critically important is when you look similar, are you similar effective or similar ineffective? And, you are claiming similar effective based on historical data that is highly likely to not be relevant to this context.

Furthermore, you are making a huge leap of faith assumption that is assuredly not true, and that is you have the exact same relative risk effect of those therapies on mortality that you have on clinical response.

DR. FRIEDLAND: I mean, these are important items and we are limited by the available data. You know, obviously, we would like to have ideal data to answer all these questions but they aren't available. I don't know, Mr. Chairman, if you want to continue just discussing this with us or is it more appropriate to discuss this during your non-inferiority margin discussion.

DR. TOWNSEND: Yes, I think we will save that for later. Thank you very much. Dr. Ohl, you have a question?

DR. OHL: Two questions actually. The first one has to do with the CPIS score. I was wondering do you have a slide with more detailed data as to what the CPIS scores were and the distributions of those scores at the time of study entry both for DORI-09 and DORI-10.

DR. FRIEDLAND: So, you would like to see the distribution of CPIS at baseline of patients enrolled in each of the trials?

DR. OHL: And, if possible, at the test of cure follow-up.

DR. FRIEDLAND: The CPIS can only be determined if patients are intubated. In DORI-09 only 20 percent of patients had VAP. So, it is only a small percentage of patients that had CPIS scores done. Slide up.

[Slide]

This is the DORI-09 data showing the distribution of scores. Again, this is the 10-point scale.

If we could put up the DORI-10 slide which has larger numbers?

[Slide]

DR. OHL: This is at study entry? Correct?

DR. FRIEDLAND: Correct, at study entry. We do

have data showing change in CPIS score in cures versus failures, which I think is quite an interesting analysis.

DR. OHL: Just to clarify then before we move on to that, for all randomized patients then the CPIS score at study entry, just to clarify, while equal, roughly equal on both arms, almost approaches half for a CPIS score less than 5 on the 10-point score. And, if you would add the microbiology data and add a point for that, you would say that that would be 6.

DR. FRIEDLAND: You get 2 points for microbiology with a positive gram stain plus a culture. Let's see if we can find the change in CPIS on treatment, and I will show you this just for DORI-10. Slide up.

[Slide]

This is the difference in the cure and failure and these are some of the objective measures I was talking to you about, and I think one can see clear distinctions between the cures and the failures in terms of objective measurements such as oral temperature, white cell count and the CPIS. This is done at the end of treatment, day 3, end of IV and test of cure.

DR. OHL: The second question that I had, and this

slide actually helps address that some, when looking at the case report form there will be several objective criteria for the investigator to fill in.

But when you get down to the final answer as cure versus not cure, how was the weight put on that? In other words, what was the investigator asked to do to determine that as to whether this was failure versus cure versus indeterminate? Was a certain point scale applied to it? How many boxes had to be checked in one category versus another? Or, was it just purely the investigator=s gestalt at the end that this patient was cured or not cured and that was the final determination as the outcome?

DR. FRIEDLAND: The measures required were specified, such as the temperature. They had to be afebrile. White count had to be less than the upper limit of normal or had to be reduced by a substantial amount. They had to document all the signs and symptoms and that none of those had worsened and that the majority of those had gotten better. They had to document that the x-ray had improved or at least had not worsened, depending on when that assessment was made.

So, the exact criteria that determined whether

they were cured or failed were specified and they had to meet all those criteria to assess the patient as a cure.

DR. OHL: Then, for DORI-09 I assume that was what was evaluated by the blinded committee.

DR. FRIEDLAND: Correct.

DR. OHL: But for DORI-10 then, what was the final score for outcome? Was it just the box that was checked on the form as cure?

DR. FRIEDLAND: It was all these parameters that I have specified, all these clinical signs and symptoms, the x-ray, the objective lab measures. Those all had to be checked and if they were all checked "yes" then the patient would be assessed as a cure.

In addition, cure could only be assessed if no additional antibiotic therapy was given. Any patients who received additional non-study antibiotic therapy for any ongoing signs and symptoms of pneumonia were counted as failures. So, we have the assurance not only with these objective measures but whether no further antibiotic therapy was given.

DR. TOWNSEND: Any more questions? Dr. Ohl?

DR. OHL: I am sorry, one additional question.

Could you elaborate why was it so difficult to get the patients within the window of the prescribed dates of the test of cure visit? I am also struck that a large number of patients fell out on that. Why was it so difficult to do that?

DR. FRIEDLAND: Many of the patients who fell out of the window was for things such as withdrawal of consent, patients being transferred to other hospitals, those kind of events that were unavoidable. I think of the number of subjects who completed intravenous therapy, there is only a very small number who did not have their test of cure assessed in that window, a small percentage, I think about 4, 5 percent. We can get the exact number for you. So, once the patients had reached the end of therapy, the vast majority did have a test of cure within the allowed window.

DR. OHL: And was there a differential in the geographic regions between the patients who fell out? Were there more, you know, Eastern European versus North American versus Western European?

DR. FRIEDLAND: Who did not fall within the time window?

DR. OHL: And within the clinical evaluable

population.

DR. FRIEDLAND: We can try to find those data. Perhaps the discontinuations by regional, I am not sure if we have that but we can look for those data and if we can find them we can show them to you.

DR. TOWNSEND: Dr. Fleming, you have a comment?

DR. FLEMING: Just related to this test of cure discussion, there are many aspects of concern about the clinical response endpoint. It is a composite of many different components, some of which are not symptoms or not direct, tangible aspects of patients, their signs, their temperatures, and white blood count, chest x-rays, sputum color, and they are very subjective. It is an open trial. You have attempted to try to get rid of some or to reduce some of that bias of an open trial and subjective judgment with your independent committee.

But, as you have noted, this is a multi-component aspect. If other antibiotics were assigned that would define failure, and those decisions were made by people who were unblinded. How do you adjust for that aspect of open bias?

DR. FRIEDLAND: We did not make any adjustment for

that type of bias of the selection of antibiotic therapy at the time of test of cure.

DR. FLEMING: And I wouldn't know how you could. That is one of the inherent weaknesses of an endpoint such as this in an open trial.

DR. TOWNSEND: Any other questions from the committee?

[No response]

Thank you very much. We will move on to presentations from the FDA.

FDA Presentations

Clinical Trials for NP and Ventilator-Associated Pneumonia (VAP): Regulatory Approach to the Non-inferiority Margin Justification

DR. SORBELLO: Good morning.

[Slide]

I am Dr. Sorbello and, along with Dr. Komo, we are going to provide a review of the Division=s approach to determination of the non-inferiority margin justification that could be used to establish the efficacy of antibacterial drugs for the treatment of nosocomial pneumonia and ventilator-associated pneumonia.

[Slide]

In terms of overview, we wanted to discuss the following issues: First, a brief discussion of background in terms of the risk for mortality in patients with nosocomial pneumonia. Second, the methodology, the approach that we use for determining a non-inferiority margin. Third, the results of our literature search in order to determine estimates of the treatment effect for placebo and active control. Dr. Komo will more specifically address issues specific to non-inferiority studies, as well as the determination of the non-inferiority margin and will also provide some additional perspectives on alternative endpoints.

[Slide]

So, first I would like to briefly discuss some historical data related to the risk for mortality for patients with nosocomial pneumonia.

[Slide]

There was a large prospective study, this was a study from France involving approximately 2,000 consecutive patients admitted to the ICU for more than 48 hours. Approximately 1,100 were mechanically ventilated and 328

developed nosocomial pneumonia. Various factors were looked at in terms of potentially being independently associated with mortality in the mechanically ventilated ICU patients.

I just wanted to point out that of the 5 factors that are listed, nosocomial pneumonia was clearly identified as an independent factor, along with others including nosocomial bacteremia, a rapidly fatal underlying disease, multi-organ dysfunction or failure and APACHE scores usually above 15 to 16.

[Slide]

More specifically, this is a data table from the same article from the Journal of the American Medical Association. This shows the comparison of the infections acquired in the ICU between survivors and non-survivors. Again, there were 328 patients in the ICU in this study who developed nosocomial pneumonia and 172 or 52 percent died. When this was analyzed as a risk factor for fatality the odds ratio was 3.84 for mortality amongst the ICU patients who developed nosocomial pneumonia in this study.

[Slide]

Now, there have been a number of other publications which have looked at other factors in the

subgroup of patients with nosocomial pneumonia who may further enhance the risk for death.

I just wanted to briefly focus upon two of them, which are here, namely, the bacterial pathogen and inappropriate initial antibiotic therapy. But, certainly, there are others which, again, have some overlap with the previous study, including age, elevated APACHE scores, progressive respiratory failure, shock and ultimately fatal underlying disease.

[Slide]

I did want to digress for a minute though just to comment a bit about how inappropriate, inadequate and delayed antibiotic therapy are defined in the literature. In general, inappropriate or inadequate antibiotic therapy for nosocomial pneumonia is based on the concept that a low respiratory pathogen has been isolated that is resistant to either one or more of the antibiotics or antibacterial components of the empiric regimen. However, I did want you to see that there are some variations in that definition depending on various source journal articles.

[Slide]

The other concept is that of delayed initiation of

appropriate therapy. This really was derived from one particular study out of the European Respiratory Journal which in particular looked at using the clinical pulmonary infection score of greater than or equal to 5 in terms of initiating therapy compared to clinical diagnosis. In cases in which there was a delay in initiating treatment based on clinical diagnosis compared to the CPIS score, that was considered delayed initiation in that particular study.

[Slide]

This is a bar chart slide just to show the comparison of mortality rates from 4 studies in patients who received what was considered appropriate initial therapy compared to inappropriate, inadequate or delayed initial therapy for nosocomial pneumonia and ventilator-associated pneumonia. In each case appropriate initial therapy was associated with a lower mortality rate. We will come back to these studies in a few minutes.

[Slide]

The other point related to bacterial pathogens is that in this particular study they looked at pathogens which were associated with an adequate antimicrobial treatment of ventilator-associated pneumonia. The most frequently

isolated pathogens in that setting included Pseudomonas aeruginosa, Staphylococcus aureus and Acinetobacter species, all of which are bacteria which have the propensity to either exhibit or develop antibacterial resistance.

[Slide]

So, at this point what I would like to do is just to briefly describe the approach that we used, the basic steps that the Division team used in trying to determine a non-inferiority, and then go through some of the data from the literature search.

In general, you can consider that we have three main components to our approach, one of which was to try to determine the primary endpoint that we felt was appropriate for this non-inferiority margin; then, to then determine the treatment effect of active control over placebo--again, those two components were based primarily upon our literature search; then, to take that information; and then determine what would be an appropriate non-inferiority margin for valid non-inferiority trials for this indication.

[Slide]

So, in terms of our literature search, let me just provide you an overview. We focused primarily upon original

journal articles, publications dated back to 1970 up to through 2008. As has been described previously by an earlier speaker, there were no placebo-controlled clinical trials that were published in the medical literature for this indication so we had to then look at other data which could indirectly give us an estimate of the placebo effect.

We used two sources of data for that, one which was alluded to previously was historical studies involving patients administered inappropriate, delayed or inadequate initial therapy, which were performed between 1988 and 2007 and had a primary endpoint of all-cause mortality. But we also supplemented that with two observational studies that reported mortality data on patients who were hospitalized with Pseudomonas aeruginosa pneumonia but were left untreated. These studies were published in the early '70s but actually they were retrospective studies involving data from the late 1960s.

In terms of our active control agents and attempts to determine effect for the active control, we utilized data from published comparative clinical trials in which the primary endpoint was clinical response although there was some all-cause mortality data reported.