BRIEFING DOCUMENT

Doripenem (NDA 22,171)
for the Indication of Nosocomial Pneumonia,
Including Ventilator-associated Pneumonia

Anti-Infective Drug Advisory Committee Meeting
July 16, 2008

US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products

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INTRODUCTION

Nosocomial pneumonia (NP or HAP) refers to pneumonia that occurs 48 hours or more after hospital admission and that was not incubating at the time of admission.[1] Ventilator-associated pneumonia (VAP) refers to pneumonia that arises more than 48-72 hours following endotracheal intubation. Nosocomial pneumonia is the third most common cause of healthcare-associated infections following urinary tract infections and surgical site infections in frequency, but it is also the leading cause of death among all healthcare-associated infections accounting for 35,967 deaths in hospitals in the United States in 2002.[2]

The pathogenesis of NP is multi-factorial, including the following factors that can enhance infection risk: (1) impairment in host defenses, (2) use of nasogastric and endotracheal intubation, which bypass normal airways protective mechanisms (mucociliary ladder and cough reflex) and provide a direct pathway for bacteria to access the lower respiratory airways, (3) bacterial formation of biofilms on endotracheal tubes, (4) aspiration risks from nasogastric feedings and supine positioning in bed, (5) sinusitis as a complication of nasotracheal and nasogastric intubation, and (6) inappropriate use or overuse of broad-spectrum antimicrobial agents in the hospital, which can enhance colonization of the oropharynx with antimicrobial-resistant Gram-positive and Gram-negative bacteria that are respiratory pathogens.[3]

The causative bacteria for NP differ depending on the hospital day of onset. Early-onset NP occurs within the first 4 days of hospitalization, and late-onset NP occurs after 5 days or more of hospitalization.[4] The distinction between the two types is crucial since early-onset NP is usually caused by bacteria that are considered susceptible to many antimicrobial agents, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and methicillin-susceptible *Staphylococcus aureus*. However, late onset NP and VAP are more typically associated with multi-drug resistant pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter sp.*, *S. maltophilia,* and methicillin-resistant *S. aureus*.[5] Based on their broad Gram-negative spectrum and antipseudomonal activity, carbapenem antibiotics (imipenem and meropenem) are frequently employed in treating NP.

The diagnosis of HAP and VAP is suspected in patients with a new or progressive lung infiltrate in associations with leukocytosis, fever, purulent sputum production, and poor arterial oxygenation. However, the diagnosis can be particularly difficult using clinical and radiographic criteria only, as aspiration, pulmonary edema, hypersensitivity pneumonitis, acute respiratory distress syndrome, thromboembolic disease, alveolar hemorrhage, and atelectasis can present diagnostic dilemmas in affected patients.[6,7] Bronchoscopic sampling using quantitative culture by bronchoalveolar lavage (BAL) or protected specimen brush are frequently employed modalities in patients with NP and VAP. Simultaneous recovery of the same bacterium from respiratory specimens and from blood, lung biopsy tissue, or pleural fluid can also provide confirmatory evidence for the microbiologic etiology for NP.

The empiric treatment of NP frequently involves the early use of broad-spectrum antibiotics (usually antimicrobial combinations) followed by de-escalation to a more narrow spectrum regimen based on susceptibility testing of the identified respiratory tract pathogen(s). This approach attempts to optimize antibacterial coverage in the initial stages of management in order to reduce morbidity, mortality, and length of hospitalization, which can be adversely affected if inappropriate or poorly effective antimicrobials are used. Guidelines for the management of HAP and VAP were published in 2005 by the American Thoracic Society.[4]

The carbapenems are a class of parenteral beta-lactam antibiotics that includes four FDA-approved agents, imipenem-cilastatin, meropenem, ertapenem, and doripenem. Only imipenem and meropenem are approved for use in treating pneumonia. Diarrhea (including *Clostridium difficile*-related diarrhea and colitis), nausea, headache, rash, and transient elevations of liver enzymes are adverse reactions reported in various clinical studies involving each of those drugs.[8] Imipenem-cilastatin has a propensity to induce seizures (especially with high doses and in renal impairment) requiring careful monitoring of patients at risk for neurotoxicity. Phlebitis and infusion-site reactions have been reported more frequently with ertapenem.[9] Interactions between carbapenems (meropenem and ertapenem) and valproic acid (VPA) resulting in sub-therapeutic valproic acid serum levels and enhanced risk for seizure recurrence have also been described in the medical literature.[10,11]

BACKGROUND

Johnson & Johnson Pharmaceutical Research & Development (J&J PRD) submitted NDA 22,171 for doripenem for the indication of nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), on June 5, 2007. The NDA included two comparative Phase 3 clinical trials conducted by the Sponsor: DORI-09 was a multi-center, randomized, comparison study of the safety and efficacy of doripenem and piperacillin/tazobactam in non-ventilated subjects with NP and subjects with early-onset VAP (<5 days of mechanical ventilation). DORI-10 was a multi-center, randomized, comparison study of the safety and efficacy of doripenem and imipenem in subjects with VAP (early-onset and late-onset [≥5 days of mechanical ventilation]).

Four drugs have been FDA-approved for the indication of NP: ciprofloxacin, levofloxacin, linezolid, and piperacillin/tazobactam. There are no FDA-approved drugs indicated for NP that include the specific indication of VAP. Antibacterial drugs approved for the treatment of serious respiratory tract infections (caused by susceptible organisms) include tobramycin, gentamicin, and imipenem-cilastatin sodium.

Similar to other contemporaneous clinical trials for antibacterial drug development, the doripenem Phase 3 clinical trials were designed to demonstrate the non-inferiority of doripenem to an approved comparator. For the indication of NP, including VAP, a non-inferiority (NI) margin of 20% was proposed by the Sponsor. It is noteworthy, however, that there have been a number of public discussions in recent years regarding the appropriateness of using active-controlled clinical trials to demonstrate non-inferiority as the basis for FDA approval of antibacterial drug products. These discussions have focused primarily on outpatient upper respiratory tract infections and community-acquired pneumonia. FDA has recently issued a draft guidance on the use of non-inferiority studies to support the approval of antimicrobial drugs. (Appendix A: Guidance for Industry, Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval).

CLINICAL DEVELOPMENT

Doripenem is an injectable, synthetic, broad-spectrum carbapenem in the beta-lactam (β-lactam) class of antibacterial agents. It binds to penicillin-binding proteins and inhibits cell wall synthesis in both gram-positive and gram-negative bacteria. This mode of action results in bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria commonly encountered in complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). The drug's *in vitro* spectrum includes *E. coli*, other Enterobacteriaceae, and *B. fragilis*. Additional *in vitro* activity includes methicillin-susceptible staphylococci, streptococci, ampicillin-susceptible *Enterococcus faecalis*, *Pseudomonas aeruginosa*, ceftazidime-susceptible *Acinetobacter* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Prevotella* spp., *Clostridium* spp., and other gram-positive anaerobes. The product was launched initially in Japan on September 16, 2005 under the trade name Finibax® for the treatment of moderate to severe bacterial infections.

J&J PRD submitted NDA 22,106 to the Agency for doripenem for the indications of cUTI and cIAI in adults on 12/12/2006; the NDA was approved subsequently for both indications on 10/12/2007. No doripenem pediatric clinical trials had been conducted for those indications. The Sponsor completed various phase 1 and 2 studies and a definitive Phase 1 QT/QTc study in support of the four phase 3 clinical trials related to the use of doripenem in the treatment of adult patients with cUTI and cIAI. The cUTI efficacy and safety database consisted of one adequate and well-controlled Phase 3 clinical trial (DORI-05) comparing doripenem to levofloxacin, one single arm, non-comparative Phase 3 clinical trial (DORI-06) of doripenem in the treatment of cUTI, and one Phase 2 dose-ranging study of doripenem in hospitalized subjects with cUTI (DORI-03). The cIAI efficacy and safety database consisted of two adequate and well-controlled clinical trials comparing doripenem to meropenem, DORI-07 and DORI-08. There were a total of 1,276 doripenem-treated and 841 comparator-treated (372 levofloxacin and 469 meropenem) patients in the pooled phase 3 doripenem cUTI and cIAI trials in the intent-to-treat (ITT) population. In the cUTI studies, there were 376 doripenem-treated and 372 levofloxacin-treated subjects in DORI-5 and 423 doripenem-treated in DORI-06. There were a total of 477 doripenem-treated subjects and 469 meropenem-treated subjects in the combined cIAI studies**.** Based on the results of the Phase 3 clinical trials, doripenem 500 mg IV every 8 hours (60 minute infusion) was demonstrated to be non-inferior to levofloxacin in the treatment of cUTI and doripenem (same dosing regimen) was demonstrated to be non-inferior to meropenem in the treatment of cIAI. The most common adverse drug reactions reported in doripenem-treated patients were nausea, diarrhea, headache, rash, and phlebitis. Indication-specific differences in the incidence of certain treatment-emergent adverse events (TEAEs) were observed in the Phase 3 clinical trials, involving asymptomatic bacteriuria, UTI, and anemia. In addition, there was a relative imbalance in the frequency of renal failure/renal impairment-related TEAEs between the doripenem- and comparator-treated groups in the Phase 3 cUTI and cIAI studies.

On June 5, 2007, J&J PRD submitted NDA 22,171 for doripenem for the indication of NP (including VAP) in adults. The NDA included two Phase 3 studies conducted by the Sponsor: DORI-09 was a multi-center, randomized, comparative study of the safety and efficacy of doripenem and piperacillin/tazobactam in non-ventilated subjects with NP and subjects with early-onset VAP. DORI-10 was a multi-center, randomized, comparative study of the safety and efficacy of doripenem and imipenem in subjects with early-onset and late-onset VAP. In DORI-09, doripenem was dosed at 500 mg 1-hour infusion q8h whereas a 4-hour infusion of the same dosage was used in DORI-10. The prolonged infusion was employed in DORI-10 to enhance antibacterial coverage for the less susceptible pathogens frequently encountered in VAP. No pediatric clinical trials of doripenem for this indication had been conducted.

The Sponsor's proposed dosing regimens for the treatment of NP, including VAP, are provided below:

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Nosocomial pneumonia, including ventilator-associated pneumonia	500 mg	q8h	1 or 4*	7-14 days**

*One hour infusions are recommended for treatment of patients with nosocomial pneumonia. For patients who are at risk for infections with less susceptible pathogens, four-hour infusions are recommended.

** Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

Primary efficacy endpoint:

The primary efficacy endpoint was the clinical cure rate at the TOC visit. The primary efficacy analyses were performed in the CE and cMITT (using the cMITT_1 analysis) at TOC as co-primary efficacy analysis populations.

Analysis populations:

Intent-to-Treat (ITT): This analysis population included all randomized subjects who received any amount of i.v. study drug therapy.

Clinical Modified Intent-to-Treat (cMITT): The cMITT analyses account for all subjects with the minimum diagnosis of pneumonia randomized to study drug therapy, including those subjects without a valid clinical outcome assessment at the TOC visit. This analysis population was a subset of the ITT analysis analysis population, consisting of all subjects who met the minimal definition of pneumonia (i.e., the presence of a new or progressive infiltrate on chest radiograph), and at least 1 of the following: 1) Fever, defined as an oral temperature >38°C (100.4°F) or a rectal/core temperature >39°C (102.2°F) or hypothermia, defined as a rectal/core body temperature of <35°C (95.2°F), or 2) Elevated total peripheral WBC count ($\geq$10,000/mm^3) or >15% immature forms (bands) regardless of total peripheral WBC count; or leukopenia with total peripheral WBC <4,500/mm^3 (caused by the infection).

Two different methods were used to impute clinical response in subjects who do not have any determinate post-treatment assessment. The 2 different analyses are denoted as cMITT_1 and cMITT_2. The cMITT_1 analysis set was used for a co-primary analysis and the cMITT_2 analysis was used for sensitivity analysis. In the cMITT_1 analysis, subjects whose clinical response was indeterminate or missing, including subjects who discontinued from the study due to an AE considered possibly or probably related to study drug therapy, were counted as clinical failures. In rare cases, there were subjects who had a TOC visit too early (within 5 days after the completion of study drug therapy) and had a clinical outcome of cure; these subjects were excluded from the cMITT1 analysis. In the cMITT_2 analysis, subjects who discontinued from the study due to an AE, regardless of its relationship to study drug therapy, were counted as missing.

Clinically Evaluable at TOC (CE at TOC): This analysis population was a subset of the cMITT subjects who met the disease definition of NP, including pneumonia acquired from long-term care facilities who were compliant to study drug therapy (i.e., received at least 48 hours of i.v. study drug therapy, did not miss more than one dose of i.v. study drug therapy in the first 72 hours of study drug therapy, and received between 80% to 120% of the required treatment duration of total study drug therapy), had a valid TOC visit assessment, for whom sufficient information was available to determine the subject's outcome at the TOC visit, and who had no confounding events that interfered with the assessment of that outcome. Further, it was required that if baseline LRT pathogens were isolated, at least 1 was susceptible to the i.v. study drug therapy received. Because they were unlikely to have a diagnosis of pneumonia, ventilated subjects with a culture-negative baseline tracheal aspirate (or other appropriate LRT specimen) without a recent (within 72 hours) change or addition of antibacterial therapy, were excluded from the CE analysis population.

Microbiologically Evaluable at TOC (ME at TOC): This analysis population was a subset of the CE at TOC analysis analysis population, consisting of CE subjects who had at least 1 bacterial LRT pathogen identified at baseline, which was susceptible to the i.v. study drug therapy received.

MICROBIOLOGY

From the Microbiology perspective, the primary concern regarding the data in this submission is the development of reduced susceptibility to doripenem and the consequences this may have on patient care. There is concern that *Pseudomonas aeruginosa* with decreased susceptibility to doripenem may lead to treatment failure in nosocomial pneumonia (NP) patients, particularly ventilator-associated pneumonia (VAP) patients and that this *P. aeruginosa* may be transmitted to other hospital patients. This is felt to be a **safety concern** based on the following data**:**

- Surveillance data on susceptibility of pathogens to doripenem;
- Elevated MICs among cystic fibrosis isolates *in vitro*;
- Studies on selection of resistance *in vitro*;
- Monte Carlo simulation data;
- Large increases in MICs for *P. aeruginosa* clinical isolates during therapy.

Surveillance Studies

Approximately 17,000 organisms each year for three years (2003—05) were tested through a global surveillance program. Isolates were collected from a variety of body sites. The geographic distribution of sites covered three regions: North America, Latin America and Europe with approximately 20 sites per region. The results from North America for the organisms sought for the nosocomial pneumonia (NP) indication are highlighted.

Table 1. Doripenem Susceptibility Surveillance Data from North America

Organism	MIC (mcg/mL) 2003		2004		2005	
	MIC90	Range	MIC90	Range	MIC90	Range
S. aureus (all)	ND	ND	ND	ND	8	≤0.06-->8
S. aureus (MSSA)	≤0.06	0.016-->16	0.06	0.016--0.5	≤0.06	≤0.06--2
S. aureus (MRSA)	ND	ND	ND	ND	>8	≤0.06-->8
S. pneumoniae	1	≤0.008--1	0.5	≤0.008--2	0.5	≤0.06--1
E. coli	0.03	≤0.008--0.25	0.03	≤0.008--4	≤0.06	≤0.06--0.25
Klebsiella spp.	0.06	0.016-->16	0.06	0.016-->16	≤0.06	≤0.06-->8
Enterobacter spp.	0.12	≤0.008--4	0.12	0.016--2	0.12	≤0.06-->8
E. cloacae	ND	ND	0.12	0.016--1	0.12	≤0.06-->8
P. aeruginosa	2	0.06-->16	4	0.016--16	4	≤0.06-->8
Acinetobacter spp.	2	0.06-->16	4	0.016--16	4	≤0.06-->8
H. influenzae	0.25	≤0.008--1	0.5	≤0.008--2	0.5	≤0.06--0.5

Source: Appendix 2.1, Microbiology Section, this submission.

Data from North American isolates in 2005 show *P. aeruginosa* and *A. baumannii* have MIC90s = 4 mcg/mL, three steps higher than the next highest MIC among these organisms listed and two steps higher than the established susceptible breakpoint of ≤ 2 mcg/mL for *P. aeruginosa* or ≤1 mcg/mL for *Acinetobacter baumannii* in the current doripenem package insert based on data from complicated intra-abdominal infections and complicated urinary tract infections that included pyelonephritis. Methicillin-resistant

Staphylococcus aureus (MRSA) has a MIC90 at least one step higher than *P. aeruginosa* and *A. baumannii*. Similar results are seen for surveillance data from Europe and Latin America in 2005.

Elevated Doripenem MICs among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* Isolates Resistant to Other Antimicrobials

MICs for antibiotic resistant *A. baumannii* and *P. aeruginosa* isolates as well as cystic fibrosis isolates from a number of studies are shown in Table 2.

Table 2. Doripenem Susceptibility among Multi-Drug Resistant Isolates

			Doripenem MIC (mcg/mL)		Applicant
Species	N	Range	MIC50	MIC90	Reference
Acinetobacter baumannii	33	0.03->32	0.5	16	22
(ceftazidime-susceptible)	10	0.06-1	0.12	1	28
	20	0.12-1	0.25	1	3
(ceftazidime-nonsusceptible)	10	0.25->16	1	>16	3
Pseudomonas aeruginosa	35	0.06-1	0.25	0.5	22
	150	0.03-16	0.25	1	21
	78	0.25-16	0.25	1	29
	54	0.05-0.25	0.8	12.5	24
	20	0.06-4	0.12	1	23
(CF-isolates)	82	0.25-256	0.25	2	29
(CF-isolates) mucoid	200	0.25-512	8	32	33
(CF-isolates) non-mucoid	200	0.25-512	8	64	33
(beta-lactamase-positive)	15	0.5-8	2	4	30
(ceftazidime-resistant)	39	0.06-16	2	8	25
(carbapenem-sensitive)	83	0.06-8	0.25	2	25
(carbapenem-resistant)	32	16-Feb	8	8	25
	34	0.5->32	8	>32	2
(ciprofloxacin-resistant)	16	0.12-8	0.5	8	25
(gentamicin-resistant)	37	0.06-16	0.5	8	25
(metallo-beta-lactamases)	15	4->32	>32	>32	2
	15	4->64	64	64	30

Source: Appendices 1.2 and 1.3, Clinical Microbiology Studies, this submission.

Among *A. baumannii* isolates non-susceptible to ceftazidime, the doripenem MIC90 was >16 mcg/mL while for isolates susceptible to ceftazidime the doripenem MIC90s = 1 mcg/mL. These data should be viewed with some caution as the "MIC90" for isolates non-susceptible to ceftazidime numbered only 10.

Doripenem MIC90s for cystic fibrosis (CF) isolates were much higher than doripenem MICs for non-CF isolates (MIC90s ranging from 0.5 to 12.5 mcg/mL). Mucoid CF isolates demonstrated a doripenem MIC90 of 32 mcg/mL, while non-mucoid CF isolates demonstrated a MIC90 of 64 mcg/mL. This represents a 5 step and 6 step increase in MIC compared to the MIC90 for three of the studies (MIC90 = 1 mcg/mL). Metallo-beta-lactamase containing isolates displayed a doripenem MIC90 of 64 mcg/mL.

Resistance Development Studies

One serial passage study examined the increase in doripenem MICs using a set of six *P. aeruginosa* isolates (baseline doripenem MIC values ranged from 2-8 mcg/mL) plated on doripenem alone or doripenem combined with gentamicin. In this study, selection with doripenem led to MIC increases that were >8-fold in three isolates, 2-fold in one isolate and were unchanged in two isolates. Selection with doripenem and gentamicin resulted in one isolate with a 4-fold doripenem MIC increase, two isolates with a 2-fold increase and three isolates with unchanged MIC values.

A serial passage experiment in the presence of doripenem, imipenem and meropenem was performed with single *S. aureus*, *E. coli* and *P. aeruginosa* isolates to determine the maximum MIC values achievable for each compound

Table 3. *P. aeruginosa* ATCC 25619 Multiple Passage Study

Passage #	DOR MIC (μg/mL)			MEM MIC (μg/mL)			IPM MIC (μg/mL)		
	DOR	MEM	IPM	DOR	MEM	IPM	DOR	MEM	IPM
1	0.06	0.03	0.5	0.06	0.03	0.5	0.06	0.03	0.5
4	0.25	0.25	0.5	1	0.25	16	0.12	0.12	1
8	4	2	8	4	4	16	2	2	16
12	4	4	16	4	8	16	2	2	16
14	4	4	16	4	8	16	4	4	16

DOR= doripenem, MEM=meropenem, IPM=imipenem
Source: Table 19, this submission.

The MIC values increased for all isolates upon incubation with increasing concentrations of each agent. In *P. aeruginosa*, the doripenem MIC increased from 0.06 mcg/mL to 4 mcg/mL, an increase of six dilution steps. Mechanisms of resistance were not evaluated in this study.

Monte Carlo Simulations

Species-specific target attainment values were calculated to determine the probability of attaining a specific target at a selected dose of doripenem against a specific pathogen in a defined disease. Studies by the Applicant indicate that the time above the MIC (T > MIC) is the pharmacokinetic parameter that correlates with *in vivo* efficacy. In the overall assessment of each indication, the target attainment for each pathogen species was weighted by the pathogen's natural frequency of occurrence in each clinical syndrome. A summary table for species of interest at the doses of 500 mg q8h for a 1 and 4h infusion for NP pathogens is presented in Table 4.

Table 4. Specific Target Attainment for NP Pathogens Based on Doripenem Dosing Regimens.

	500 mg, q8h, 1h infusion			500 mg, q8h, 4 h infusion		
Species specific target attainment	25% T>MIC	30% T>MIC	35% T>MIC	25% T>MIC	30% T>MIC	35% T>MIC
Enterobacteriaceae	99.88	99.75	99.61	99.97	99.97	99.96
Non-Enterobacteriaceae	90.46	87.59	84.79	93.18	92.8	92.28
Pseudomonas aeruginosa	89.48	86.31	83.25	92.48	92.06	91.48
Acinetobacter spp.	77.67	76.85	75.43	77.76	77.69	77.61
Burkholderia spp.	23.36	13.76	8.36	29.94	24.78	19.54
Stenotrophomonas maltophilia	7.68	5.07	3.42	9.66	8.93	8
Other gram-negative	100	99.8	98.84	100	100	100
Haemophilus spp.	100	99.96	99.87	100	100	100
Enterococcus spp.	79.39	65.79	53.78	93.1	92.02	90.17
Enterococcus faecalis	79.39	65.79	53.78	93.1	92.02	90.17
Staphylococcus spp.	86.07	85.39	84.84	86.61	86.44	86.23
Staphylococcus aureus Oxa-S	100	100	99.99	100	100	100
Streptococcus *pneumoniae*	99.98	99.89	99.63	99.99	99.99	99.99
Streptococcus spp. (other than *S. pneumoniae*)	97.75	96.41	95.45	99.58	99.46	99.21
Other gram-positive	100	99.94	99.62	100	100	100

Source: Table 61, this submission.

These data demonstrate that target attainment of 25-35% for the pathogens found in the clinical trials for NP, e.g., *Enterobacteriaceae*, non-*Enterobacteriaceae*, *Haemophilus* spp. *Staphylococcus* spp., *S. pneumoniae*, and *Streptococcus* spp. other than *S. pneumoniae*, was in the range customarily considered of relevance for *in vivo* efficacy (>90%). Target attainment for *Enterobacteriaceae, S. pneumoniae, Haemophilus* spp. and MSSA was 90% or greater at the 35% T >MIC; however, target attainment for *P. aeruginosa* and *Acinetobacter* spp. for 35% T > MIC was 83.25% and 75.43%, respectively, when doripenem was dosed at 500mg q8h for a one hour infusion; these values are below 90% attainment, a measure considered relevant for *in vivo efficacy*. Target attainments for *P. aeruginosa* and *Acinetobacter* spp. for 35% T > MIC was 91.48% and 77.61%, respectively, when doripenem was dosed at 500mg q8h for a four hour infusion. These data suggest that a four hour infusion may be more appropriate for the treatment of infections due to *P. aeruginosa*. In the case of *Acinetobacter* spp. no change is seen between the one and four hour infusions.

Analysis of Doripenem MIC Increases During Therapy

Pairs of clinical isolates that exhibited ≥ 2 step increases in doripenem MICs during doripenem treatment in the NP trials were analyzed to determine if their MICs now made them non-susceptible to doripenem in relation to the current interpretive criteria and what the clinical outcome was for these isolates. Table 5 presents doripenem and meropenem MIC increases as well as clinical outcomes among patients in both cohorts and both clinical trials.

Table 5. Doripenem MIC Increases among All Isolates from DORI-09 and DORI-10

Trial #	Cohort	Patient ID	Organism	DOR MICs Initial	DOR MICs Final	DOR Step Increase	MER Step Increase	Clinical Outcome
DORI-10	DOR	12302047	*P. aeruginosa*	0.12	4	5	5	
DORI-10	DOR	12302566	*P. aeruginosa*	4	32	3	1	
DORI-10	DOR	13402058	*P. aeruginosa*	0.12	4	5	5	
DORI-10	DOR	14401501	*P. aeruginosa*	0.5	8	4	5	
DORI-10	DOR	14402547	*P. aeruginosa*	0.12	1	3	5	
DORI-10	DOR	20506501	*P. aeruginosa*	0.12	4	5	5	
DORI-10	DOR	20506559	*P. aeruginosa*	0.25	2	3	4	
DORI-10	DOR	60203515	*P. aeruginosa*	0.5	8	4	4	
DORI-10	DOR	75306011	*P. aeruginosa*	1	4	2	2	
DORI-10	DOR	50603502	*K. pneumoniae*	0.03	0.12	2	0	
DORI-10	DOR	14402572	*E. aerogenes*	0.03	0.25	3	2	
DORI-10	IMP	1506524	*P. aeruginosa*	0.25	4	4	4	**FAILURE**
DORI-10	IMP	3106030	*P. aeruginosa*	0.06	1	4	5	
DORI-10	IMP	10902038	*P. aeruginosa*	1	8	3	2	
DORI-10	IMP	11102537	*P. aeruginosa*	0.12	4	5	5	**FAILURE**
DORI-10	IMP	20106020	*P. aeruginosa*	1	8	3	3	**FAILURE**
DORI-10	IMP	21006548	*P. aeruginosa*	0.25	2	3	3	
DORI-10	IMP	50203023	*P. aeruginosa*	0.25	2	3	4	
DORI-10	IMP	50204511	*P. aeruginosa*	0.25	4	4	4	
DORI-10	IMP	70406529	*P. aeruginosa*	0.5	4	3	4	
DORI-10	IMP	75406550	*P. aeruginosa*	0.25	2	3	3	
DORI-10	IMP	10701005	*E. aerogenes*	0.06	0.5	3	2	
DORI-09	DOR	94101007	*S. aureus*	1	16	4	NA	**FAILURE**
DORI-09	DOR	31004017	*P. aeruginosa*	0.25	8	5	NA	**FAILURE**
DORI-09	Pip-tazo	93002031	*S. aureus*	8	32	2	NA	
DORI-09	Pip-tazo	40103009	*K. pneumoniae*	0.25	1	2	NA	
DORI-09	Pip-tazo	20406505	*E. faecalis*	4	16	2	NA	

Eleven patients from the DORI-10 study treated with doripenem had pathogens exhibiting two or more step increases in their doripenem MIC after treatment with doripenem. Two of the patients had *P. aeruginosa* that had a baseline doripenem MIC ≥ 1 mcg/mL. Of these eleven patients, nine were infected with *Pseudomonas aeruginosa*. Interestingly, none of the eleven patients were clinical failures.

Eleven patients from the DORI-10 study and treated with imipenem were infected with pathogens exhibiting two or more step increases in doripenem MIC. Two of the patients had pathogens that had a baseline doripenem MIC ≥ 1 mcg/mL. Of these eleven patients, ten were infected with *Pseudomonas aeruginosa*. However, three of the eleven patients were clinical failures.

Only two patients from the DORI-09 study treated with doripenem were infected with pathogens that exhibited a two or more step increase in their doripenem MIC after treatment with doripenem. The *S. aureus* had a baseline doripenem MIC of 1 mcg/mL and the *P. aeruginosa* had a doripenem baseline MIC of 0.25 mcg/mL. Both patients were clinical failures.

Only three patients from the DORI-09 study and treated with piperacillin-tazobactam were infected with pathogens exhibiting two or more step increases in doripenem MIC. Two of the patients had pathogens that had a baseline doripenem MIC ≥ 1 mcg/mL. Of these three patients, none were infected with *Pseudomonas aeruginosa*. None of the patients were clinical failures.

Analysis of Clinical Failures

The characteristics of pathogens from patients who were clinical failures in DORI-09 and DORI-10 were analyzed. These data are summarized in Table 6. Individual data are found in the appendix.

Table 6. Summary Table of Characteristics of Clinical Failure Patients

	Doripenem			Comparator		
	DORI-09	DORI-10	Combined	DORI-09	DORI-10	Combined
polymicrobial infections	2/13	5/22	8/35	4/20	9/32	13/52
baseline doripenem MIC > 1 μg/mL	6/13	5/22	11/35	8/20	5/32	12/52
2 or more step increase in doripenem MIC	2/13	3/22	6/35	2/20	5/32	9/52
MRSA infection	5/13	3/22	10/35	3/20	4/32	7/52
P. aeruginosa infection	3/13	5/22	8/35	5/20	11/32	17/52

Comparator in DORI-09 was piperacillin-tazobactam; comparator in DORI-10 was imipenem.

Thirteen patients infected with fifteen pathogens were clinical failures in the doripenem cohort of the DORI-09 study. Three patients were infected with *P. aeruginosa*. Two of these patients had polymicrobial infections, one infected with *E. coli* and *A. baumannii* and the other patient with *E. aerogenes* and *S. aureus*. Six of the fifteen pathogens had a baseline doripenem MIC ≥ 1 mcg/mL. Two pathogens (one *S. aureus* and one *P. aeruginosa*) exhibited a two step or greater increase in doripenem MIC between baseline and TOC. However, ten of these fifteen pathogens did not have MIC values at TOC. All five *S. aureus* isolates were MRSA.

Twenty-two patients infected with 28 pathogens were clinical failures in the doripenem cohort of the DORI-10 study. Five patients were infected with *P. aeruginosa*. Five of these patients had polymicrobial infections, one infected with *M. morganii* and *K. pneumoniae,* another patient with *S. aureus* and *K. pneumoniae,* another patient infected with *E. cloacae* and *E. coli*, another patient with *S. aureus* and *H. influenzae*, *H. influenzae* and *S. pneumoniae*, and another patient with *E. cloacae* and *S. aureus*. Five of the 27 pathogens (three *P. aeruginosa* and two *S. aureus*) had a baseline doripenem MIC ≥ 1 mcg/mL. Three pathogens exhibited a two step or greater increase in doripenem MIC between baseline and TOC. However, 10 of these 28 pathogens did not have MIC values at TOC. Three of eight *S. aureus* isolates were MRSA.

Twenty patients infected with 24 pathogens were clinical failures in the piperacillin-tazobactam cohort of the DORI-09 study. Five patients were infected with *P. aeruginosa*. Four of these patients had polymicrobial infections, two infected with *P. aeruginosa* and *K. pneumoniae,* another patient with *E. cloacae* and *K. pneumoniae* and another patient with *M. morganii* and *K. pneumoniae*. Eight of the 24 pathogens had a

baseline doripenem MIC ≥ 1 mcg/mL. Two pathogens (both *P. aeruginosa*) exhibited a two step or greater increase in doripenem MIC between baseline and TOC. However, 18 of these 24 pathogens did not have MIC values at TOC. All three *S. aureus* isolates were MRSA.

Thirty-two patients infected with 45 pathogens were clinical failures in the imipenem cohort of the DORI-10 study. Eleven patients were infected with *P. aeruginosa*. Nine of these patients had polymicrobial infections, eight of these patients were infected with either *S. aureus* or *P. aeruginosa*. Five of the 44 pathogens had a baseline doripenem MIC ≥ 1 mcg/mL. Five pathogens (four *P. aeruginosa* and one *H. influenzae*) exhibited a two step or greater increase in doripenem MIC between baseline and TOC. However, 16 of these 28 pathogens did not have MIC values at TOC. Four of ten *S. aureus* isolates were MRSA.

Of the DORI-09 patients treated with doripenem and with piperacillin-tazobactam, and of the DORI-10, patients treated with doripenem and imipenem, nine of 13 patients, 12 of 20 patients, 16 of 22 patients and 16 of 32 patients, respectively had either:

- Polymicrobial infections,
- Baseline MICs of ≥ 1 μg/mL,
- MRSA infections,
- *Pseudomonas aeruginosa* or
- A two step or greater increase in doripenem MIC during therapy.

CONCLUSIONS

- Examination of the spectrum of activity of doripenem from surveillance data reveals that doripenem has the least amount of activity against methicillin-resistant *S. aureus* and non-fermentative Gram-negative bacteria, particularly *P. aeruginosa* and *A. baumannii* among bacteria surveyed.
- *In vitro* susceptibility data demonstrate that multidrug-resistant cystic fibrosis isolates displayed elevated MIC90 values of 32 μg/mL and 64 μg/mL for mucoid and non-mucoid isolates, respectively categorizing them as non-susceptible to doripenem. *P. aeruginosa* isolates with metallo-β-lactamases demonstrated MIC90 of > 64 μg/mL also categorizing them as non-susceptible to doripenem
- The results of a doripenem serial passage study with six isolates of *P. aeruginosa* showed MIC increases that were >8-fold in three isolates, 2-fold in one isolate and unchanged in two isolates. Serial passage in doripenem and gentamicin resulted in one isolate with a 4-fold doripenem MIC increase, two isolates with a 2-fold increase and three isolates with unchanged MIC values. The results of multiple passage studies on one isolate of *P. aeruginosa* demonstrate doripenem MICs increased by 6 dilution steps when passaged in *P. aeruginosa*.
- Monte Carlo simulation data indicate that the probability of target attainment is below the range considered relevant to *in vivo* efficacy (≥ 90%) in some cases. During one-hour infusions of 500 mg, q8h, *P. aeruginosa* had a target attainment at 35% T>MIC for 83.3% of the population of potential patients and *A. baumannii*

had a target attainment at 35% T>MIC for 75.4% of the population of potential patients.

- An examination of pathogens with doripenem MIC increases during therapy indicated:
  - ❖ Most of the pathogens exhibiting a ≥ 2 step increase in doripenem MIC during therapy were *P. aeruginosa*; this is particularly apparent in DORI-10 in which the majority of patients were intubated.
  - ❖ Pathogens exhibiting a ≥ 2 step increase in doripenem MIC during therapy also exhibited a ≥ 2 step increase in meropenem MIC during therapy.
  - ❖ Patients with pathogens exhibiting a ≥ 2 step increase in doripenem MIC during therapy were not necessarily clinical failures.
- An overwhelming majority of patients who were doripenem clinical failures had:
  - ❖ Polymicrobial infections,
  - ❖ Pathogens with doripenem baseline MICs of ≥ 1 μg/mL,
  - ❖ MRSA infections,
  - ❖ *Pseudomonas aeruginosa* infections or
  - ❖ Pathogens with two step or greater increase in doripenem MIC during therapy.

CLINICAL STUDIES AND DESIGNS

There were two phase 3 studies submitted for this indication. Details on the dosing and study designs are as follows:

Study DORI-09:
This was a Phase 3, multicenter, prospective, randomized (1:1), open-label study (but with in-house blinding) of doripenem 500 mg q8h i.v. 60-minute infusion versus piperacillin/tazobactam 4.5 g q6h i.v. 30 minute infusion in non-ventilated male and female subjects aged ≥ 18 years and similar subjects with early-onset ventilator associated pneumonia (VAP)(< 5 days of mechanical ventilation). Randomization was stratified by mechanical ventilation association (non-ventilator associated vs. early-onset VAP), and severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score ≤ 15 or > 15), and geographic region (North America, South America and Europe/Other). In all subjects, an adequate sputum specimen was to be collected within 24 hours of enrollment and prior to the initiation of study drug therapy. The pathogen(s) isolated in the local laboratory were shipped to a central laboratory for confirmation of identification and antimicrobial susceptibility testing. Intravenous administration of study drug was initiated on Day 1 and continued for 3 to 14 days. To allow for the hospital discharge of subjects who improved during the study, a transition from i.v. to oral antibacterial therapy was permitted. After 72 hours of i.v. study drug therapy (9 doses of doripenem or 12 doses of piperacillin/tazobactam), subjects could have been switched to oral study drug therapy (levofloxacin 750 mg daily) if they met all of the criteria, indicating sufficient clinical improvement. Although investigators had the option to switch to oral therapy, they were encouraged to continue i.v study drug for the entire duration of therapy. Adjunctive amikacin therapy was initiated with the initiation of i.v. study drug therapy for potential *Pseudomonas aeruginosa* infection, as indicated by the product label in some countries. If *P. aeruginosa* infection was confirmed, treatment with amikacin was to be continued in subjects assigned to the piperacillin/tazobactam arm (as per the product label) for approximately 5 days. In subjects assigned to doripenem, amikacin therapy was discontinued, at the discretion of the investigator, if the subject had improved clinically and the *P. aeruginosa* isolate was not resistant to meropenem. Concomitant vancomycin therapy was permitted for methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The sponsor assessed subject evaluability for primary and secondary endpoints in a blinded fashion. To compensate for the open-label design of the study, a Blinded Evaluation Committee (BEC) was convened.

Efficacy: Clinical outcome was based on the BEC's assessment. The primary efficacy endpoint was the clinical cure rate at the test-of-cure (TOC) visit. The primary efficacy analyses were performed in the primary efficacy analysis population, CE at TOC, and in the co-primary cMITT (using the cMITT_1 analysis) analysis population. Secondary efficacy endpoints included clinical cure rate at TOC (in the ME at TOC analysis population); clinical cure rate in the cMITT analysis population (using the cMITT_2 analysis); clinical cure rate at TOC in the VAP subset of the CE at TOC, and also clinical cure rate in the VAP subset of the cMITT (using the cMITT_1 analysis) analysis

population; per-subject favorable microbiological response (i.e., eradication or presumed eradication) in the ME at TOC and in the VAP subset of the ME at TOC analysis population, decreased susceptibility to study drug received (in the microbiological modified intent-to-treat [mMITT] analysis population); per-pathogen microbiological outcome rate (in the ME at TOC analysis population); clinical relapse rate and per-subject microbiological recurrence rate at LFU (in the CE at LFU, and ME at LFU analysis sets, respectively); favorable clinical outcome (i.e., clinical cure or improvement) rate at EOT(i.v.) in the CE at TOC analysis set; and the super infection (up to EOT[i.v. or oral]) and new infection rates (after EOT[iv or oral]) in the cMITT analysis population with valid baseline cultures.

Statistical Methods: The primary efficacy analysis was to establish non-inferiority of doripenem to piperacillin/tazobactam at the TOC visit in the CE at TOC analysis set. Based on sponsor's proposal, non-inferior efficacy of doripenem was concluded if the lower limit of the 2-sided 95% confidence interval (CI) for the difference in clinical cure rates (doripenem minus piperacillin/tazobactam) was ≥ –20%. The FDA's perspective on estimating the NI margin based on clinical response is discussed later in section VI. The clinical cure rate at TOC in the cMITT analysis population was a co-primary analysis. The 2-sided 95% CI was calculated using the normal approximation to the difference of 2 binomial proportions with continuity correction. The primary and co-primary endpoints were also analyzed by strata, including the association to mechanical ventilation (non-VAP vs. ≥ VAP) and severity of illness (APACHE II scores ≤ 15 or >15). Safety analyses were conducted in the ITT analysis population. Safety endpoints included the proportion of subjects in each treatment group with any treatment-emergent adverse events (TEAEs), the proportion who experienced any TEAE that resulted in discontinuation of study drug therapy, the proportion of serious adverse events (SAEs) observed during study drug therapy administration and up to 30 days post-therapy (i.v. and oral), and the proportion of subjects with laboratory abnormalities.

Study DORI-10:
This was a Phase 3, multicenter, prospective, randomized (1:1), open-label study (but with in-house blinding) of doripenem 500 mg q8h i.v. 4-hour infusion versus imipenem 500 mg q6h i.v. 30-minute infusion or 1000 mg q8h i.v. 60-minute infusion, in the treatment of male and female patients aged ≥ 18 years adults with VAP. Randomization was stratified by region (North America, South America, and Other) and within each region by duration of mechanical ventilation (early-onset VAP [defined as < 5 days] vs. late-onset VAP [defined as ≥ 5 days]) and severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score ≤ 15 or > 15). For subjects who met the criteria for VAP, a specimen of lower respiratory tract (LRT) secretions was obtained by endotracheal aspiration (or bronchoscopy, if scheduled) prior to inclusion in the study and randomization. The pathogen(s) isolated in the local laboratory were tested for susceptibility to the study drugs (meropenem was used as a surrogate for doripenem). In addition, all pathogens were shipped to a central laboratory for confirmation of identification and antimicrobial susceptibility testing. Concomitant amikacin and vancomycin therapies were permitted for *P. aeruginosa* and for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, respectively. Clinical progress was monitored

using the clinical pulmonary infection score (CPIS). Study drug therapy was administered for at least 2 days after the CPIS was decreased by at least 2 points from baseline. The TOC and LFU visits were scheduled at 7 to 14 days and 28 to 35 days after completion of i.v. study drug therapy, respectively.

Efficacy: The clinical cure rate at the TOC visit in the CE and in the cMITT analysis population (using the cMITT_1 analysis) were the co-primary efficacy analyses, respectively. Key secondary efficacy endpoints included clinical cure rate at the TOC visit (in the ME at TOC analysis population); favorable per-subject microbiological response (i.e., eradication or presumed eradication) rate at the TOC visit (in the ME at TOC analysis population); and decreased susceptibility rates for *P. aeruginosa* that were isolated from post-baseline LRT culture specimens (in the cMITT analysis population).

Statistical Methods: The primary efficacy analysis was to establish non-inferiority of doripenem to imipenem at the TOC visit in the CE at TOC analysis population. Based on the sponsor's proposal, non-inferior efficacy of doripenem was concluded if the lower limit of the 2-sided 95% confidence interval (CI) for the difference in clinical cure rates (doripenem minus imipenem) was ≥ -20%. The FDA's perspective on estimating the NI margin based on clinical response is discussed later in section.VI. The clinical cure rate in the cMITT analysis population was a co-primary analysis. Both co-primary analyses were conducted using normal approximation to the difference between 2 binomial distributions with continuity correction. If non-inferiority of doripenem with respect to the primary endpoint was established, then the key secondary efficacy endpoints were evaluated in a hierarchical manner. The primary and co-primary endpoints were also analyzed by strata, including duration of mechanical ventilation (< 5 vs. ≥5 days) and severity of illness (APACHE II scores ≤ 15 or > 15). Safety analyses were conducted in the ITT analysis population. Safety endpoints included the proportion of subjects in each treatment group with any treatment emergent AE (TEAE), the proportion who experienced any TEAE that resulted in discontinuation of study drug therapy, the proportion of serious adverse events (SAEs) observed during study drug therapy administration and up to 30 days post-therapy, and the proportion of subjects with laboratory abnormalities.

FDA APPROACH TO NON-INFERIORITY MARGIN JUSTIFICATION FOR NP, INCLUDING VAP

Regulatory Background

Contemporary clinical trials for antibacterial drug development have been designed primarily to demonstrate the non-inferiority of the study drug to an active control agent. In recent years, the use of non-inferiority studies as the basis for antibacterial drug approval has been re-evaluated. The 2007 *Guidance for Industry on Antibacterial Drug Products: Use of Non-inferiority Studies to Support Approval* [12]was published to inform industry of the need to provide adequate evidence to support a defined effect size for the control treatment so that the proposed non-inferiority (NI) margin can be justified. In instances where data is insufficient to support a non-inferiority design, other study designs (e.g., superiority designs) should be considered.

Overview:

Based on an FDA analysis of relevant data from the English-language medical literature, there is sufficient scientific evidence to support a 6% non-inferiority (NI) margin for the indication of NP (including VAP) based on all-cause mortality as the primary endpoint. The 6% NI margin preserves a fraction of the active control agent antibacterial effect over placebo and remains clinically relevant. It may be possible to extrapolate from the 6% NI margin based on all-cause mortality to a different NI margin for a clinical response endpoint, and this issue is discussed below. The Sponsor's proposed NI margin for this indication is 20% based on clinical response.

FDA Approach to Non-inferiority Margin Justification for NP and VAP:

The selection of a non-inferiority (NI) margin involves a multi-step process as follows:

1. Determination of the treatment effect on mortality of the active comparator over placebo (M1):
    a) Estimate the mortality rate for the placebo
    b) Estimate the mortality rate for the active comparator agents
2. Determination of the NI margin based on the mortality difference between (1a) and (1b) and the clinically acceptable loss of efficacy in active comparator treatment effect

Step 1a: Estimation of the placebo mortality rate

A search of the English-language medical literature confirmed that there were no published placebo-controlled clinical trials for this indication. Thus, the placebo success rate in the treatment of patients with NP and VAP could not be determined directly. Due to the lack of placebo outcome data, we pursued a similar approach to the Sponsor by focusing our analysis on published observational studies that assessed the association between inadequate, delayed, or inappropriate initial antibacterial treatment of NP and VAP and subsequent mortality. In this manner, the placebo mortality rate could be estimated indirectly noting that this approach may overestimate the actual placebo rate. Mortality outcome results from historical observational studies of patients with NP due to *P. aeruginosa* who were left untreated were also analyzed and provided supportive data.

Table 7 summarizes four observational studies identified in the medical literature during the FDA review that provided mortality data for patients with NP and VAP who were treated with appropriate and inappropriate, delayed, or inadequate initial antibacterial regimens. All of those studies were included as part of the Sponsor's analysis. However, one additional study[13] included in the Sponsor's analysis of the placebo success rate was excluded from the FDA analysis, because it was not possible to clearly delineate the number of subjects and the number of deaths in each of the treatment subgroups.

Table 7: Summary of Mortality Rates for Observational Studies of Appropriate compared to Inappropriate, Delayed, or Inadequate Initial Antibacterial Treatment* for NP and VAP

Author [Reference]	Year Published	Study Design	Crude Mortality Rates n/N (%)		Mortality Difference (%) Inappropriate – Appropriate (95% confidence interval†)
			Appropriate treatment	Inappropriate treatment	
Celis [14]	1988	Prospective case finding, case-control study; 120 consecutive episodes of NP involving 118 adults	33/108 (31%)	11/12 (92%)	61 (39, 84)
Kollef [15]	1998	Prospective cohort study of 130 mechanically vented adults with suspected VAP	17/51 (33%)	31/51 (61%)	28 (7, 48)
Luna [16]	2006	Prospective cohort study of 76 mechanically vented adults with VAP	7/24 (29%)	33/52 (64%)	35 (9, 60)
Leone [17]	2007	Prospective study of 115 patients who developed VAP in the ICU	10/100 (10%)	4/15 (27%)	17 (-10, 44)

*regardless of etiologic agent; †CI uses continuity correction

Celis and colleagues[14] used a prospective case finding, case control approach to study 120 consecutive episodes of NP involving 118 adult patients over a 17 month period in a 1,000 bed teaching hospital. The overall fatality rate for the adult patients with NP was 36.6%. Eight factors were identified as being significantly associated with increased mortality by univariate analysis: age greater than 60 years, place of hospitalization (ICU > medical ward > surgical ward), ultimately or rapidly fatal underlying condition, high-risk microorganism (*P. aeruginosa*, Enterobacteriaceae and other Gram-negative bacilli, *S. faecalis*, *S. aureus*, *Candida* sp., *Aspergillus* sp., and polymicrobial episodes of pneumonia), bilateral lung involvement on chest x-ray, shock, respiratory failure, and inappropriate antibacterial treatment. High-risk microorganisms and inappropriate antibacterial therapy were notable in that they were associated with a ≥25-fold increase in the relative odds ratio of death. Although the subset of patients administered inappropriate antibacterial therapy was only 10% (12/118) of the overall study population, the 92% (11/12) fatality rate among those patients was noteworthy considering that only three of the subjects had ultimately fatal underlying conditions.

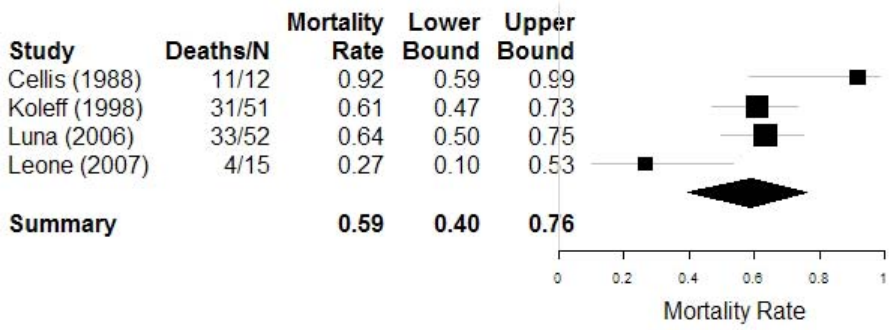
Kollef and Ward[15] conducted a prospective cohort study of 130 mechanically ventilated adults undergoing mini-bronchoalveolar lavage (BAL) for suspected VAP at a single hospital. The overall fatality rate for the adult patients with NP was 40%. Two factors identified as being significantly associated with an increased odds ratio for mortality were immunocompromise and receipt of inadequate antibacterial therapy. A mortality rate of almost 61% was reported for patients whose initial antibacterial regimen was changed compared to 33% for patients where prior antibiotic administration or their absence was unchanged and 14% for the subgroup of patients for which prior antibiotics were discontinued.

Luna and colleagues[16] conducted a prospective cohort study of 76 mechanically ventilated patients with bacteriologically confirmed VAP at six hospitals in Argentina over a 48 month period. The overall mortality rate was 52.6%. A total of 52 patients (68.4%) received either inappropriate (n=16) or delayed (n=36) therapy with a mortality rate of 63.5% for the combined group, which was statistically different compared to the 29.2% mortality rate for the patient subgroup that received adequate therapy. No statistical differences were reported for age, APACHE II at admission, reason for mechanical ventilation, pathogens, days on prior mechanical ventilation or time from VAP onset and weaning or death between the adequate therapy subgroup and the combined inappropriate/delayed therapy subgroup.

Leone and colleagues[17] conducted a prospective study involving 115 adults who developed VAP during a three year period in a university M-SICU in France. Of the 115 patients studied, 100 had received appropriate antibiotics, whereas 15 had been treated with inappropriate antibiotics. There were 10 deaths related to VAP among the 100 patients (10%) who had received appropriate treatment, while there were 4 deaths related to VAP among the 15 who had been treated with inappropriate antibiotics. Independent risk factors for receiving inappropriate antibiotics were infection with high risk bacteria (*P. aeruginosa*, *Acinetobacter baumannii*, and oxacillin-resistant *S. aureus*), age >45 years, and Simplified Acute Physiology Score II (SAPS) >40.

Figure 1 below depicts the random effects meta-analysis of the above four studies. The meta-analysis reveals that the overall mortality rate for patients given inappropriate, delayed, or inadequate initial antibiotic therapy for NP and VAP is 59% with a 95% confidence interval (CI) of (40%, 76%). Of note, there is a substantial heterogeneity between studies, and the study population sizes are small.

Figure 1: Mortality Rate subsequent to Inappropriate, Delayed, or Inadequate Initial Antibacterial Therapy for NP and VAP



In order to substantiate the estimate described above, two published observational studies from the 1970's that provided mortality data on patients with NP due to *P. aeruginosa* who were left untreated were also examined. The results are presented in the table below:

Table 8: Summary of Mortality Rates from Observational Studies of NP due to *P. aeruginosa* involving Patients left untreated

Author [Reference]	Year Published	Study Design	Crude Mortality Rates n/N (%)	
			Appropriate treatment	Left Untreated
Smith [18]	1970	Retrospective; 325 adults with (+) culture for *P. aeruginosa*; 85 had pseudomonas pneumonia	37/77 (48%)	5/8 (62%)
Stevens [19]	1974	Retrospective: 782 adults in ICU; 75 with Pseudomonas pneumonia	33/41 (80%)	20/34 (59%)

Smith and colleagues[18] conducted a retrospective analysis of the efficacy of various antibiotics and antibiotic regimens (colistin, streptomycin, tetracycline, chloramphenicol, ampicillin, penicillinase-resistant penicillin, and combination drug regimens) in the treatment of pneumonia due to *P. aeruginosa* based on a review of the medical records of all patients whose cultures contained that bacterium from January – June, 1968 at a single hospital. The overall mortality rate in the all treated group was 48% compared to 62% among patients left untreated. The lowest mortality rates were reported with streptomycin (30%) and the colistin-ampicillin (30%) combination regimen, but the total number of treated subjects in each of those subgroups was small (n=10).

In the retrospective analysis of 158 episodes of pneumonia involving 153 ICU patients in a single hospital, Stevens and colleagues[19] reported mortality rates of 80% for patients treated with recommended antibiotics (carbenicillin, gentamicin, and polymyxin B as monotherapy or in various combinations) compared to 59% for patients left untreated

with pneumonia due to *P. aeruginosa*. The authors commented that the severity of illness was comparable between survivors and those who died, and that two patients (one treated and one untreated) had bloodstream infections with the bacterium

Figure 2 depicts the random effects meta-analysis of the above two studies. The meta-analysis reveals that the overall mortality rate for patients left untreated with nosocomial pseudomonal pneumonia is 60% with a 95% confidence interval (CI) of (44%, 73%). Thus, the results from studies conducted in the 1970's involving patients with NP due to *P. aeruginosa* who were left untreated are similar to and consistent with those derived from studies conducted between 1990 and 2000 involving patients who were administered inappropriate, delayed, or inadequate initial antibacterial therapy.

Figure 2: Mortality Rates for Patients Left Untreated with NP due to *P. aeruginosa*

Step 1b: Estimation of the active control (piperacillin/tazobactam and imipenem) mortality rates

In order to derive estimates of the active control mortality rates for piperacillin/tazobactam and imipenem, a search of the English-language scientific literature yielded four comparative, active controlled clinical efficacy studies involving pipercillin/tazobactam and two studies involving imipenem. In order to maintain consistency with the approach used previously to analyze the mortality data from the four observational studies involving inadequate, delayed, or inappropriate initial therapy for NP and VAP, any active-controlled, comparative efficacy trials that did not report all cause mortality in the ITT population were excluded from the FDA analysis. Table 9 below summarizes relevant data regarding the four comparative, controlled clinical trials used by the FDA to determine the mortality rate for piperacillin/tazobactam.

Table 9: Summary of Mortality Rates from Four Clinical Studies evaluating Piperacillin/tazobactam in the treatment of NP and VAP, ITT population

Author [Reference]	Year Published	Study Design	Crude Mortality Rates n/N (%)	
			Pip/Taz	Active Comparator
Brun-Buisson [20]	1998	Open-label, multicenter, randomized study comparing Pip/Taz 4.5 gm q6h + Amikacin to Ceftazidime 1 gm q6h + Amikacin in patients with VAP	18/98 (18)	22/99 (22)
Alvarez-Lerma [21]	2001	Open-label, multicenter, randomized (2:1) study comparing Pip/Taz 4.5 gm q6h + Amikacin to Ceftazidime 2 gm q8h + amikacin in patients with NP	27/88 (31)	8/36 (22)
Joshi [22]	2006	Double-blind, randomized multicenter study of Pip/Taz 4.5 gm q6h + aminoglycoside compared to Imipenem 500 mg q6h + aminoglycoside in subjects with acute NP	23/222 (10)	17/215 (8)
Schmitt [23]	2006	Double-blind, randomized multicenter study of Pip/Taz 4.5 gm q8h + aminoglycoside compared to Imipenem 1 gm q8h + aminoglycoside for subjects with NP; Aminoglycoside added for coverage of *P. aeruginosa*	17/107 (16)	11/110 (10)

Pip/Taz = piperacillin/tazobactam

Brun-Buisson and colleagues[20] conducted an open-label, multicenter, randomized study comparing piperacillin/tazobactam 4.5 gm q6h i.v. + amikacin to ceftazidime 1 gm q6h i.v. + amikacin in patients with VAP hospitalized in 27 ICUs in France. VAP was diagnosed using either bronchoalveolar lavage, protected brush sampling via bronchoscopy, or protected telescoping catheter sampling blindly or by bronchoscopy. There were 204 patients randomized in the study including 197 in the overall evaluable population (intent-to-treat, ITT) and 127 with microbiologically confirmed VAP. *P. aeruginosa* accounted for 32% of all episodes. The 30-day post-therapy mortality rates in the ITT were 18% (18/98) in the piperacillin/tazobactam group and 22% (22/99) in the ceftazidime group.

Alvarez-Lerma and associates[21] conducted an open-label, multicenter, randomized (2:1) study comparing piperacillin/tazobactam 4.5 gm q6h i.v. + amikacin to ceftazidime 2 gm q8h i.v. + amikacin in 124 patients with NP hospitalized in nine ICUs in Spain. VAP was microbiologically diagnosed using tracheal aspiration, protected specimen brush, or bronchoalveolar lavage, which were performed blindly or directed by fiberoptic bronchoscopy. There were 88 patients in the piperacillin/tazobactam group and 36 in the ceftazidime group in the ITT population. Gram-negative bacteria were the most common

pathogens, and *P. aeruginosa* was the most frequent isolate in that group. The crude mortality rate was 31% (27/88) in the piperacillin/tazobactam group and 22% (8/36) in the ceftazidime group.

Joshi and colleagues[22] conducted a double-blind, randomized (1:1) multicenter study of piperacillin/tazobactam 4.5 gm q6h i.v. + aminoglycoside compared to imipenem 500 mg q6h i.v. + aminoglycoside in hospitalized subjects with acute NP in the United States and Canada. There were 437 patients in the ITT population (222 in the piperacillin/tazobactam group and 215 in the imipenem group). The most frequently isolated Gram-positive bacterium was *S. aureus*, and the most common Gram-negative isolates were *H. influenzae*, *P. aeruginosa*, and *K. pneumoniae*. Overall, forty patients died in the study. The mortality rates were 10% (23/222) in the piperacillin/tazobactam group and 8% (17/215) in the imipenem group.

Schmitt and colleagues[23] conducted a double-blind, randomized multicenter study of piperacillin/tazobactam 4.5 gm q8h i.v. compared to imipenem 1 gm q8h i.v. in hospitalized subjects with NP in 33 centers in Germany, Hungary, and the Czech Republic. An aminoglycoside was added if *P. aeruginosa* was present. Lower respiratory tract samples were obtained by endotracheal aspiration, bronchoalveolar lavage, protected brush specimen, or sputum specimen. There were 217 patients in the ITT, including 107 in the piperacillin/tazobactam group and 110 in the imipenem group. Enterobacteriaceae were the most frequently isolated organisms. There were 28 deaths in the study. The mortality rates were 10% (11/110) in the imipenem group and 16% (17/107) in the piperacillin/tazobactam group.

Figure 3 below depicts the random effects meta-analysis of the above four studies. The meta-analysis reveals that the overall mortality rate for patients treated with piperacillin/tazobactam for NP and VAP is 18% with a 95% confidence interval (CI) of (11%, 28%).

Figure 3: Mortality Data from Clinical Trials evaluating Piperacillin/Tazobactam in the Treatment of NP and VAP

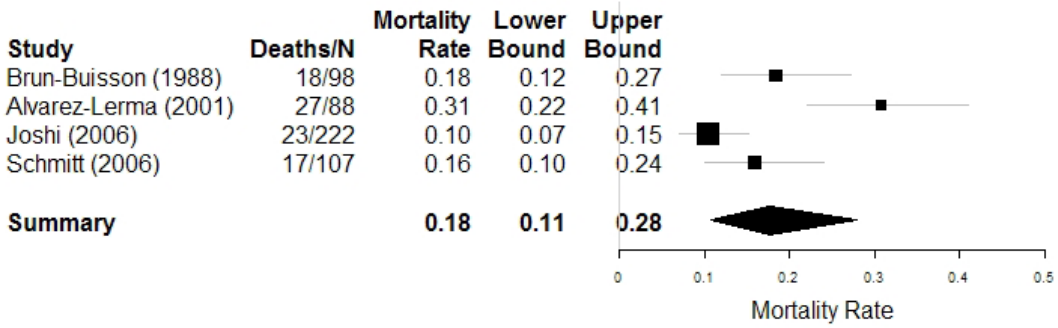


Table 10 below summarizes relevant data regarding the two comparative, controlled clinical trials used by the FDA to determine the mortality rate for imipenem.

Table 10: Summary of Mortality Rates from Four Clinical Studies evaluating Imipenem in the treatment of NP and VAP, ITT population

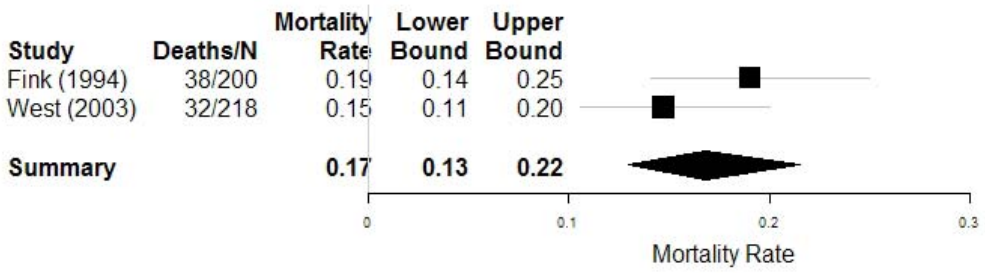
Author [Reference]	Year Published	Study Design	Crude Mortality Rates n/N (%)	
			Imipenem	Active Comparator
Fink [24]	1994	Double-blind, randomized, multicenter study of imipenem 1 gm q8h compared to Cipro 400 mg q8h in severe NP	38/200 (19)	43/202 (21)
West [25]	2003	Open label, randomized multicenter study of imipenem 500 mg q6-8h compared to Levofloxacin 750 mg qDay followed by oral Cipro 750 mg q12h; For P. aeruginosa, add amikacin for Imipenem arm or Ceftazidime for Levofloxacin arm	32/218 (15)	38/220 (17)

Fink and associates[24] conducted a double-blind, randomized, multicenter study of imipenem 1 gm q8h i.v. compared to ciprofloxacin 400 mg q8h i.v. in patients with severe NP hospitalized in 20 medical centers in the United States. The microbiological assessment included bacteria pathogens isolated primarily from blood and sputum specimens. There were 402 patients in the ITT, including 202 in the ciprofloxacin group and 200 in the imipenem group. *P. aeruginosa* was the most common pathogen among patients in the ITT population. There were 81 deaths in the ITT. The mortality rates were 21% (43/202) in the ciprofloxacin group and 19% (38/200) in the imipenem group.

West and colleagues[25] conducted an open label, randomized multicenter study of imipenem 500 mg q6-8h i.v. followed by oral ciprofloxacin 750 mg q12h compared to levofloxacin 750 mg QD i.v. followed by oral levofloxacin 750 mg QD in 67 centers in the United States and Canada; For coverage of infection due to *P. aeruginosa*, amikacin was added for patients in the imipenem arm and ceftazidime was added for patients in the levofloxacin arm. Specimens used for microbiological assessment included expectorated sputum samples, bronchoalveolar lavage, protected specimen brush, endotracheal aspiration, or lung biopsy. *S. aureus* and *P. aeruginosa* were the most frequent pathogens. There were 438 subjects in the ITT population, including 220 in the levofloxacin group and 218 in the imipenem group. The mortality rate was 17% (38/220) in the levofloxacin group compared to 15% (32/218) in the imipenem group.

Figure 4 depicts the random effects meta-analysis of the above two studies. The meta-analysis reveals that the overall mortality rate for piperacillin/tazobactam in NP and VAP is 17% with a 95% confidence interval (CI) of (13%, 22%).

Figure 4: Mortality Rates from Clinical Trials Evaluating Imipenem in the Treatment of NP and VAP



Step 2: Determination of the NI margin based on the mortality difference between (1a) and (1b) and the clinically acceptable loss of efficacy in active comparator treatment effect

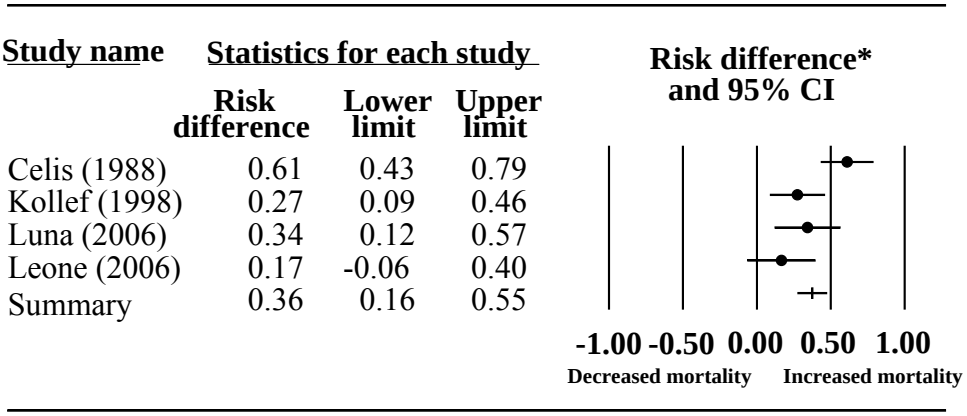
For the purpose of the FDA determination of the NI margin, the mortality rate derived from the observational studies of patients treated with inappropriate, delayed, or inadequate antibacterial therapy was used as a surrogate for the placebo rate. In addition, the mortality rates derived from the efficacy outcome clinical trials for the individual active comparators (piperacillin/tazobactam and imipenem) were used for the active control treatment effect, since that data was most relevant to the design of the two doripenem clinical trials in NP (including VAP) as conducted by the Sponsor.

The results of the previously described meta-analyses were used to estimate the NI margin for the indication of NP, including VAP. The treatment effect on mortality for each active control drug (piperacillin/tazobactam and imipenem) was determined based on the differences between the lower bound of the 95% CI for the mortality rate from the studies of inadequate, inappropriate, or delayed initial treatment (as a surrogate for the placebo rate) and the upper bound of the 95% CI of the mortality rates of the individual active comparator drugs. The results of the meta-analyses of the mortality rate for the inappropriate, delayed, or inadequate initial antibiotic treatment groups in the four studies was 60% with a 95% CI of (40%, 76%). Based on the results of the comparative efficacy clinical trials, the mortality rate for the piperacillin/tazobactam group was 18% with a 95% CI of (11%, 28%) and the mortality rate for the imipenem group was 17% with a 95% CI of (13%, 22%). Therefore, the estimated treatment effect based on mortality for piperacillin/tazobactam is 40% - 28% = 12% and the estimated treatment effect for imipenem is 40% - 22% = 18%.

As a supportive analysis to buttress the results obtained from the active comparator mortality difference described above, the mortality data from the patient subgroups treated with appropriate initial antibacterial therapy that were part of the four observational studies analyzed previously which assessed the association of inappropriate, delayed, or inadequate initial antibacterial therapy with subsequent mortality were examined. Using the appropriate initial treatment subgroups as a surrogate for the individual active control drugs, the treatment effect of appropriate initial therapy

on mortality was estimated based on the lower 95% confidence bound of the difference between inappropriate, delayed, or inadequate initial therapy and appropriate initial treatment. This approach eliminated cross study differences that were inherent in the previously described analysis involving the efficacy outcome trials. A random effects meta-analysis of this data is depicted in Figure 5 below. Based on the random effects meta-analysis of the four studies involving adequate and inadequate, delayed, or inappropriate initial therapy, the overall treatment effect (Inappropriate initial therapy – Appropriate initial therapy) on mortality in NP and VAP is 36% with a 95% confidence interval (CI) of (16%, 55%). A conservative estimate of the treatment effect is 16% based on the lower bound of the 95% confidence interval.

Figure 5: Mortality Risk Difference based on Historical Observational Studies that assessed the association between Inadequate, Delayed, and Inappropriate Initial Antibacterial Therapy and subsequent Mortality



*Risk difference = Inappropriate – Appropriate

The results of the random effects meta-analysis presented earlier demonstrate that there is a statistically significant reduction in mortality with the use of active control antibacterial agents, and the effect is 12% for piperacillin/tazobactam and 18% for imipenem. The finding of a treatment effect of 16% based on the historical studies comparing inappropriate, delayed, or inadequate initial therapy to appropriate initial therapy is within range of those results and provides additional supportive data. Note that the mortality rate associated with the use of inappropriate therapy (40%) based on the historical studies was used to compute the above estimates. Assuming that inappropriate initial therapy is at least as effective as placebo and likely is more so, the treatment difference on mortality should be larger than the estimate above. Thus, an M1 estimate of 12% is likely underestimated because patients who received inappropriate initial therapy still may have received some benefit from the administered antibacterial therapy. Therefore, the choice for the treatment effect (M1) of antibacterial agents is in the range of 12% to 18%. Choosing a conservative estimate for M1 of 12% is based on applying appropriate discounting on the treatment effect.

In conclusion, based on the previously described FDA analysis of the all-cause mortality rates, a non-inferiority margin of 6% is justifiable for the indication of NP and VAP

utilizing all-cause mortality as the primary endpoint. The above NI margin would preserve half of the estimated antibacterial treatment effect (M1) of 12%. This level of preservation of the treatment effect was chosen due to concerns about excess mortality.

Limitations associated with the published observational studies and clinical trials reviewed for the FDA analysis:

There were several limitations associated with the source historical observational studies and efficacy outcome clinical trials used to derive the FDA's 6% NI margin for all-cause mortality. First, there were no placebo-controlled studies of NP and VAP identified, such that the treatment effect could not be estimated directly. Second, there was marked variability across studies in terms of the methodological differences in study design and conduct, and there were evolving medical standards of care. The studies reviewed spanned a 40 year time period from the late 1960s to the present day during which progressive advances in antibiotic treatment options, new life support technologies, and enhanced capabilities to diagnose and manage NP and VAP contributed to a lack of constancy of the antibacterial drug treatment effect over time. Third, there was substantial heterogeneity in the mortality rates between various studies, most notably related to data from the observational studies of inappropriate, delayed, or inadequate initial antibacterial therapy.

Various clinical study designs were employed in the historical observational studies evaluating the association between inadequate, delayed, or inappropriate initial therapy and subsequent mortality, including prospective cohort, retrospective, and case-control. Randomization and blinding were not employed uniformly, the study populations were small in some instances, and the clinical experience with potentially drug-resistant bacterial pathogens (such as *Pseudomonas* and *Acinetobacter)* was quite variable across studies and was not reported consistently. Many study populations were derived from single centers, which limited generalizability. Confounding from age, severity of illness, and co-morbid conditions were another concern, and there were inconsistencies in diagnostic criteria and in the definitions used for appropriate and inappropriate or inadequate initial antibiotic therapy. The cause of death was not clearly ascertained from all of the studies, also.

Among the various efficacy outcome clinical trials reviewed, most of the studies permitted concomitant aminoglycoside use, which could contribute to an overestimation of the treatment effect of the individual active comparator agents, piperacillin/tazobactam and imipenem. Many of the clinical trials were multi-center, which enhanced generalizability. The study populations tended to be heterogenous with respect to ventilated and non-ventilated patients with NP.

Clinical Response as an alternative endpoint:

In contemporary clinical trials, the availability of alternative drugs and drug combinations, improvements in diagnosis, advancements in medical technology, and improvements in life support underscore a greater likelihood that a patient treated with a failing study drug regimen could be rescued successfully resulting in lowered mortality

rates, overall. However, extrapolating quantitative estimates of treatment benefit from a mortality endpoint to newer definitions of 'clinical failure' raises questions for non-inferiority trials. The clinical failure rates following treatment with a placebo cannot be determined due to the absence of studies reporting such clinical response data in the published scientific literature. In addition, attempts to discern clinical response based only upon mortality data must be tempered by several concerns. First, mortality is a definitive objective endpoint, whereas clinical response is soft and subjective endpoint and it relies on investigator interpretation of various clinical signs and symptoms, laboratory test results, and results of medical imaging tests. Second, missing outcomes can be problematic, especially in non-inferiority studies if the incidence of death is small as a sub-component of the clinical failure outcome.

In view of the lack of placebo data for clinical response, it is not possible to directly estimate the treatment effect of antibacterial agents. However, a plausible approach is to assume that the treatment effect based on mortality from historical studies is similar to the treatment effect for a clinical response endpoint that includes mortality as a subset of clinical failure. Based on this premise, preserving a smaller fraction of the treatment effect for clinical response may be possible due to the potential to rescue patients on a failing regimen from a fatal outcome in a present-day clinical trial. Thus, a larger NI margin could be postulated. The NI margin chosen for clinical response should preserve at least part of the 12% treatment effect in order to ensure that the study drug is more effective than placebo. Hence, in view of the previously described assumptions and the lack of placebo data, a non-inferiority margin of 10% for a clinical response endpoint is recommended. Finally, it is important to note that any differential effect on mortality should be assessed independent of the clinical response endpoint.

EFFICACY RESULTS

DORI-09

Demographic and baseline characteristics

Four hundred forty-eight patients were randomized to receive one of the study therapies: 225 to receive doripenem and 223 to receive piperacillin/tazobactam. Sixty-eight sites enrolled patients: 24 sites in North America, 18 sites in South America, and 26 sites in Europe and other regions; no site enrolled more than approximately 10% of the patients. Table 11 shows the demographic characteristics of the randomized population.

Table 11. Demographic and Baseline Characteristics (Randomized)

	Doripenem (N=225)		Piperacillin/tazobactam (N=223)	
	n	(%)	n	(%)
Gender				
Male	159	(71)	153	(69)
Female	66	(29)	70	(31)
Age (years)				
18-44	62	(28)	52	(23)
45-64	63	(28)	68	(30)
65-74	47	(21)	43	(19)
≥75	53	(24)	60	(27)
Median	59		63	
Range	19-94		18-97	
Race				
White	167	(74)	173	(78)
Hispanic or Latino	37	(16)	36	(16)
Black	14	(6)	13	(6)
Asian	2	(1)	0	(0)
American Indian/Alaska Native	1	(<1)	0	(0)
Other	4	(2)	1	(<1)
Region				
Europe	97	(43)	100	(45)
South America	72	(32)	71	(32)
North America	46	(20)	47	(21)
U.S.	39	(17)	38	(17)
Other	10	(4)	5	(2)
Ventilator-associated				
No	161	(72)	161	(72)
Yes	64	(28)	62	(28)
Baseline APACHE II score				
≤15	166	(74)	166	(74)
>15	59	(26)	57	(26)

Evaluability

Table 12 summarizes the applicant's determinations of patient evaluability.

Table 12. Applicant's Accounting of Patient Evaluability

	Doripenem (N=225)		Piperacillin/tazobactam (N=223)	
	n	(%)	n	(%)
Clinical Modified Intent-to-Treat (cMITT)	**217**	**(96)**	**212**	**(95)**
Not cMITT evaluable	**8**	**(4)**	**11**	**(5)**
Inadequate evidence of pneumonia	4		1	
Study therapy not received	2		2	
Site 198	2		7	
Other	0		1	
Clinically Evaluable (CE)	**134**	**(60)**	**119**	**(53)**
Not CE	**91**	**(40)**	**104**	**(47)**
Excluded from cMITT analysis population	8		11	
Protocol-defined disease definition not met	12		7	
Failure on previous therapy and negative baseline culture	8		8	
Ventilated, negative culture, and no prior therapy	7		5	
Inadequate study drug therapy	17		22	
Prior antimicrobial therapies violation	4		1	
Concomitant antimicrobial therapies violation	25		22	
Confounding baseline or intercurrent event	17		16	
Test of cure window violation or indeterminate outcome assessment	32		37	
Only baseline resistant pathogens isolated	19		32	
Only Gram-positive pathogen and treated with ≥24 hours of vancomycin	9		9	
Microbiologically Evaluable	**84**	**(37)**	**83**	**(37)**

More than one reason for exclusion could have been recorded for a patient.
Adapted from DORI-09 study report, Tables 10 and 11

The applicant's cMITT analysis population included 124 patients (28.9%) with VAP (63 in the doripenem group and 61 in the piperacillin/tazobactam group); of these, 123 had a CPIS recorded. In the doripenem group (n=62), 31 (50%) patients had a CPIS of ≤6, which indicates a low likelihood of pneumonia. In the piperacillin/tazobactam group, 25 (41%) patients had a CPIS of ≤6. The applicant's CE analysis population included 55 patients (21.7%) with VAP (29 in the doripenem group and 26 in the piperacillin/tazobactam group); all had a CPIS recorded. In the doripenem group, 14 (48.3%) patients had a CPIS of ≤6. In the piperacillin/tazobactam group, 7 (26.9%) patients had a CPIS of ≤6.

Data from 9 patients from site 198 were excluded by the applicant from all efficacy analyses (but not from safety analyses) because of noncompliance discovered during site monitoring; the number of doses of study drug recorded on the case report forms did not match the number of vials provided. The site was terminated before the study was completed.

Review of case report forms and the database revealed several major concerns that limit the ability to evaluate the efficacy of doripenem in this study:

1. There are questions regarding the interpretation of chest radiographs. Many patients appear to lack convincing radiographic evidence of pneumonia. The inclusion criteria required the presence of a new or progressive infiltrate on chest radiograph, yet the radiology reports frequently differ and cite more likely explanations for abnormal films. For example, for patient 927-02503, the screening radiology report states, "Minimal right apical pneumothorax, smaller than on prior study. Small bilateral pleural effusions. Right greater than left bibasilar opacities most likely represent atelectasis." For patient 948-02036, the screening radiology report states, "There is atelectasis and/or infiltrate within the lung bases which appear similar to the previous study [1 day previously]. Impression: bibasilar infiltrate/atelectasis with no significant overall change identified." Assessment of cure required improvement or lack of progression in all chest x-ray abnormalities, but review of the CRFs revealed cases in which patients with worsening chest x-rays were evaluated as cures, as noted with patients 197-05001 and 304-04014 described above. In other cases (e.g., patient 948-02036), no chest x-ray was obtained at the TOC visit.

The division requested the applicant to explain the process for review of chest x-rays and to review x-ray reports to identify patients who did not have new or progressive infiltrates consistent with pneumonia. In a partial response (S-015, 1/14/08), the applicant stated, "Radiologists were generally not part of the study personnel and were likely to have evaluated the radiographic findings objectively, in isolation from detailed information on the clinical status of the patient. In cases where the radiology report and the investigator's description in the CRF differed, the investigator's interpretation was generally regarded as more definitive." The applicant subsequently (S-022, 2/19/08) identified patients who did not have new or progressive infiltrates consistent with pneumonia; this determination was based only on a radiologist's report and included patients with missing reports. The applicant reported that 18 patients (4.3%) in the cMITT population (11 in the doripenem group and 7 in the piperacillin/tazobactam group) and 6 patients (2.4%) in the CE population (3 in each group) did not meet strict radiologic criteria for pneumonia. This includes 9 patients in the cMITT population and 3 patients in the CE population for whom no formal radiology report of the screening chest film was available.

2. The results of the Gram stain examinations of the screening lower respiratory tract specimens that fulfilled the microbiologic inclusion criteria for patients in DORI-09 and DORI-10 were not recorded on the CRFs and are not included in the datasets. In response to a query from the division, the applicant stated the following (S-014, 1/14/08):

> Based on evaluation of routine practices at sites and prior experience, it was expected that the exact cell counts would not be routinely recorded by the local laboratory. Most laboratories only record qualitative data and the interpretation of this qualitative data may vary slightly from site to site. This variability and likelihood that quantitative findings would not be recorded in laboratory records was thought to be problematic for source verification and therefore were not recorded on the case report forms (CRF). Furthermore, as discussed below, the reliability of cell counts as determined by gram stain, is variable. Thus, we

> believe it is unlikely that the Gram stain result would have improved the validity of the sputum culture results. Screening gram stain results were not evaluated for the purpose of determining evaluability in the DORI-09 and DORI-10 trials and were not captured in J&JPRD's study database and FDA's requested database cannot be generated. Furthermore, as discussed above, it is anticipated that this information will generally not be available at the study sites.

The response goes on to state that local laboratories

> were instructed to follow their standard practice for processing microbiologic specimens. Greater than 90% of the local laboratories used one of two reference manuals approved by the American Society of [sic] Microbiology, the Clinical Microbiology Procedures Handbook, the Reference in Microbiology of the French Society of Microbiology (REMIC), guidelines provided by the local Government Ministry of Health in Belarus or other similar guidelines. The ASM Clinical Microbiology Procedures Handbook recommends rejection of either sputum or tracheal aspirate for culture if it has >10 epithelial cells. It is unlikely, therefore, that a significant number of the cultured specimens that were obtained at baseline did not qualify. There is unlikely to be any impact on the ME analysis population.

The applicant subsequently obtained Gram stain reports from local laboratories for expectorated sputum specimens from 129 patients (S-033, 4/28/08). These results were reported semiquantitatively using scales of 0 to 3+ for both squamous epithelial cells and polymorphonuclear leukocytes; acceptable specimens contained 0 to 1+ squamous epithelial cells and 3+ polymorphonuclear leukocytes. One hundred of the 129 specimens (77.5%) met these criteria.

In the cMITT analysis population, lower respiratory tract cultures were obtained from 294 patients with NP that was not ventilator-associated. The most common lower respiratory tract specimen in these patients was expectorated sputum (222/294; 76%); 83% of these patients (183/222) had pathogens isolated. Lower respiratory tract cultures were obtained from 129 patients with VAP. The most common lower respiratory tract specimen in these patients was an endotracheal aspirate (103/129; 80%); 80% of these patients (82/103) had pathogens isolated.

3. The evaluation of clinical response for most patients is confounded by the prolonged use of adjunctive amikacin therapy. Upon enrollment in DORI-09, in addition to study drug, patients were to be treated with amikacin, 7.5 mg/kg q 12h for patients with normal renal function, for potential *P. aeruginosa* infection. Alternative dosing or aminoglycoside regimens were permitted with sponsor approval. The final version of the protocol, dated 4/18/06, stated (p.45):

> Once culture and susceptibility results are available and a *P. aeruginosa* infection is not confirmed by culture, amikacin should be discontinued, at the discretion of the investigator. If *P. aeruginosa* infection is confirmed, treatment with amikacin

should be continued in patients assigned to the piperacillin/tazobactam arm (as per the product label) for approximately 5 days. For patients assigned to doripenem, amikacin can be discontinued, at the discretion of the investigator, if the patient has improved clinically and the *P. aeruginosa* isolate is susceptible to meropenem (surrogate for doripenem).

These instructions permitted investigators to continue amikacin even when *P. aeruginosa* was not isolated. Table 13 shows the duration of use of adjunctive anti-pseudomonal coverage in the CE population.

Table 13. Adjunctive Therapy for *Pseudomonas aeruginosa* (Clinically Evaluable)

	Doripenem (N=134)				Piperacillin/tazobactam (N=119)			
	Total	Baseline *P. aeruginosa*, n (%)			Total	Baseline *P. aeruginosa*, n (%)		
	n (%)	Yes	No	Unk	n (%)	Yes	No	Unk
Use of any adjunctive anti-pseudomonal therapy								
No	29 (22)	2 (7)	26 (90)	1 (3)	18 (15)	2 (11)	15 (83)	1 (6)
Yes	105 (78)	16 (15)	88 (84)	1 (1)	101 (85)	17 (17)	83 (82)	1 (1)
≤2 days	10 (7)	1 (10)	9 (90)	0	11 (9)	0	10 (91)	1 (9)
3 to 5 days	52 (39)	5 (10)	47 (90)	0	50 (42)	2 (4)	48 (96)	0
> 5 days	43 (32)	10 (23)	32 (74)	1 (2)	40 (34)	15 (38)	25 (63)	0
Use of amikacin								
Yes	104 (78)	16 (15)	87 (84)	1 (1)	100 (84)	17 (17)	82 (82)	1 (1)
≤2 days	9 (7)	1 (11)	8 (89)	0	11 (9)	0	10 (91)	1 (1)
3 to 5 days	52 (39)	5 (10)	47 (90)	0	49 (41)	2 (4)	47 (96)	0
> 5 days	43 (32)	10 (23)	32 (74)	1 (2)	40 (34)	15 (38)	25 (63)	0
Unk = unknown								

Adapted from DORI-09 study report, Attachment 7.5

In the doripenem group, 95 of 134 patients (71%) were treated with adjunctive anti-pseudomonal therapy for 3 days or more; 43 patients (32%) were treated for >5 days, although only 18 patients (13%) had *P. aeruginosa* isolated at baseline, and no isolates were resistant to meropenem or doripenem.

Use of vancomycin was permitted if MRSA was isolated or was a suspected pathogen. The final version of the protocol stated (p.46):

> If MRSA is isolated or is one of the suspected pathogens (based on the incidence of MRSA at the institution), the use of vancomycin may be instituted, at the discretion of the investigator. The use of vancomycin should be discontinued if MRSA is not confirmed by culture results. Empiric vancomycin therapy should be considered when MRSA is prevalent in the institution (e.g., >20% of *S. aureus* isolates are methicillin-resistant) or in patients previously found to be colonized with MRSA. Vancomycin should be discontinued within 48 hours if the respiratory specimen and blood culture are negative for MRSA. The dosage of vancomycin chosen should conform to institutional standards. Alternatives to vancomycin for MRSA can be considered after discussion with the Sponsor or designated medical monitor.

Table 14 shows the duration of use of adjunctive anti-MRSA coverage in the CE population.

Table 14. Adjunctive Therapy for Methicillin-Resistant *Staphylococcus aureus* (Clinically Evaluable)

	Doripenem (N=134)				Piperacillin/tazobactam (N=119)			
	Total	Baseline MRSA, n (%)			Total	Baseline MRSA, n (%)		
	n (%)	Yes	No	Unk	n (%)	Yes	No	Unk
Use of any adjunctive anti-MRSA therapy								
No	117 (87)	3 (3)	109 (93)	5 (4)	98 (82)	0	97 (99)	1 (1)
Yes	17 (13)	2 (12)	15 (88)	0	21 (18)	4 (19)	16 (76)	1 (5)
≤2 days	3 (2)	0	3(100)	0	2 (2)	0	2(100)	0
3 to 5 days	7 (5)	0	7(100)	0	9 (8)	1 (11)	8 (89)	0
> 5 days	7 (5)	2 (29)	5 (71)	0	10 (8)	3 (30)	6 (60)	1 (10)
Use of vancomycin								
Yes	17 (13)	2 (12)	15 (88)	0	21 (18)	4 (19)	16 (76)	1 (5)
≤2 days	3 (2)	0	3(100)	0	2 (2)	0	2(100)	0
3 to 5 days	7 (5)	0	7(100)	0	9 (8)	1 (11)	8 (89)	0
> 5 days	7 (5)	2 (29)	5 (71)	0	10 (8)	3 (30)	6 (60)	1 (10)
Unk = unknown								

Adapted from DORI-09 study report, Attachment 7.7

In the doripenem group, 14 of 134 patients (10%) were treated with adjunctive vancomycin therapy for 3 days or more; 7 patients (5%) were treated for >5 days, although only 2 patients (1%) had MRSA isolated at baseline.

The provision for a switch from study drug to oral therapy complicates the evaluation of study drug effect even further. In the doripenem group, 60 of 134 patients (44.8%) received combined iv and oral therapy; the median duration of iv therapy was 7 days, and the median duration of oral therapy was 5 days. In the 74 patients (55.2%) in the doripenem group who received only iv study drug, the median duration of therapy was 10 days. When the use of prolonged adjunctive anti-pseudomonal therapy is considered together with the use of oral therapy in a substantial number of patients, the exposure to doripenem as a single agent is limited. In response to a request by the division, the applicant created a dataset listing of days of single agent therapy for the study drugs (S-018, 1/17/08); this listing considered only protocol-approved adjunctive therapy. Among the 109 patients in the doripenem group who were considered to be clinically evaluable cures, 19 (17%) never received doripenem as a single agent, 11 (10%) received doripenem as a single agent for 1 day, and 9 (8%) received doripenem as a single agent for 2 days. These are conservative figures; the dataset the applicant created is likely to overestimate of use of doripenem as a single agent, since it excluded non-protocol-approved therapies; for example, if a patient received ceftriaxone along with doripenem on the first day, this was considered one day of single-agent doripenem.

Efficacy

Clinical Outcomes

The primary endpoint for this trial was clinical response at the TOC visit 7 to 14 days after completion of therapy; the clinically evaluable and clinical modified intent-to-treat (cMITT) populations served as co-primary populations for analysis of efficacy. The applicant expanded the TOC window to 6 to 20 days post-therapy so that more patients could be evaluated. At the division's recommendation, patients with TOC visits earlier than 6 days post-therapy were considered indeterminate in the cMITT analysis and not evaluable in the per-protocol (CE) analysis. Table 15 shows the proportions of CE and cMITT patients with satisfactory outcomes at the TOC visit.

Table 15. Clinical Outcomes at Test of Cure (Clinically Evaluable and Clinical MITT)

	Doripenem	Piperacillin/tazobactam	Difference	
Analysis set	n/N (%)	n/N (%)	%	(95% CI)
Clinically evaluable	109/134 (81.3)	95/119 (79.8)	1.5	(-9.1, 12.1)
Clinical MITT	148/213 (69.5)	134/209 (64.1)	5.4	(-4.1, 14.8)
n/N = number with satisfactory outcome/number evaluable; CI = confidence interval				

Adapted from DORI-09 study report, Table 15

The BEC did not agree with the investigators' outcome assessments for 13 patients (3%) in the cMITT population. In the doripenem arm, the BEC overruled the investigators for 4 patients: for 1 patient, the clinical outcome was changed from cure to failure, for 1 patient, the clinical outcome was changed from failure to cure, and for 2 patients, the clinical outcome was changed from indeterminate to failure. In the piperacillin/tazobactam arm, the BEC overruled the investigators for 6 patients: for 3 patients, the clinical outcome was changed from cure to indeterminate, for 2 patients, the clinical outcome was changed from failure to cure, and for 1 patient, the clinical outcome was changed from indeterminate to failure. In addition, there were 3 doripenem patients for whom the BEC had agreed with the investigators' original outcome assessments, but the investigators changed their assessments after BEC review.

Table 16 shows clinical outcomes at the TOC visit in the CE population according to geographic region, ventilator status, baseline APACHE II score, and demographic group. Cure rates were substantially higher for sites in Europe than for those in North America or South America. At sites in the United States, cure rates were 61.5% (8/13) for patients treated with doripenem and 76.9% (10/13) for patients treated with piperacillin/tazobactam. The applicant attributed this finding to differences in numbers of patients with ventilator-associated pneumonia and the distribution of APACHE II scores. Cure rates were higher for patients with pneumonia that was not ventilator-associated than for those with VAP, and for VAP patients treated with doripenem (69.0%; 20/29) than for VAP patients treated with piperacillin/tazobactam (57.7%; 15/26). Cure rates were higher for patients with baseline APACHE II scores $\leq$15 than for those with baseline APACHE II scores >15. For patients with baseline APACHE II scores $\leq$15, cure rates were higher for those treated with doripenem (89.9% vs. 83.5%), while for patients with baseline APACHE II scores >15, cure rates were higher for those

treated with piperacillin/tazobactam (67.9% vs. 57.1%). Cure rates in age, sex, and racial subgroups were similar in both arms.

Table 16. Clinical Outcomes at Test of Cure (Clinically Evaluable Subgroups)

	Doripenem		Piperacillin/tazobactam		Difference	
	n/N	(%)	n/N	(%)	%	(95% CI)
Region						
North America	14/19	(73.7)	14/17	(82.4)	-8.7	
US	8/13	(61.5)	10/13	(76.9)	-15.4	
South America	28/41	(68.3)	25/37	(67.6)	0.7	(-22.6, 24.0)
Europe	64/70	(91.4)	54/62	(87.1)	4.3	(-7.8, 16.5)
Other	3/4	(75.0)	2/3	(66.7)	8.3	
Ventilator-associated						
No	89/105	(84.8)	80/93	(86.0)	-1.3	(-12.1, 9.6)
Yes	20/29	(69.0)	15/26	(57.7)	11.3	
Baseline APACHE II						
≤15	89/99	(89.9)	76/91	(83.5)	6.4	(-4.3, 17.1)
>15	20/35	(57.1)	19/28	(67.9)	-10.7	
Age (y)						
<65	61/74	(82.4)	54/66	(81.8)	0.6	(-13.5, 14.8)
≥65	48/60	(80.0)	41/53	(77.4)	2.6	(-14.3, 19.6)
Sex						
Male	79/98	(80.6)	59/74	(79.7)	0.9	(-12.4, 14.1)
Female	30/36	(83.3)	36/45	(80.0)	3.3	(-16.0, 22.7)
Race						
White	85/101	(84.2)	76/94	(80.9)	3.3	(-8.4, 15.0)
Black	4/6	(66.7)	0/2	(0.0)	66.7	
Hispanic or Latino	17/23	(73.9)	19/23	(82.6)	-8.7	
Other	3/4	(75.0)	0/0			

n/N = number with satisfactory outcome/number evaluable
CI = confidence interval (if N>30 in both arms)

Adapted from DORI-09 study report, Table 17

Table 17 shows an analysis submitted by the applicant of clinical outcomes in microbiologically evaluable patients. As discussed above, the applicant failed to collect and submit Gram stain data confirming the acceptability of most lower respiratory tract culture specimens.

Table 17. Clinical Outcomes at Test of Cure (Microbiologically Evaluable and Microbiologic MITT)

	Doripenem		Piperacillin/tazobactam		Difference	
Analysis set	n/N	(%)	n/N	(%)	%	(95% CI)
Microbiologically evaluable	69/84	(82.1)	65/83	(78.3)	3.8	(-9.4, 17.1)
Microbiologic MITT	94/139	(67.6)	97/144	(67.4)	0.3	(-11.4, 11.9)

n/N = number with satisfactory outcome/number evaluable; CI = confidence interval

Adapted from DORI-09 study report, Table 18

Nineteen patients in the microbiologically evaluable population had baseline bacteremia; 11 of these patients had the same pathogen isolated from the respiratory tract. Cure rates were 50% (1/2) for doripenem-treated patients and 89% (8/9) for piperacillin/tazobactam-treated patients.

Clinical relapse rates at the late follow-up visit were low in both groups: 3.0% (3/99) in the doripenem arm and 3.6% (3/84) in the piperacillin/tazobactam arm.

Table 18 shows all-cause mortality in the ITT population at various intervals. Mortality was greater during iv therapy in the doripenem group. Twenty-eight day mortality and mortality during study therapy plus 30 days were similar in the groups.

Table 18. All-Cause Mortality (Intent-to-Treat)

	Doripenem (N=223)		Piperacillin/tazobactam (N=221)		Relative Risk (Dori/Pip-tazo)	
Time	n	(%)	n	(%)	(95% CI)	
During iv therapy	21	(9.4)	9	(4.1)	2.3	(1.1, 4.9)
Days 1-28	34	(15.2)	31	(14.0)	1.1	(0.7, 1.7)
During therapy + 30 days	43	(19.3)	38	(17.2)	1.1	(0.8, 1.7)
CI = confidence interval using a continuity correction						

Microbiologic Outcomes

The two tables in this section show the analyses submitted by the applicant of microbiologic outcomes in microbiologically evaluable patients. As discussed above, the applicant failed to collect and submit Gram stain data confirming the acceptability of most lower respiratory tract culture specimens.

Table 19. Microbiologic Outcomes at Test of Cure (Microbiologically Evaluable)

	Doripenem		Piperacillin/tazobactam		Difference	
Analysis set	n/N	(%)	n/N	(%)	%	(95% CI)
Microbiologically evaluable	71/84	(84.5)	67/83	(80.7)	3.8	(-8.9, 16.5)
n/N = number with satisfactory outcome/number evaluable; CI = confidence interval						

Adapted from DORI-09 study report, Table 19

Table 20 presents the pretreatment pathogen outcomes and clinical response rates at the TOC visit for patients with selected lower respiratory tract isolates. The organisms listed are those in the applicant's proposed label for this indication.

Table 20. Pretreatment Pathogen Outcomes and Clinical Outcomes at Test of Cure (Microbiologically Evaluable)

	Doripenem					Piperacillin/tazobactam				
		Pretreatment pathogen outcome		Clinical outcome			Pretreatment pathogen outcome		Clinical outcome	
Pathogen	N	n	%	n	%	N	n	%	n	%
Staphylococcus aureus	17	14	82	14	82	15	15	100	15	100
Streptococcus pneumoniae	7	6	86	6	86	6	5	83	5	83
Haemophilus influenzae	8	8	100	7	87	10	7	70	8	80
Klebsiella pneumoniae	14	11	79	12	86	11	7	64	7	64
Enterobacter cloacae	11	11	100	10	91	6	5	83	5	83
Escherichia coli	9	7	78	7	78	8	6	75	7	87
Pseudomonas aeruginosa	18	15	83	15	83	17	11	65	12	71
Acinetobacter baumannii	6	4	67	4	67	3	1	33	1	33
N = number of patients; n = number with satisfactory outcome										

Two patients in the doripenem arm had baseline bacteremia with the same pathogen isolated from the respiratory tract: one with *H. influenzae* (clinical cure), and one with *E. coli* (clinical failure). Nine patients in the piperacillin/tazobactam arm had baseline bacteremia with the same pathogen isolated from the respiratory tract: four with *S. aureus* (three clinical cures) and one each with *S. pneumoniae*, *K. pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, and *Acinetobacter calcoaceticus* (all clinical cures).

DORI-10

Demographic and baseline characteristics

Five hundred thirty-one patients were randomized to receive one of the study therapies: 264 to receive doripenem and 267 to receive imipenem/cilastatin. Eighty-four sites enrolled patients: 37 sites in North America, 33 sites in Europe, and 14 sites in Australia and other regions (2 sites in Estonia and 1 site in Serbia and Montenegro were counted as other regions by the data collection system); no site enrolled more than approximately 9% of the patients. Table 21 shows the demographic characteristics of the randomized population.

Table 21. Demographic and Baseline Characteristics (Randomized)

	Doripenem (N=264)		Imipenem/cilastatin (N=267)	
	n	(%)	n	(%)
Gender				
Male	208	(79)	204	(76)
Female	56	(21)	63	(24)
Age (years)				
18-44	102	(39)	98	(37)
45-64	80	(30)	92	(34)
65-74	42	(16)	43	(16)
≥75	40	(15)	34	(13)
Median	51		53	
Range	18-93		18-86	
Race				
White	229	(87)	218	(82)
Black	23	(9)	31	(12)
Hispanic or Latino	10	(4)	11	(4)
Asian	0	(0)	5	(2)
American Indian/Alaska Native	1	(<1)	0	(0)
Other	1	(<1)	2	(1)
Region				
North America	126	(48)	129	(48)
U.S.	126	(48)	127	(48)
Europe	92	(35)	93	(35)
Other	46	(17)	45	(17)
Ventilator-associated status				
Early-onset (<5 days)	105	(40)	106	(40)
Late-onset (≥5 days)	159	(60)	161	(60)
Baseline APACHE II score				
≤15	122	(46)	129	(48)
>15	142	(54)	138	(52)

Evaluability

Table 22 summarizes the applicant's determinations of patient evaluability.

Table 22. Applicant's Accounting of Patient Evaluability

	Doripenem (N=264)		Imipenem/cilastatin (N=267)	
	n	(%)	n	(%)
Clinical Modified Intent-to-Treat (cMITT)	**249**	**(94)**	**252**	**(94)**
Not cMITT evaluable	**15**	**(6)**	**15**	**(6)**
Inadequate evidence of pneumonia	13		11	
Study therapy not received	2		4	
Clinically Evaluable (CE)	**126**	**(48)**	**122**	**(46)**
Not CE	**138**	**(52)**	**145**	**(54)**
Excluded from cMITT analysis set	15		15	
Protocol-defined disease definition not met	13		12	
Failure on previous therapy and negative baseline culture	12		13	
Ventilated, negative culture, and no prior therapy	22		17	
Inadequate study drug therapy	41		31	
Patient received both study drugs	2		1	
Concomitant antimicrobial therapies violation	59		75	
Confounding baseline or intercurrent event	26		23	
Test of cure window violation or indeterminate outcome assessment	59		54	
Only baseline resistant pathogens isolated	5		15	
Only Gram-positive pathogen and treated with >24 hours of vancomycin	9		9	
Other	0		1	
Microbiologically Evaluable	**116**	**(44)**	**110**	**(41)**

More than one reason for exclusion could have been recorded for a patient.
Adapted from DORI-10 study report, Tables 10 and 11

In the applicant's cMITT analysis population, 500 patients (99.8%) had a CPIS recorded (248 in the doripenem group and 252 in the imipenem/cilastatin group). In the doripenem group, 86 (34.7%) patients had a CPIS of $\leq$6, which indicates a low likelihood of pneumonia. In the imipenem/cilastatin group, 103 (40.9%) patients had a CPIS of $\leq$6. The applicant's CE analysis population included 248 patients (126 in the doripenem group and 122 in the imipenem/cilastatin group); all had a CPIS recorded. In the doripenem group, 49 (38.9%) patients had a CPIS of $\leq$6. In the imipenem/cilastatin group, 44 (36.1%) patients had a CPIS of $\leq$6.

As with DORI-09, review of case report forms and the database for DORI-10 revealed several major concerns that limit the ability to evaluate the efficacy of doripenem in this study:

1. There are questions regarding the interpretation of chest radiographs. Many patients appear to lack convincing radiographic evidence of pneumonia. The inclusion criteria required the presence of a new or progressive infiltrate on chest radiograph, yet the radiology reports frequently differ and cite more likely explanations for abnormal films.

For example, patient 033-06023 had a notation on page 14 of the CRF (chest x-ray, screening visit) stating, "Infiltrate right lob [sic] air space disease." However, the screening radiology report states, "Compared to the previous check, improved findings in that the suspected infiltrates from parenchymal compression in the cardio diaphragmatic angle, on the right, have decreased in density and intensity. Compared to yesterday's check, retrogression of the atelectasis of the inferior pulmonary lobes" (translated from the German). Patient 134-02516 had a notation on page 14 of the CRF (chest x-ray, screening visit) stating simply, "Left basilar opacity." However, the screening radiology report states, "There has been a possible interval decrease in the left basilar opacity [compared with image 3 days earlier]. There is no significant change in diffuse interstitial edema," and then, "Impression: Interval slight decrease in the left basilar opacity, suggestive of resolving atelectasis, focal edema, or pneumonia." For patient 502-03023, the screening radiology report states, in comparison with a previous film, "The appearances in the lungs have not significantly changed in the interval." On the same page (122 of 133), there are handwritten notations dated 2 months later stating, "4 quadrant opacity, with marked opacity in right upper lobe. The opacity in the right upper lobe is new + localised. On this basis, "localised" was used for the CPIS." Patients from several European sites in DORI-10 do not have radiology reports submitted, but instead have a form titled, "Results of X ray reports provided by the study centre," which appears to be derived from the CRF chest x-ray pages. In other cases (e.g., patient 104-02062), no chest x-ray was obtained at the TOC visit.

The division requested the applicant to explain the process for review of chest x-rays and to review x-ray reports to identify patients who did not have new or progressive infiltrates consistent with pneumonia. In a partial response (S-015, 1/14/08), the applicant stated, "Radiologists were generally not part of the study personnel and were likely to have evaluated the radiographic findings objectively, in isolation from detailed information on the clinical status of the patient. In cases where the radiology report and the investigator's description in the CRF differed, the investigator's interpretation was generally regarded as more definitive." The applicant subsequently (S-024, 2/22/08) identified patients who did not have new or progressive infiltrates consistent with pneumonia; this determination was based only on a radiologist's report and excluded patients with missing reports. The applicant reported that 68 patients (13.8%) in the cMITT population (32 in the doripenem group and 36 in the imipenem/cilastatin group) and 38 patients (15.3%) in the CE population (18 in the doripenem group and 20 in the imipenem/cilastatin group) did not meet strict radiologic criteria for pneumonia.

Regarding the radiology reports from European sites, the applicant stated (S-024, 2/22/08) that many sites in Europe did not have formal radiology reports of chest x-rays and that investigators' interpretations of films were entered on worksheets. For some patients, a "note to file" was provided, and the interpretation was entered directly into the case report form rather than on a worksheet. "The interpretation on the worksheets was considered equivalent to X-ray reports (as provided in other regions) and was the basis for inclusion in the study." "In summary, the worksheet detailing the chest x-ray findings were [sic] part of the source documentation and served as an authoritative interpretation of radiographic findings by the physicians caring for the subjects enrolled in the study

and as the only documented interpretations at those sites. All subjects with worksheets that identified an infiltrate using acceptable terms were included in the PS [pneumonia strict] analysis population" (i.e., as meeting strict radiologic criteria for pneumonia).

In response to a follow-up query to identify all patients in DORI-10 for whom no formal radiology report of the screening chest film was available and to identify all patients whose reported radiographic findings were derived from the worksheets described above or for whom a "note to file" was provided, with direct entry of the interpretation into the case report form, the applicant stated (S-029, 3/21/08):

> All subjects who enrolled in France, Spain, Serbia, Estonia, Netherlands, and Belgium had the worksheet only, and their reported radiographic findings in the CRF were derived from the worksheet. These subjects accounted for 117 of 123 radiographic findings that were derived from the worksheet. In addition, all 8 subjects with a "note to file" are from a few Australian sites where formal radiology reports were not immediately available prior to enrollment.

The applicant reported that 133 patients (27.0%) in the cMITT population (62 in the doripenem group and 71 in the imipenem/cilastatin group) and 76 patients (30.6%) in the CE population (36 in the doripenem group and 40 in the imipenem/cilastatin group) did not have formal radiology reports of screening chest films.

The group that did not meet strict radiologic criteria for pneumonia and the group that did not have formal radiology reports overlap somewhat. When these groups are combined, 176 patients (35.7%) in the cMITT population (82 in the doripenem group and 94 in the imipenem/cilastatin group) and 99 patients (39.9%) in the CE population (48 in the doripenem group and 51 in the imipenem/cilastatin group) either did not meet strict radiologic criteria for pneumonia or did not have formal radiology reports of screening chest films.

2. The results of the Gram stain examinations of the screening lower respiratory tract specimens that fulfilled the microbiologic inclusion criteria for patients in DORI-09 and DORI-10 were not recorded on the CRFs and are not included in the datasets.

The applicant subsequently obtained Gram stain reports from local laboratories for expectorated sputum specimens from 6 nonintubated patients (S-033, 4/28/08). These results were reported semiquantitatively using scales of 0 to 3+ for both squamous epithelial cells and polymorphonuclear leukocytes; acceptable specimens contained 0 to 1+ squamous epithelial cells and 3+ polymorphonuclear leukocytes. Only one specimen met these criteria.

In the cMITT analysis population, lower respiratory tract cultures were obtained from 497 patients with VAP, 488 (98%) of whom were intubated or ventilated. The most common lower respiratory tract specimen in these patients was an endotracheal aspirate (305/488; 62.5%); 86% of these patients (263/305) had pathogens isolated. Specimens

were obtained bronchoscopically in 161 patients (33.0%); 96% of these patients (154/161) had pathogens isolated.

3. The evaluation of clinical response for some patients in DORI-10 is confounded by the prolonged use of adjunctive amikacin therapy, although this was not as significant as in DORI-09. Use of adjunctive therapy was more strictly limited in DORI-10. The final version of the protocol, dated 5/12/06, stated (p.42):

> In addition, if *P. aeruginosa* is suspected (e.g., patient hospitalized ≥7 days or prior broad spectrum antibacterial therapy), adjunctive amikacin can be included in the initial study drug regimen according to the following recommendations. For patients assigned to the doripenem arm, adjunctive amikacin should only be added at the discretion of the investigator, if a carbapenem-resistant *P. aeruginosa* is a concern (e.g., patients have previously received carbapenem therapy or carbapenem resistance rate in ICU exceeds 15%). For patients assigned to imipenem therapy, it is recommended that amikacin be added if *P. aeruginosa* pneumonia is suspected (regardless of susceptibility).

Regarding discontinuation of adjunctive therapy, the protocol stated (p. 43):

> Once culture and susceptibility results are available (see DORI-10.6 for description of culture procedures), amikacin should be discontinued if a *P. aeruginosa* infection is not confirmed (generally, within 48 hours). If a *P. aeruginosa* is confirmed in patients assigned to imipenem it is recommended that amikacin be continued (usually for a total of 5 to 7 days).

For doripenem patients who received adjunctive therapy and had *P. aeruginosa* isolated, the protocol stated (p. 43):

> In patients assigned to doripenem, if amikacin was started empirically, it should be discontinued if the isolate is not resistant (i.e., susceptible or intermediate) to meropenem and the patient is stable or has improved clinically.

These instructions more explicitly limited the use of amikacin in DORI-10. Table 23 shows the duration of use of adjunctive anti-pseudomonal coverage in the CE population.

Table 23. Adjunctive Therapy for *Pseudomonas aeruginosa* (Clinically Evaluable)

	Doripenem (N=126)				Imipenem/cilastatin (N=122)			
	Total n (%)	Baseline *P. aeruginosa*, n (%)			Total n (%)	Baseline *P. aeruginosa*, n (%)		
		Yes	No	Unk		Yes	No	Unk
Use of any adjunctive anti-pseudomonal therapy								
No	101 (80)	12 (12)	88 (87)	1 (1)	92 (75)	5 (5)	86 (93)	1 (1)
Yes	25 (20)	8 (32)	17 (68)	0	30 (25)	9 (30)	21 (70)	0
≤2 days	9 (7)	1 (11)	8 (89)	0	11 (9)	3 (27)	8 (73)	0
3 to 5 days	7 (6)	2 (29)	5 (71)	0	12 (10)	2 (17)	10 (83)	0
> 5 days	9 (7)	5 (56)	4 (44)	0	7 (6)	4 (57)	3 (43)	0
Use of amikacin								
Yes	15 (12)	6 (40)	9 (60)	0	18 (15)	6 (33)	12 (67)	0
≤2 days	6 (5)	1 (17)	5 (83)	0	4 (3)	2 (50)	2 (50)	0
3 to 5 days	4 (3)	2 (50)	2 (50)	0	10 (8)	2 (20)	8 (80)	0
> 5 days	5 (4)	3 (60)	2 (40)	0	4 (3)	2 (50)	2 (50)	0
Use of other anti-pseudomonal therapy								
Yes	11 (9)	2 (18)	9 (82)	0	14 (11)	3 (21)	11 (79)	0
≤2 days	4 (3)	0	4 (100)	0	9 (7)	1 (11)	8 (89)	0
3 to 5 days	3 (2)	0	3 (100)	0	2 (2)	0	2 (100)	0
> 5 days	4 (3)	2 (50)	2 (50)	0	3 (2)	2 (67)	1 (33)	0

Unk = unknown

Adapted from DORI-10 study report, Attachment 7.5

In the doripenem group, 16 of 126 patients (13%) were treated with adjunctive anti-pseudomonal therapy for 3 days or more; 9 patients (7%) were treated for >5 days. Twenty patients (16%) had *P. aeruginosa* isolated at baseline, and no isolates were resistant to doripenem (based on tentative breakpoints).

Use of vancomycin was permitted if MRSA was isolated or was a suspected pathogen. The final version of the protocol stated (p.43):

> If MRSA is one of the suspected pathogens (e.g., in centers where ≥20% of *S. aureus* isolates are methicillin-resistant or an MRSA has been isolated from the patient previously), the use of vancomycin may be instituted, at the discretion of the investigator. Vancomycin should be discontinued within 48 hours if the respiratory specimen culture is negative for MRSA.

Table 24 shows the duration of use of adjunctive anti-MRSA coverage in the CE population.

Table 24. Adjunctive Therapy for Methicillin-Resistant *Staphylococcus aureus* (Clinically Evaluable)

	Doripenem (N=126)				Imipenem/cilastatin (N=122)			
	Total	Baseline MRSA, n (%)			Total	Baseline MRSA, n (%)		
	n (%)	Yes	No	Unk	n (%)	Yes	No	Unk
Use of any adjunctive anti-MRSA therapy								
No	89 (71)	0	84 (94)	5 (6)	88 (72)	1 (1)	84 (95)	3 (3)
Yes	37 (29)	11 (30)	24 (65)	2 (5)	34 (28)	6 (18)	27 (79)	1 (3)
≤2 days	10 (8)	0	9 (90)	1 (10)	7 (6)	0	7 (100)	0
3 to 5 days	12 (10)	1 (8)	10 (83)	1 (8)	18 (15)	1 (6)	16 (89)	1 (6)
> 5 days	15 (12)	10 (67)	5 (33)	0	9 (7)	5 (56)	4 (44)	0
Use of vancomycin								
Yes	37 (29)	11 (30)	24 (65)	2 (5)	34 (28)	6 (18)	27 (79)	1 (3)
≤2 days	10 (8)	0	9 (90)	1 (10)	7 (6)	0	7 (100)	0
3 to 5 days	12 (10)	1 (8)	10 (83)	1 (8)	18 (15)	1 (6)	16 (89)	1 (6)
> 5 days	15 (12)	10 (67)	5 (33)	0	9 (7)	5 (56)	4 (44)	0
Other anti-MRSA therapy								
Yes	1 (1)	1 (100)	0	0	1 (1)	1 (100)	0	0
≤2 days	1 (1)	1 (100)	0	0	1 (1)	1 (100)	0	0
Unk = unknown								

Adapted from DORI-10 study report, Attachment 7.7

In the doripenem group, 27 of 126 patients (21%) were treated with adjunctive anti-MRSA therapy for 3 days or more. Fifteen patients (12%) were treated for >5 days. Eleven patients (9%) had MRSA isolated at baseline.

Efficacy

Clinical Outcomes

The primary endpoint for this trial was clinical response at the TOC visit 7 to 14 days after completion of therapy; the clinically evaluable and clinical modified intent-to-treat (cMITT) populations served as co-primary populations for analysis of efficacy. The applicant expanded the TOC window to 6 to 20 days post-therapy so that more patients could be evaluated. At the division's recommendation, patients with TOC visits earlier than 6 days post-therapy were considered indeterminate in the cMITT analysis and not evaluable in the per-protocol (CE) analysis. Table 25 shows the proportions of CE and cMITT patients with satisfactory outcomes at the TOC visit.

Table 25. Clinical Outcomes at Test of Cure (Clinically Evaluable and Clinical MITT)

	Doripenem	Imipenem/cilastatin	Difference	
Analysis set	n/N (%)	n/N (%)	%	(95% CI)
Clinically evaluable	86/126 (68.3)	79/122 (64.8)	3.5	(-9.1, 16.1)
Clinical MITT	144/244 (59.0)	144/249 (57.8)	1.2	(-7.9, 10.3)
n/N = number with satisfactory outcome/number evaluable; CI = confidence interval				

Adapted from DORI-10 study report, Table 15

Table 26 shows clinical outcomes at the TOC visit in the CE population according to geographic region, duration of mechanical ventilation at baseline, baseline APACHE II

score, and demographic group. In North America, cure rates were substantially higher for patients in the doripenem arm (75.5%) than for patients in the imipenem/cilastatin arm (58.0%), while in Europe and other regions, cure rates were lower in the doripenem arm (pooled cure rate 63.0% for doripenem vs. 69.4% for imipenem/cilastatin). The applicant stated that "no clear explanation for this finding was found." Cure rates were higher for patients with late-onset VAP than for those with early-onset VAP. For patients with baseline APACHE II scores ≤15, cure rates were similar between arms, while for patients with baseline APACHE II scores >15, cure rates were higher for those treated with doripenem (68.7% vs. 60.7%). Cure rates in age and racial subgroups were similar in both arms. Cure rates were higher for female patients in the doripenem arm than for those in the imipenem/cilastatin arm.

Table 26. Clinical Outcomes at Test of Cure (Clinically Evaluable Subgroups)

	Doripenem		Imipenem/cilastatin		Difference	
	n/N	(%)	n/N	(%)	%	(95% CI)
Region						
North America	40/53	(75.5)	29/50	(58.0)	17.5	(-2.4, 37.3)
Europe	31/47	(66.0)	34/47	(72.3)	-6.4	(-27.1, 14.4)
Other	15/26	(57.7)	16/25	(64.0)	-6.3	
Days of mechanical ventilation at baseline						
Late-onset (≥5 d)	58/78	(74.4)	52/73	(71.2)	3.1	(-12.4, 18.7)
Early-onset (<5 d)	28/48	(58.3)	27/49	(55.1)	3.2	(-18.5, 25.0)
Baseline APACHE II						
≤15	40/59	(67.8)	42/61	(68.9)	-1.1	(-19.4, 17.3)
>15	46/67	(68.7)	37/61	(60.7)	8.0	(-10.1, 26.1)
Age (y)						
<65	61/87	(70.1)	58/90	(64.4)	5.7	(-9.3, 20.6)
≥65	25/39	(64.1)	21/32	(65.6)	-1.5	(-26.7, 23.6)
Sex						
Male	67/102	(65.7)	59/91	(64.8)	0.9	(-13.6, 15.3)
Female	19/24	(79.2)	20/31	(64.5)	14.7	
Race						
White	72/108	(66.7)	71/106	(67.0)	-0.3	(-13.9, 13.2)
Black	9/12	(75.0)	6/8	(75.0)	0.0	
Hispanic or Latino	4/5	(80.0)	1/4	(25.0)	55.0	
Other	1/1	(100.0)	1/4	(25.0)	75.0	

n/N = number with satisfactory outcome/number evaluable
CI = confidence interval

Adapted from DORI-10 study report, Table 17

Table 27 shows an analysis submitted by the applicant of clinical outcomes in microbiologically evaluable patients. As discussed above, the applicant failed to collect and submit Gram stain data confirming the acceptability of lower respiratory tract culture specimens.

Table 27. Clinical Outcomes at Test of Cure (Microbiologically Evaluable and Microbiologic MITT)

Analysis set	Doripenem n/N (%)	Imipenem/cilastatin n/N (%)	Difference % (95% CI)
Microbiologically evaluable	80/116 (69.0)	71/110 (64.5)	4.4 (-8.7, 17.6)
Microbiologic MITT	117/202 (57.9)	118/201 (58.7)	-0.8 (-10.9, 9.3)
n/N = number with satisfactory outcome/number evaluable; CI = confidence interval			

Adapted from DORI-10 study report, Table 15

Twenty-three patients in the microbiologically evaluable population had baseline bacteremia; 13 of these patients had the same pathogen isolated from the respiratory tract. Cure rates were 67% (4/6) for doripenem-treated patients and 43% (3/7) for imipenem/cilastatin-treated patients.

Clinical relapse rates at the late follow-up visit were low in both groups: 7.5% (4/53) in the doripenem arm and 7.8% (4/55) in the piperacillin/tazobactam arm.

Table 28 shows all-cause mortality in the ITT population at various intervals. Mortality during each interval was similar in the groups.

Table 28. All-Cause Mortality (Intent-to-Treat)

Time	Doripenem (N=262) n (%)	Imipenem/cilastatin (N=263) n (%)	Relative Risk (Dori/Imipenem) (95% CI)
During iv therapy	13 (5.0)	14 (5.3)	0.9 (0.4, 1.9)
Days 1-28	30 (11.5)	26 (9.9)	1.2 (0.7, 1.9)
During therapy + 30 days	34 (13.0)	32 (12.2)	1.1 (0.7, 1.7)
CI = confidence interval using a continuity correction			

Microbiologic Outcomes

The two tables in this section show the analyses submitted by the applicant of microbiologic outcomes in microbiologically evaluable patients. As discussed above, the applicant failed to collect and submit Gram stain data confirming the acceptability of lower respiratory tract culture specimens.

Table 29. Microbiologic Outcomes at Test of Cure (Microbiologically Evaluable)

Analysis set	Doripenem n/N (%)	Imipenem/cilastatin n/N (%)	Difference % (95% CI)
Microbiologically evaluable	85/116 (73.3)	74/110 (67.3)	6.0 (-6.8, 18.8)
n/N = number with satisfactory outcome/number evaluable; CI = confidence interval			

Adapted from DORI-10 study report, Attachment 9.2

Table 30 presents the pretreatment pathogen outcomes and clinical response rates at the TOC visit for patients with selected lower respiratory tract isolates. The organisms listed are those in the applicant's proposed label for this indication.

Table 30. Pretreatment Pathogen Outcomes and Clinical Outcomes at Test of Cure (Microbiologically Evaluable)

	Doripenem					Imipenem/cilastatin				
		Pretreatment pathogen outcome		Clinical outcome			Pretreatment pathogen outcome		Clinical outcome	
Pathogen	N	n	%	n	%	N	n	%	n	%
Staphylococcus aureus	20	15	75	10	50	23	17	74	14	61
Streptococcus pneumoniae	9	8	89	4	44	7	7	100	7	100
Haemophilus influenzae	32	25	78	22	69	37	30	81	26	70
Klebsiella pneumoniae	15	12	80	10	67	10	6	60	5	50
Enterobacter cloacae	16	12	75	11	69	10	7	70	7	70
Escherichia coli	12	9	75	9	75	17	10	59	10	59
Pseudomonas aeruginosa	20	13	65	16	80	14	5	36	6	43
Acinetobacter baumannii	7	7	100	7	100	7	6	86	6	86

N = number of patients; n = number with satisfactory outcome

Six patients in the doripenem arm had baseline bacteremia with the same pathogen isolated from the respiratory tract: two with *S. aureus* (one clinical cure and one clinical failure), two with *E. cloacae* (both clinical cures), and one each with *P. aeruginosa* (clinical cure) and *Citrobacter koseri* (clinical failure). Seven patients in the imipenem/cilastatin arm had baseline bacteremia with the same pathogen isolated from the respiratory tract: two with *S. aureus* (both clinical cures), two with *K. pneumoniae* (one clinical cure and one clinical failure), and one each with *H. influenzae*, *P. aeruginosa*, and *Enterobacter aerogenes* (all clinical failures).

SAFETY

Overview

The safety database for doripenem for the indication of NP, including VAP, consisted of two pivotal Phase 3 NP clinical trials supported by six Phase 1 studies in healthy subjects, two Phase 1 studies in patients with renal impairment, one Phase 2 study in hospitalized subjects with cUTI, two Phase 3 clinical trials for cUTI, and two Phase 3 clinical trials for cIAI. Overall, there were a total of 1,338 doripenem-treated patients in the five pooled, comparative, Phase 3 clinical trials involving subjects with cUTI, cIAI, and NP. In the two NP clinical trials, there were a total of 485 doripenem-treated, 221 piperacillin-tazobactam-treated, and 263 imipenem-treated patients. Of the doripenem treated patients, 223 received doripenem 500 mg q8h 1-hour infusion and 262 received doripenem 500 mg q8h 4-hour infusion.

Most patients in both NP clinical trials experienced at least one treatment-emergent adverse event (TEAE) as depicted in Table 31. The cross study frequency of TEAEs was higher in the doripenem 500 mg q8h 4-hr infusion group (95%) from DORI-10 compared to the doripenem 500 mg q8h 1-hr infusion group (76.7%) from DORI-09. However, the frequencies of TEAEs for the two treatment arms within DORI-09 and DORI-10 were similar. Assessment of the clinical significance of the cross study disparity in the frequency of TEAEs between the two doripenem groups was confounded by the inherent disparities in demographics between the two clinical trials study populations, the lack of substantial within study differences between the treatment arms, and the overall low incidence of TEAEs. Patients enrolled in DORI-10 had more severe underlying illnesses, longer ICU stays, younger median age, and higher APACHE scores compared to DORI-09.

The overall rates of serious and drug-related TEAEs were com parable across the treatment arms within the two NP studies. There were more deaths in the doripenem 500 mg q8h 1-hr infusion group compared to the doripenem 500 mg q8h 4-hr infusion group. This finding can be attributed in part to the greater number of older persons in DORI-09 (45.3% were ≥ 65 years old) compared to DORI-10 (29.5% were ≥ 65 years old) and possibly to the larger number of subjects who died or experienced serious TEAEs due to pneumonia in DORI-09 compared to DORI-10.

Table 31: FDA Medical Officer's Summary of the Frequency of AEs, TEAEs, and Deaths, DORI-09 and DORI-10, ITT Population

	DORI-09		DORI-10	
	Doripenem N=223 n (%)	Pip/Tazo N=221 n (%)	Doripenem N=262 n (%)	Imipenem N=263 n (%)
≥1 adverse event	171 (76.7)	172 (77.8)	249 (95)	238 (90.5)
Treatment-emergent adverse events (TEAE)	171 (76.7)	172 (77.8)	249 (95)	238 (90.5)
Drug-related TEAE (Investigator designated)	36 (16.1)	39 (17.6)	45 (17.2)	46 (17.5)
Serious TEAE	67 (30)	58 (26.2)	70 (26.7)	72 (27.4)
Deaths as a TEAE	43 (19.3)	39 (17.6)	35 (13.4)	32 (12.2)
All-cause mortality	45 (20.2)*	39 (17.6)	35 (13.4)	33 (12.5)**

*Two patients died after having received ≤1 day of study drug.
**One patient died after having received ≤2 days of study drug.

Discontinuations due to Treatment-emergent Adverse Events

As depicted in the following table, the discontinuation rate due to TEAEs was slightly higher in the piperacillin/tazobactam group compared to the doripenem group in DORI-09 and in the doripenem group compared to the imipenem group in DORI-10. The discontinuations due to drug-related TEAEs were similar among the treatment arms of both studies. Serious TEAEs accounted for more discontinuations in the comparator arm of DORI-09, whereas the incidence of discontinuation due to serious TEAEs was similar among the doripenem and comparator arms in DORI-10.

Table 32: FDA Medical Officer's Summary of Discontinuations of Subjects, DORI-09 and DORI-10, ITT

	DORI-09		DORI-10	
	Doripenem N=223 n,(%)	Pip/Tazo N=221 n,(%)	Doripenem N=262 n,(%)	Imipenem N=263 n,(%)
Discontinuations due to TEAE	9 (4.0)	14 (6.3)	17 (6.5)	15 (5.7)
Discontinuations due to drug-related TEAE (Investigator designated)	3 (1.3)	3 (1.4)	8 (3.1)	7 (2.7)
Discontinuations due to a Serious TEAE	5 (2.2)	11 (5.0)	9 (3.4)	8 (3.0)

Table 33: FDA Medical Officer's Summary of Discontinuations of Subjects stratified by System Organ Class, DORI-09 and DORI-10, ITT

	DORI-09		DORI-10	
Study Drug	Dori	Pip/Taz	Dori	Imi
Total Subjects, n (%), ITT	223 (100%)	221 (100%)	262 (100%)	263 (100%)
# Subjects discontinued due to any TEAE, n (%)	9 (4.0%)	14 (6.3%)	17 (6.5%)	15 (5.7%)
Blood and Lymphatic System Disorders	0	1 (0.5%)	0	0
Cardiac Disorders	0	0	1 (0.4%)	0
Ear and Labyrinth	0	0	0	0
Gastrointestinal	1 (0.4%)	3 (1.4%)	1 (0.4%)	0
General Disorders and Administration Site	0	1 (0.5%)	0	2 (0.8%)
Hepatobiliary Disorders	0	0	1 (0.4%)	0
Immune System	0	0	0	0
Infections and Infestations	3 (1.3%)	4 (1.8%)	5 (1.9%)	6 (2.3%)
Injury, Poisoning, and Procedural Complications	0	0	0	0
Investigations	0	0	4 (1.5%)	1 (0.4%)
Metabolism and Nutrition	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	0	0	0	0
Neoplasms benign, malignant, and unspecified	0	1 (0.5%)	0	0
Nervous System Disorders	0	2 (0.9%)	1 (0.4%)	4 (1.5%)
Psychiatric Disorders	1 (0.4%)	0	0	0
Renal and Urinary Disorders	1 (0.4%)	0	1 (0.4%)	0
Reproductive System and Breast Disorders	0	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders	4 (1.8%)	1 (0.5%)	0	0
Skin and Subcutaneous Disorders	0	1 (0.5%)	2 (0.8%)	2 (0.8%)
Surgical and Medical Procedures	0	0	1 (0.4%)	0
Vascular Disorders	0	1 (0.5%)	2 (0.2%)	0

Dori=doripenem, Imi=imipenem, Pip/Taz=piperacillin/tazobactam

Among the adverse events leading to subject discontinuation in DORI-09, diarrhea was noted in three subjects. One doripenem-treated subject (# 20506058) and two piperacillin/tazobactam-treated subjects developed diarrhea (#50006112 and 92902042). None of those cases was assessed as serious in nature or severe in quality. Other adverse events that were assessed by investigators as related or possibly related to study drug included bronchospasm and anxiety in two doripenem-treated patients and angioneurotic edema in a piperacillin/tazobactam-treated patient.

Among the adverse events leading to subject discontinuation in DORI-10, one of the six doripenem-treated subjects experienced severe diarrhea (Subject # 50204507) and two experienced adverse drug reactions (ADR) that were assessed as serious in nature, including rash (Subject # 00306039) and liver function test abnormal (Subject # 50203025). Four imipenem-treated subjects experienced serious ADRs, including rash (Subject # 14701027 and 20706041) and convulsions (Subject # 12302574 and 21106513). The rash experienced by subject # 14701027 (erythema multiforme) and the convulsion experienced by subject # 21106513 were assessed as severe in quality. Other adverse events that were assessed by investigators as related or possibly related to study drug included increased cholesterol, acute renal failure, hypotension, and abdominal pain in doripenem-treated patients and pyrexia, tremor, and increased hepatic enzymes in imipenem-treated patients.

Mortality Data

In the NP studies, there was a total of 78 deaths in the pooled doripenem groups (43 in DORI-09 and 35 in DORI-10) and 71 deaths in the pooled comparator groups (39 in the piperacillin/tazobactam and 32 in the imipenem treatment groups) assessed as TEAEs. The mortality rates in each treatment group within the individual studies were comparable. In terms of all-cause mortality, there were two additional deaths in the doripenem group in DORI-09 and one additional death in the imipenem group in DORI-10 (see Table 31 above). None of the deaths were attributable to an adverse drug reaction or study drug intolerance.

Patient Deaths in DORI-09:

Pneumonia was the most frequent cause for death among the doripenem 500 mg q8h 1-hour infusion group, whereas septic shock was the most frequent cause for death in the piperacillin-tazobactam treated patients. There was an imbalance in the number of patients who died from pneumonia in the doripenem treatment arm (9 deaths) compared to the piperacillin-tazobactam arm (1 death). Many of the deaths due to pneumonia among the doripenem-treated patients were study subjects assessed as clinical failures, indeterminate outcomes, or relapses at their final study visit (EOT, TOC, or LFU), a finding suggestive of a lack of study drug efficacy. One subject in the piperacillin/tazobactam group (subject # 30303019) died before receiving study drug.

Patient Deaths in DORI-10:

Respiratory failure was the most frequent cause for death among the doripenem 500 mg q8h 4-hour infusion group, whereas multiple organ failure was the most frequent cause for death in the imipenem-treated patients. In contrast to the DORI-09 experience,

pneumonia was an infrequent cause for death in both treatment groups (one doripenem-treated and two imipenem-treated subjects), and no imbalance in the frequency of pneumonia-related deaths was observed. Respiratory failure was an expected event considering that most all subjects in the study were receiving mechanical ventilatory support. One subject in the imipenem group (subject # 80906035) died before receiving study drug.

Serious TEAEs

Among all subjects in DORI-09, the most frequent serious TEAEs involved the system organ classes Infections and Infestations (13.5% doripenem vs 8.6% for comparator) and Respiratory, thoracic, and mediastinal disorders (9.9% for doripenem vs 6.3% of comparator) with higher frequencies observed in the doripenem group. These findings are illustrated in the table below.

Table 34: FDA Medical Officer Summary Table of Serious TEAEs stratified by System Organ Class (SOC) for DORI-09, ITT

System Organ Class	Dori N=223	Pip/Taz N=221
	n (%)	n (%)
Blood and lymphatic system disorders	0 (0.0)	1 (0.5)
Cardiac disorders	9 (4.0)	7 (3.2)
Gastrointestinal disorders	6 (2.7)	13 (5.9)
General disorders and administration site conditions	3 (1.3)	5 (2.3)
Infections and infestations	30 (13.5)	19 (8.6)
Injury, poisoning and procedural complications	1 (0.4)	1 (0.5)
Investigations	0 (0.0)	1 (0.5)
Metabolism and nutrition disorders	2 (0.9)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1 (0.5)
Nervous system disorders	6 (2.7)	11 (5.0)
Renal and urinary disorders	3 (1.3)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	22 (9.9)	14 (6.3)
Vascular disorders	1 (0.4)	2 (0.9)

In the Infections and Infestations SOC, there was a marked imbalance with a higher number of subjects having pneumonia in the doripenem treatment arm (12/223, 5.38%) compared to the piperacillin/tazobactam arm (3/221, 1.36%). Many of those subjects were assessed as clinical failures indicative of a lack of study drug efficacy. The Respiratory, Thoracic, and Mediastinal Disorders SOC predominantly involved subjects with respiratory failure and acute respiratory failure (pooled frequencies of 3.6% [8/223] for doripenem and 1.4% [3/221] for piperacillin/tazobactam). In addition, there were three subjects who experienced renal failure and acute renal failure as a serious TEAE in the doripenem group compared to one subject in the piperacillin/tazobactam group. One piperacillin/tazobactam treated subject experienced a convulsion, whereas no doripenem-treated subjects developed seizures assessed as serious TEAEs in DORI-09.

In DORI-10, the most frequently reported serious TEAEs involved the SOCs Infections and Infestations (7.3% doripenem vs 9.5% for comparator) and Respiratory, Thoracic, and Mediastinal Disorders (7.3% for doripenem vs 6.8% of comparator). These findings are illustrated in the table below.

Table 35: FDA Medical Officer Summary Table of Serious TEAEs stratified by System Organ Class for DORI-10, ITT

System Organ System	Dori N=262	Imi N=263
	n (%)	n (%)
Cardiac disorders	11 (4.2)	16 (6.1)
Gastrointestinal disorders	6 (2.3)	7 (2.7)
General disorders and administration site conditions	5 (1.9)	7 (2.7)
Hepatobiliary disorders	1 (0.4)	0 (0.0)
Infections and infestations	19 (7.3)	25 (9.5)
Injury, poisoning and procedural complications	4 (1.5)	5 (1.9)
Investigations	1 (0.4)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	0 (0.0)
Nervous system disorders	14 (5.3)	11 (4.2)
Psychiatric disorders	1 (0.4)	0 (0.0)
Renal and urinary disorders	3 (1.1)	4 (1.5)
Respiratory, thoracic and mediastinal disorders	19 (7.3)	18 (6.8)
Skin and subcutaneous tissue disorders	1 (0.4)	3 (1.1
Vascular disorders	6 (2.3)	5 (1.9)

In the Infections and Infestations SOC, sepsis was the most frequently reported serious TEAE with both treatment groups having comparable incidences (2.3% each). In contrast to the DORI-09 experience, there was no imbalance in the number of subjects having pneumonia in DORI-10. The frequency of pneumonia as a serious TEAE was less frequent in the doripenem group (0.6%) compared to the imipenem group (1.9%) in DORI-10. The Respiratory, Thoracic, and Mediastinal Disorders SOC predominantly involved subjects with respiratory failure and acute respiratory failure (pooled frequencies of 2.3% [6/262] for doripenem and 2.7% [7/263] for imipenem). In addition, there were three subjects who experienced renal failure and acute renal failure as a serious TEAE in the doripenem group compared to four subjects in the imipenem group. Three imipenem-treated subjects experienced a convulsion, whereas two doripenem-treated subjects developed seizures assessed as serious TEAEs in DORI-10.

Common TEAEs

The most commonly reported TEAEs in the pooled doripenem 500 mg (1-h + 4-h inf) group were reported at rates that were within range of those reported for the comparator groups. The only TEAE that occurred in the doripenem 500 mg (1-h + 4-h inf) treatment group at a rate >2% higher than in both comparator groups was pneumonia, which occurred in 5.4% of subjects in the pooled doripenem group, 2.7% in the piperacillin/tazobactam group, and 3.0% in the imipenem group. The following table illustrates this data. Causality has not been established in all instances.

Table 36: FDA Medical Officer Table of all TEAEs with frequency >5% in pooled doripenem and comparator groups, DORI-09 and DORI-10, ITT

Preferred Term	Pooled Dori 500 mg 1 hr & 4 hr infusion	Dori 500mg q8h 1 hr infusion	Dori 500 mg q8h 4 hr infusion	Imipenem	Pip/Taz
Diarrhea	58 (11.96%)	22 (9.87%)	36 (13.74%)	45 (17.11%)	24 (10.86%)
Urinary tract infection	44 (9.07%)	11 (4.93%)	33 (12.60%)	39 (14.83%)	7 (3.17%)
Decubitus ulcer	42 (8.66%)	10 (4.48%)	32 (12.21%)	19 (7.22%)	11 (4.98%)
Constipation	38 (7.84%)	9 (4.04%)	29 (11.07%)	31 (11.79%)	5 (2.26%)
Vomiting	34 (7.01%)	13 (5.83%)	21 (8.02%)	20 (7.60%)	3 (1.36%)
Nausea	33 (6.80%)	4 (1.79%)	29 (11.07%)	28 (10.65%)	7 (3.17%)
Insomnia	31 (6.39%)	5 (2.24%)	26 (9.92%)	30 (11.41%)	6 (2.71%)
Anemia	29 (5.98%)	15 (6.73%)	14 (5.34%)	12 (4.56%)	24 (10.86%)
Hypotension	27 (5.57%)	12 (5.38%)	15 (5.73%)	19 (7.22%)	7 (3.17%)
Agitation	27 (5.57%)	9 (4.04%)	18 (6.87%)	18 (6.84%)	6 (2.71%)
Pneumonia	26 (5.36%)	17 (7.62%)	9 (3.44%)	8 (3.04%)	6 (2.71%)
Rash	26 (5.36%)	5 (2.24%)	21 (8.02%)	13 (4.94%)	3 (1.36%)

Across all treatment groups, the most commonly reported TEAEs were within the Infections and Infestations SOC and Gastrointestinal Disorders SOC; the rates of events in these SOCs for the pooled doripenem 500 mg (1-h + 4-h inf) treatment group were within the range of the comparator groups. The most commonly reported AEs in the doripenem 500 mg (1-h + 4-h inf) group were diarrhea (12.0%), UTI (9.1%), and decubitus ulcer (8.7%). Each of these events in the doripenem 500 mg (1-h + 4-h inf) treatment group was within the range of the comparator groups: 10.9%, 3.2%, and 5.0%, respectively, in the piperacillin/tazobactam group, and 17.1%, 14.8%, and 7.2%, respectively, in the imipenem group. The incidence of phlebitis was low in the NP studies: 2.1% in the doripenem 500 mg (1-h + 4-h inf) group, 2.3% in the piperacillin/tazobactam group, and 0.8% in the imipenem group.

Adverse Drug Reactions (ADR):

Adverse drug effects that have been reasonably associated with the use of doripenem are summarized in the table of adverse drug reactions below. The incidence of elevated hepatic enzymes is overestimated in this approach and can be better assessed based on objective hepatic enzyme laboratory data (not shown).

Table 37: FDA Medical Officer Summary of the frequency of Adverse Drug Reactions (ADR) stratified by Treatment Group, DORI-09 and -10, ITT

		Dori 500 mg q8h 1-h inf N=223	Pip/Taz N=221	Dori 500 mg q8h 4-h inf N=262	Imipenem N=263
ADR	n	n (%)	n (%)	n (%)	n (%)
C difficile colitis	13	1 (0.4%)	2 (0.9%)	4 (1.5%)	6 (2.3%)
Diarrhea	127	22 (9.9%)	24 (10.9%)	36 (13.7%)	45 (17.1%)
Elevated hepatic enzymes	51	12 (5.4%)	10 (4.5%)	19 (7.3%)	10 (3.8%)
Headache	27	8 (3.6%)	5 (2.3%)	6 (2.3%)	8 (3.0%)
Hypersensitivity	1	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Nausea	68	4 (1.8%)	7 (3.2%)	29 (11.1%)	28 (10.6%)
Oral candidiasis	20	2 (0.9%)	1 (0.5%)	11 (4.2%)	6 (2.3%)
Phlebitis	17	9 (4.0%)	5 (2.3%)	1 (0.4%)	2 (0.8%)
Pruritus	13	1 (0.4%)	1 (0.5%)	6 (2.3%)	5 (1.9%)
Rash	54	8 (3.6%)	7 (3.2%)	23 (8.8%)	16 (6.1%)
Seizures	22	3 (1.3%)	6 (2.7%)	3 (1.1%)	10 (3.8%)
Vulvomycotic infection	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

Review of Selected TEAEs

Convulsions/Seizures:

In the doripenem Phase 3 clinical trials encompassing cUTIs, cIAIs, and NP, a total of 23 study subjects experienced seizures including one levofloxacin-treated, no meropenem-treated, six doripenem-treated, six piperacillin-tazobactam-treated, and 10 imipenem-treated subjects. All of the doripenem-treated subjects who developed seizures in the Phase 3 clinical trials had participated in one of the NP trials. Four of the six doripenem-treated affected subjects had a pre-disposing primary brain/central nervous system condition or a history of epilepsy. Of the two subjects who did not have a primary central nervous system condition or a history of epilepsy, one had a negative rechallenge with doripenem and the other patient had received theophylline, which has been associated with seizure development.

Various reports in the medical literature have described an interaction between carbapenem antibiotics and valproic acid in which patients administered both drugs concomitantly experienced sub-therapeutic serum valproic acid levels with an increased risk of seizure. In the doripenem NP clinical trials, 16 subjects received valproic acid as a concomitant or prior medication, including three treated with doripenem 500 mg q8h 1-hr infusion, one treated with piperacillin/tazobactam, and six each treated with doripenem 500 mg q8h 4-hr infusion and imipenem. One doripenem-treated and one imipenem-treated subject experienced a seizure during the study. The seizure reported in the doripenem-treated subject occurred as a post-treatment event three days after completion of study drug therapy. In order to assess the potential for interactions between doripenem and valproic acid, the Sponsor plans to conduct a Phase 1 study to evaluate changes in plasma valproic acid levels when the drug is co-administered with doripenem.

Renal Failure/Renal Impairment:

In the doripenem phase 3 NP clinical trials, 35 subjects experienced 38 renal failure or renal impairment-related TEAEs. There were 18 affected subjects in DORI-09 (9 doripenem-treated and 9 piperacillin-tazobactam treated subjects) and 17 in DORI-10 (8 doripenem-treated and 9 imipenem treated subjects). However, causality assessment in relation to study drug was confounded by multiple factors, including age (many of the affected patients were elderly), serious underlying medical disorders, and high incidence of exposure to diuretics and concomitant nephrotoxic antibiotics (vancomycin and aminoglycosides) that could have predisposed subjects to develop renal impairment.

Cardiac Adverse Events:

Overall, bradycardia was the most common cardiac TEAE reported in all treatment groups in the two comparative NP clinical trials. Within the NP studies, cardiac adverse events were reported more frequently in DORI-10 compared to DORI-09, but the frequency of such events was comparable between the two treatment arms of DORI-10. There were no episodes of QT prolongation among the doripenem-treated subjects in the various phase 3 clinical trials. One doripenem-treated subject (#905–02007) in DORI-09 developed non-fatal torsades de pointes that was unrelated to study drug exposure. The

adverse event occurred on Day 7 of an 11 day course of doripenem, and did not recur despite continued exposure to the drug. Haloperidol appeared to be the most probable drug associated with the onset of torsades de pointes; no further episodes occurred once that drug had been discontinued.

Safety Review of Laboratory Data:

Missing Safety Laboratory Data:
In the Clinical Study Report for DORI-09, the Sponsor identified several Eastern Europe regions and sites that experienced significant logistical issues with the pick-up, transportation, and shipment of the safety laboratory samples. Several corrective action plans were implemented by the Sponsor and regional CROs to address the ongoing courier issue, but a substantial number of safety laboratory samples from those sites were either lost or did not arrive at the Central Laboratory within the acceptable time window for accurate testing. As a result, laboratory data for those subjects was counted as missing.

In total, 191 subjects were enrolled in DORI-09 from four Eastern European countries [Belarus (6), Ukraine (40), Georgia (29), and Russia (116)], accounting for 43% of all patients in the safety population for the clinical trial. Overall, study subjects from Eastern Europe were missing at least one screening lab test most frequently. When stratified by country, at least one screening laboratory test result was missing in 68% of subjects from Ukraine and 50% from Belarus. At least one test-of-cure (TOC) laboratory test result was missing for 83% of subjects from Georgia. There were few missing end-of-therapy and late follow-up test results. Complete screening safety laboratory tests (chemistry, hematology, and urinalysis) were missing for 52.2% of subjects from the Ukraine and approximately 80% of the TOC safety laboratory data was missing for subjects enrolled from Georgia. Among subjects from Russian sites, about 36% were missing complete safety lab data for at least one post-screening on-therapy study visit (through end-of therapy). Due to the missing safety laboratory data as described above, the overall assessment of potential safety signals is underestimated for on-therapy and TOC visits. The effect of missing screening safety lab results (although greater in magnitude compared to later study visits) is less critical, as patients had not yet been exposed to study drug. It is unlikely that a common, major safety signal would not be identified. However, for rare adverse events, the overall safety data should be considered incomplete and may not adequately reflect a complete assessment of all of the potentially valid safety signals.

Hy's High Rule for Hepatotoxicity:
Two sets of criteria were used to identify study subjects as fulfilling Hy's High Rule (HHR). The original criteria involved concurrent evidence of an elevated serum ALT value >3 x ULN and an elevated total bilirubin value >1.5 x ULN. The second (modified HHR) criteria added the exclusion of subjects with evidence of biliary obstruction evidenced by an elevated serum alkaline phosphatase >1.5 x ULN concurrent with the elevations in ALT and total bilirubin already described.

The percentage of subjects who fulfilled the original HHR criteria in the pooled doripenem 500 mg (1-hr and 4-hr inf) group at baseline or post-baseline was 1.1% (20/1761), which was within range of the various comparator group experience: 0.3% (1/372) for levofloxacin, 0.6% (3/469) for meropenem, 1.4% (3/221) for piperacillin/tazobactam, and 3.8% (10/263) for imipenem. The percentage of subjects who fulfilled the modified HHR criteria in the pooled doripenem 500 mg (1-hr and 4-hr inf) group at any time post-baseline was 0.3% (6/1761), which was within range of the various comparator group experience: 0.0% (0/372) for levofloxacin, 0.2% (1/469) for meropenem, 0.9% (2/221) for piperacillin/tazobactam, and 1.1% (3/263) for imipenem. Although there was no clear evidence to implicate doripenem as the causative agent for any of the HHR cases, assessment was confounded by serious underlying illnesses, concomitant hepatotoxic medications, and limited diagnostic evaluations in some patients.

Serum Chemistry Laboratory Test Abnormalities:
In DORI-09, most subjects had toxicity Grade 0 or Grade 1 for baseline serum chemistry parameters, and they were maintained throughout the study. Shifts to higher toxicity grades from baseline were most frequently observed with respect to serum ALT, AST, and alkaline phosphatase in both treatment groups. A similar pattern of serum chemistry abnormalities was reported in both treatment groups in DORI-10.

In order to further assess the overall doripenem Phase 3 database for laboratory test safety signals, the incidence of abnormal results for selected chemistry tests using thresholds selected by the FDA Medical Officer are summarized in the following table:

Table 38: FDA Medical Officer Table: Incidence of abnormal post-baseline chemistry test results* for subjects with normal baseline values, doripenem comparative clinical trials for cUTI, cIAI, and NP, ITT

		DORI-05		DORI-07 and DORI-08		DORI-09		DORI-10	
Chemistry Test	Toxicity Threshold	Dori 500 mg N=376	Levo N=372	Pooled Dori N=477	Pooled Mero N=469	Dori 500 mg 1-hr inf N=223	Pip/Taz N=221	Dori 500 mg 4-hr inf N=262	Imipenem N=263
AST/SGOT	>3x ULN	4 (1.1)	3 (0.8)	12 (2.5)	13 (2.8)	6 (2.7)	7 (3.2)	16 (6.1)	14 (5.3)
ALT/SGPT	>3 x ULN	13 (3.5)	7 (1.9)	22 (4.6)	25 (5.3)	14 (6.3)	10 (4.5)	22 (8.4)	22 (8.4)
Alk Phos	>400 U/L	1 (0.3)	4 (1.1)	12 (2.5)	9 (1.9)	10 (4.5)	4 (1.8)	14 (5.3)	11 (4.2)
Bilirubin, total	>2 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CPK, total	>3xULN	2 (0.5)	5 (1.3)	37 (7.8)	35 (7.5)	7(3.1)	4 (1.8)	12 (4.6)*	3 (1.1)*
Calcium L	<1 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Calcium-H	>1 x ULN	39 (10.4)	38 (10.2)	46 (9.6)	48 (10.2)	5 (2.2)	8 (3.6)	4 (1.5)	7 (2.7)
Glucose-L	<50 mg/dl	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glucose-H	>250 mg/dl	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phos-L	<1 x ULN	1 (0.3)	0 (0.0)	0 (.0)	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Phos-H	>2 x ULN	4 (1.1)	4 (1.1)	2 (0.4)	6 (1.2)	0 (0.0)	2 (0.9)	3 (1.1)	2 (0.7)
Potassium-L	<1 x ULN	18 (4.8)	23 (6.2)	64 (13.4)	56 (11.9)	22 (9.9)	23 (10.4)	20 (7.6)	16 (6.1)
Potassium-H	>1 x ULN	26 (6.9)	23 (6.2)	42 (8.8)	37 (7.9)	21 (9.4)	11 (5.0)	10 (3.8)	16 (6.1)
Sodium-L	<1 x ULN	19 (5.1)	15 (4.0)	33 (6.9)	45 (9.6)	41 (18.4)	27 (12.2)	28 (10.7)	22 (8.4)
Sodium-H	>1 x ULN	15 (4.0)	14 (3.8)	21 (4.4)	25 (5.3)	21 (9.4)	19 (8.6)	19 (7.3)	28 (10.6)
Uric acid –H	>1 x ULN	99 (26.3)	104 (28.0)	78 (16.4)	77 (16.4)	36 (16.1)	35 (15.8)	20 (7.6)	30 (11.4)

Statistically significant difference: P=0.02; -L=low, -H=high; *excludes subjects with missing baseline data
Dori=doripenem, Levo=levofloxacin, Mero=meropenem, Imi=imipenem, Pip/Taz=piperacillin/tazobactam

As depicted above, there were no statistically significant differences between the treatment arms in terms of the incidence of the select laboratory test abnormalities for study DORI-05 (cUTI) and pooled studies DORI-07/08 (cIAI). However, a marked imbalance in the comparative number of subjects in DORI-10 (NP) who exhibited a total CPK elevation >3 x ULN from a normal baseline CPK level was observed: 4.6% (12/262) in the doripenem group compared to 1.1% (3/263) in the imipenem group. Half of the 12 affected doripenem-treated subjects had CPK elevations that subsequently improved despite continued exposure to the drug, which is suggestive of a negative rechallenge. In the remaining cases, although there was a temporal association with doripenem administration, the subjects had concurrent serious traumatic brain injuries, surgical procedures, or psychotic agitation that could possibly account for the CPK elevations reported. Two imipenem-treated subjects exhibited negative rechallenge, whereas one subject developed rhabdomyolysis in the context of concurrent use of two drugs with a known propensity to induce myopathy.

Hematology Laboratory Test Abnormalities:

In DORI-09, most subjects had toxicity Grade 0 or Grade 1 baseline hematology parameters and maintained them during the study. Shifts to higher grades appeared to be most frequent with respect to WBC count (maximum#) in most treatment arms. No doripenem-treated subjects had a Grade 0 (baseline) to Grade 4 (post-baseline) shift in hematology parameters. There was one piperacillin/tazobactam treated subject who had a maximum shift in WBC count from Grade 0 at baseline to Grade 4.

In DORI-10, most subjects had Grade 0 or Grade 1 baseline hematology parameters and maintained them during the study. Shifts to higher grades appeared to be most frequent with respect to WBC count (maximum#). Shifts from Grade 0 at baseline to Grade 4 as maximum post-baseline grade in hematology parameters revealed one subject in the imipenem treatment arm who had a maximum shift in hemoglobin from Grade 0 at baseline to Grade 4 and one subject who received doripenem who had a maximum shift in WBC count from Grade 0 at baseline to Grade 4. The doripenem-treated subject who had a maximum shift in WBC count from Grade 0 at baseline to Grade 4 (Subject # 12302047) was a 57 year old black male with multiple trauma, intracranial hemorrhage, and respiratory failure who was treated with doripenem for 8 days for early-onset VAP. He had a slight total WBC elevation on Day 5 followed by progressive elevation to a peak of 43.7 x 10^9/L at TOC (day 14). A CT scan on Day 18 revealed an empyema, and a thoracotomy on Day 20 revealed necrotizing pneumonia. The WBC elevation observed post-treatment with doripenem likely reflected a reactive leukocytosis due to the serious underlying lung infection complications encountered in this patient, and could not be clearly attributed to an adverse reaction from the drug.

Exploratory Analysis of Doripenem 500 mg Infusion Duration Dependency and the Incidence of TEAEs:

In the Phase 3 NP studies, the doripenem 500 mg dose was infused i.v. over one hour in DORI-09, whereas it was administered i.v. over 4 hours in DORI-10. The Sponsor's rationale for the prolonged infusion time in DORI-10 was to enhance coverage of potentially less susceptible bacteria associated with VAP (such as *P. aeruginosa*) by improving target attainment (% Time > MIC) for organisms with doripenem MIC ≤4 µg/mL. This approach was based on Phase 1 pharmacokinetic data, surveillance MIC values for clinically relevant organisms, and pharmacokinetic/pharmacodynamic targets assumed from non-clinical infection models.

Table 39: FDA Medical Officer Summary Table of the frequency distribution of treatment-emergent adverse events observed among doripenem and comparator-treated subjects in DORI-09 and DORI-10 (based on AE frequency ≥5% in the doripenem 500 mg q8h 4-hr infusion group), ITT

Adverse Event	Dori 500 mg q8h 1-h inf N=223	Dori 500 mg q8h 4-h inf N=262	Imi N=263	Pip/Taz N=221
Diarrhoea	22 (9.87%)	36 (13.74%)	45 (17.11%)	24 (10.86%)
Urinary tract infection	11 (4.93%)	33 (12.60%)	39 (14.83%)	7 (3.17%)
Decubitus ulcer	10 (4.48%)	32 (12.21%)	19 (7.22%)	11 (4.98%)
Constipation	9 (4.04%)	29 (11.07%)	31 (11.79%)	5 (2.26%)
Nausea	4 (1.79%)	29 (11.07%)	28 (10.65%)	7 (3.17%)
Insomnia	5 (2.24%)	26 (9.92%)	30 (11.41%)	6 (2.71%)
Vomiting	13 (5.83%)	21 (8.02%)	20 (7.60%)	3 (1.36%)
Rash	5 (2.24%)	21 (8.02%)	13 (4.94%)	3 (1.36%)
Agitation	9 (4.04%)	18 (6.87%)	18 (6.84%)	6 (2.71%)
Hepatic enzyme increased	5 (2.24%)	17 (6.49%)	9 (3.42%)	2 (0.90%)
Depression	3 (1.35%)	16 (6.11%)	17 (6.46%)	4 (1.81%)
Hypotension	12 (5.38%)	15 (5.73%)	19 (7.22%)	7 (3.17%)
Deep vein thrombosis	1 (0.45%)	15 (5.73%)	17 (6.46%)	0 (0.00%)
Anaemia	15 (6.73%)	14 (5.34%)	12 (4.56%)	24 (10.86%)

Dori=doripenem; Pip/Taz=piperacillin/tazobactam; Imi=imipenem

As is evident from the table above, diarrhea was the most common TEAE (frequency of approximately 10% or more) in the doripenem 500 mg 1-hr and 4-hr infusion time groups and both comparator groups in the NP clinical trials. Overall, gastrointestinal tract-related adverse events (diarrhea, constipation, vomiting, and nausea) were more common in both treatment arms of DORI-10 compared to the two treatment arms of DORI-09.

In examining the cross study frequencies of the TEAEs between the doripenem 500 mg q8h 1-hr infusion group in DORI-09 and the doripenem 500 mg q8h 4-hr infusion group in DORI-10, some notable differences were evident. There were higher incidences of the following TEAEs in the doripenem 500 mg 4-hr infusion group compared to the 500 mg 1-hr infusion group: UTI (12.6% vs 4.9%), decubitus ulcer (12.2% vs 4.5%), insomnia (9.9% vs 2.2%), rash (8.0% vs 2.2%), increased hepatic enzymes (6.5% vs 2.2%), depression (6.2% vs 1.4%), deep vein thrombosis (5.7% vs 0.5%), and oral candidiasis (4.4% vs 0.9%). In contrast, there was a higher frequency of pneumonia as a TEAE in the 500 mg 1-hr infusion group (7.6%) compared to the 500 mg 4-hr infusion group (3.4%), and the difference was statistically significant ($p = 0.04$). However, despite the cross study differences described above, there were no statistically significant differences in the frequencies of those TEAEs between the doripenem and comparator treatment groups within each clinical trial. This pattern of cross study differences that were not buttressed by within study differences was most notable with respect to rash, increased hepatic enzymes, and oral candidiasis. Those three TEAEs were reported at cross study frequencies that were statistically significantly different between the doripenem 500 mg q8h 1-hour and 4-hour infusion groups (rash: $p = 0.005$; increased hepatic enzymes: $p = 0.03$; oral candidiasis: $p = 0.02$), but the within study differences between the doripenem and comparator treatment arms were not statistically significantly different.

The capacity to assess causality in relation to the two doripenem infusion regimens based on the cross study comparisons of the frequencies of the various TEAEs described above was limited. The study populations of DORI-09 and DORI-10 differed with respect to multiple factors which made direct comparisons difficult, including patient demographics, co-morbid diseases, use of potentially nephrotoxic and hepatotoxic concurrent medications, and the severity of the underlying pneumonia. The disparity in the frequency of pneumonia between the doripenem 500 mg 4-hr infusion group compared to the 500 mg 1-hr infusion group appeared to relate to a lack of efficacy of the doripenem 500 mg 1-hour infusion regimen in the treatment of NP in the DORI-09 trial rather than indicating a novel safety signal. In addition, except for gastrointestinal tract-related TEAEs, the overall adverse event rates were low. Thus, although there were cross study differences, the lack of substantial within-study differences in the TEAE rates, the low frequency of adverse events, and the inherent disparities between the individual clinical trial populations made it difficult to draw definitive conclusions. As the safety experience with the doripenem 500 mg q8h 4-hour infusion regimen was limited (262 subjects in DORI-10) compared to the experience with the doripenem 1-hour infusion regimen (1,076 subjects in the five pooled, comparative, Phase 3 clinical trials for cUTI, cIAI, and NP), further post-marketing safety surveillance with respect to the doripenem 500 mg q8h 4-hour infusion is recommended.

ISSUES FOR DISCUSSION

1. Non-inferiority Margin Justification

- Is there sufficient scientific justification to support the Applicant's proposed non-inferiority clinical trial design with a non-inferiority margin of 20% in nosocomial pneumonia, including ventilator-associated pneumonia?
    - Has the treatment effect of antibacterials been adequately quantified and been found to be larger than the proposed 20% margin in order to assure that the drug is more effective than placebo?
    - Given the proposed margin, is it reasonable to accept this level of loss in efficacy and still be considered non-inferior to the active comparator considering the seriousness of the disease?
    - Does the Committee recommend a different non-inferiority margin for this indication? If so, what is the recommended margin?
    - Does the Committee recommend an alternative study design?

2. Clinical Efficacy

- Has the clinical efficacy of doripenem at a dosage of 500 mg 1-hour i.v. infusion been adequately demonstrated in patients with nosocomial pneumonia, including ventilator-associated pneumonia?
- Has the clinical efficacy of doripenem at a dosage of 500 mg 4-hour i.v. infusion been adequately demonstrated in patients with ventilator-associated pneumonia who are at risk for infections with less susceptible bacterial pathogens?

3. Clinical Safety (Risk):

- Based on the overall safety profile, is doripenem safe for use in the proposed indication (i.e., nosocomial pneumonia, including ventilator-associated pneumonia):
    - at a dosage of 500 mg 1-hour i.v. infusion for the proposed 7-14 day treatment duration?
    - at a dosage of 500 mg 4-hour i.v. infusion for patients who are at risk for infections with less susceptible bacterial pathogens for the proposed 7-14 day treatment duration?

4. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP:

- Can the Committee provide guidance regarding the design of future clinical trials for this indication related to the following issues:
    - Selection of appropriate study populations for NP and VAP (Proportion of VAP patients)
    - Diagnostic criteria for NP and VAP (clinical, radiologic, and microbiologic)
    - Primary endpoint (mortality, clinical response, etc.)
    - Co-primary analysis populations (ITT or MITT, CE, or ME), need to enrich for *Pseudomonas aeruginosa* at baseline
    - Use of concomitant antimicrobial agents
    - Oral switch option and the ability to estimate the treatment effect

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APPENDIX

Table A-1. Doripenem and Meropenem MICs from Patients Who Were Clinical Failures (DORI-09, Doripenem Cohort)

		DOR MICs mcg/mL		MER MICs mcg/mL		(DOR) STEP	(MER) STEP
PATIENT ID	ORGANISM	INITIAL	FINAL	INITIAL	FINAL	INCREASE	INCREASE
17306512	*A. baumannii*	>128	ND	>128	ND	0	ND
31003040	*A. baumannii*	1	ND	0.5	ND	ND	ND
19706124	*K. pneumoniae*	0.06	ND	0.06	ND	0	ND
92102505	*K. pneumoniae*	0.03	ND	0.03	ND	ND	ND
94101007	*E. aerogenes*	0.06	0.12	0.06	0.06	1	1
31003040	*E. coli*	0.03	ND	0.03	ND	ND	ND
401045202	*E. coli*	0.03	ND	≤0.015	ND	ND	ND
40503005	*P. aeruginosa*	0.25	ND	0.12	ND	ND	ND
31004017	*P. aeruginosa*	0.25	8	0.25	8	5	5
19705001	*P. aeruginosa*	1	1	2	2	0	0
94101007	*S. aureus*	1	16	2	32	4	4
17306127	*S. aureus*	0.12	ND	0.25	ND	ND	ND
30003000	*S. aureus*	>32	ND	>32	ND	ND	ND
40503021	*S. aureus*	32	ND	64	ND	ND	ND
40503506	*S. aureus*	0.03	0.03	0.06	0.06	0	ND

Note: all *S. aureus* isolates were methicillin-resistant

Table A-2. Doripenem and Meropenem MICs from Patients Who Were Clinical Failures (DORI-09, Piperacillin-Tazobactam Cohort)

		DOR MICs mcg/mL		MER MICs mcg/mL		(DOR) STEP	(MER) STEP
PATIENT ID	ORGANISM	INITIAL	FINAL	INITIAL	FINAL	INCREASE	INCREASE
17306132	*A. baumannii*	128	ND	128	ND	ND	ND
18506142	*A. baumannii*	0.5	ND	1	ND	ND	ND
19706514	*A. baumannii*	0.5	ND	0.5	ND	ND	ND
30003026	*A. baumannii*	2	ND	1	ND	ND	ND
19005008	*P. aeruginosa*	0.12	ND	0.06	ND	ND	ND
19205005	*P. aeruginosa*	0.12	0.25	0.12	0.25	0	0
30104505	*P. aeruginosa*	0.25	1	0.12	1	2	3
31204022	*P. aeruginosa*	4	ND	8	ND	ND	ND
40503033	*P. aeruginosa*	0.06	ND	0.03	ND	ND	ND
60706000	*P. aeruginosa*	0.03	0.12	≤0.015	0.06	2	2
19005008	*K. pneumoniae*	0.06	0.12	≤0.015	0.06	1	2
30603500	*K. pneumoniae*	0.06	ND	0.03	ND	ND	ND
31104512	*K. pneumoniae*	0.03	ND	0.03	ND	ND	ND
40103009	*K. pneumoniae*	0.25	0.5	0.25	0.25	1	0
40503033	*K. pneumoniae*	0.25	ND	0.25	ND	ND	ND
400504004	*K. pneumoniae*	0.06	ND	≤0.015	ND	ND	ND
30603500	*E. cloacae*	0.06	ND	0.03	ND	ND	ND
31104512	*M. morganii*	1	ND	0.25	ND	ND	ND
93102011	*E. faecalis*	4	ND	4	ND	ND	ND
40103526	*H. influenzae*	0.03	ND	0.06	ND	ND	ND
40503010	*H. influenzae*	0.12	ND	0.06	ND	ND	ND
93201503	*S. aureus*	4	2	4	4	0	0
31203529	*S. aureus*	32	ND	32	ND	ND	ND

18006044	*S. aureus*	32	ND	64	ND	ND	ND

Table A-3. Doripenem and Meropenem MICs from Patients Who Were Clinical Failures (DORI-10, Doripenem Cohort)

		DOR MICs mcg/mL		MER MICs mcg/mL		(DOR) STEP	(MER) STEP
PATIENT ID	ORGANISM	INITIAL	FINAL	INITIAL	FINAL	INCREASE	INCREASE
70406526	*M. morganii*	0.25	ND	0.12	ND	ND	ND
70406526	*K. pneumoniae*	0.03	ND	≤0.015	ND	ND	ND
50103015	*K. pneumoniae*	0.06	ND	0.03	ND	0	0
1606555	*E. cloacae*	≤0.015	≤0.015	≤0.015	≤0.015	0	0
3605538	*E. cloacae*	0.03	0.06	0.03	0.03	1	1
13202052	*E. cloacae*	≤0.015	ND	≤0.015	ND	ND	ND
1606555	*E. coli*	≤0.015	≤0.015	≤0.015	≤0.015	0	0
1806506	*E. coli*	0.03	0.03	0.03	≤0.015	0	0
20406014	*E. coli*	≤0.015	≤0.015	≤0.015	≤0.015	0	0
75306002	*P. aeruginosa*	1	1	2	1	0	0
80205535	*P. aeruginosa*	0.12	16	0.5	16	7	5
12302047	*P. aeruginosa*	0.12	0.25	0.12	0.25	1	1
20106531	*P. aeruginosa*	4	ND	8	ND	ND	ND
21006042	*P. aeruginosa*	2	ND	2	ND	ND	ND
405015	*S. aureus*	≤0.015	64	0.06	64	8	10
13202052	*S. aureus*	≤0.015	0.5	0.06	1	5	4
14402559	*S. aureus**	0.12	0.12	0.25	0.25	0	0
21005510	*S. aureus*	0.03	ND	0.06	ND	ND	ND
21206558	*S. aureus*	≤0.015	≤0.015	0.06	0.06	0	0
50103015	*S. aureus**	32	32	32	32	0	0
50103509	*S. aureus**	16	16	32	32	0	0
51304009	*S. aureus*	0.03	0.03	0.06	0.06	0	0
12302061	*H. influenzae*	0.12	0.12	0.06	0.12	0	1
21105532	*H. influenzae*	0.25	0.25	0.06	0.06	0	0
14402559	*H. influenzae*	0.25	ND	0.06	ND	ND	ND
50203018	*H. influenzae*	0.06	0.06	0.03	0.25	0	3
15202031	*H. influenzae*	0.12	ND	0.12	ND	ND	ND
15202031	*S. pneumoniae*	0.25	ND	0.25	ND	ND	ND

*Methicillin-resistant *S. aureus*

Table A-4. Doripenem and Meropenem MICs from Patients Who Were Clinical Failures (DORI-10, Imipenem Cohort)

		DOR MICs mcg/mL		MER MICs mcg/mL		(DOR) STEP	(MER) STEP
PATIENT ID	ORGANISM	INITIAL	FINAL	INITIAL	FINAL	INCREASE	INCREASE
70405520	*S. marcescens*	0.06	0.06	0.03	0.03	0	0
13802053	*E. coli*	0.03	≤0.015	≤0.015	≤0.015	**0**	**0**
14401015	*E. coli*	0.03	ND	0.03	ND	ND	ND
12802521	*E. coli*	0.03	ND	<0.015	ND	ND	ND
12401009	*E. coli*	≤0.015	ND	<0.015	ND	ND	ND
12301505	*E. coli*	0.03	0.03	<0.015	≤0.015	0	0
50104508	*A. baumannii*	0.25	0.5	0.5	1	1	1
14302042	*H. influenzae*	0.06	0.06	≤0.015	≤0.015	0	0
60104518	*H. influenzae*	0.06	0.12	0.06	0.06	1	0
21105524	*H. influenzae*	0.06	0.25	0.03	0.06	2	0
15212030	*H. influenzae*	0.06	ND	0.03	ND	ND	ND
80905533	*K. pneumoniae*	0.03	0.03	0.03	0.03	0	0
50203504	*K. pneumoniae*	0.03	0.03	0.03	<0.015	ND	ND
14402503	*K. pneumoniae*	0.06	ND	0.03	ND	ND	ND
12802521	*K. pneumoniae*	0.03	ND	0.06	ND	ND	ND
70406529	*K. oxytoca*	0.03	0.03	0.03	0.03	0	0
11102537	*K. oxytoca*	0.03	ND	0.03	ND	ND	ND
14401015	*E. aerogenes*	0.06	ND	0.06	ND	ND	ND
11102537	*E. aerogenes*	0.06	ND	0.06	ND	ND	ND
10701005	*E. aerogenes*	0.06	0.12	0.03	0.03	0	0
15202032	*E. cloacae*	0.03	ND	0.03	ND	0	0
12802521	*E. cloacae*	0.06	ND	0.03	ND	0	0
1806010	*E. cloacae*	0.06	0.06	0.06	0.06	0	0
70406529	*P. aeruginosa*	0.5	0.5	0.5	0.25	0	0
50203023	*P. aeruginosa*	0.25	0.12	0.12	0.12	0	0
21106542	*P. aeruginosa*	0.25	4	0.25	4	4	4
20106530	*P. aeruginosa*	0.25	0.12	0.12	0.12	0	0
20106220	*P. aeruginosa*	1	8	0.5	8	3	4
14401015	*P. aeruginosa*	0.12	0.12	0.06	0.06	0	0
13201026	*P. aeruginosa*	8	8	8	16	0	1
1506524	*P. aeruginosa*	0.25	4	0.25	4	4	4
10701003	*P. aeruginosa*	8	8	8	32	0	2
11102029	*P. aeruginosa*	0.12	0.12	0.12	0.12	0	0
11102537	*P. aeruginosa*	0.12	4	0.12	4	5	5
12802549	*Pseudomonas* spp	<0.015	ND	≤0.015	ND	ND	ND
805019	*S. aureus*	<0.015	≤0.015	0.06	0.06	0	0
1806510	*S. aureus*	0.03	≤0.015	0.12	0.06	0	0
12301505	*S. aureus*	0.03	0.03	0.06	0.06	0	0
13802053	*S. aureus*	0.03	ND	0.06	ND	ND	ND
14401015	*S. aureus**	0.25	0.25	0.25	0.5	0	1
14402503	*S. aureus*	0.03	ND	0.06	ND	ND	ND
15202032	*S. aureus**	0.12	ND	0.25	ND	ND	ND
50104508	*S. aureus**	16	16	32	32	0	0
50204501	*S. aureus**	16	8	32	16	0	0
70405519*	*S. aureus*	≤0.015	ND	0.06	ND	ND	ND