Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Doripenem for Injection for the Treatment of Nosocomial Pneumonia

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Meeting of Anti-Infective Drugs Advisory Committee
July 16, 2008

Advisory Committee Briefing Book

JNJ-38174942 (Doripenem)
NDA 22-171

Issue/Report Date: 13 JUNE 2008
Prepared by: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Department: Drug Development
Document No.: EDMS-PSDB-8416352: 3.0

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
BEC	blinded evaluation committee
CE	clinically evaluable
CFU	colony forming units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cIAI	complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institute
cMITT	clinical modified intent-to-treat
CNS	central nervous system
CPIS	Clinical Pulmonary Infection Score
CPMP	Committee for Proprietary Medicinal Products
CrCl	creatinine clearance
cUTI	complicated urinary tract infection
DHP-I	dehydropeptidase-I
EOT	end of therapy
EOT(i.v.)	end of therapy (intravenous)
ESBL	extended spectrum β-lactamase
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GLP	Good Laboratory Practice
HAP	hospital-acquired pneumonia
HHR	Hy's High Risk Classification
IC_{50}	concentrations resulting in 50% inhibition
ICH	International Conference on Harmonisation
ICU	intensive care unit
IDSA	Infectious Disease Society of America
ITT	intent-to-treat
i.v.	intravenous
IVRS	Interactive Voice Response System
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development, L. L. C.
LFU	late follow-up
LRT	lower respiratory tract
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
mMITT	microbiological modified intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NDA	New Drug Application

ABBREVIATIONS AND DEFINITIONS OF TERMS (CONTINUED)

Abbreviation	Explanation
NOAEL	no observed adverse effect level
NP	nosocomial pneumonia
OECD	Organisation for Economic Co-operation and Development
PAE	post-antibiotic effect
PBP	penicillin-binding protein
PD	pharmacodynamic
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PPI	Peninsula Pharmaceuticals, Inc.
PRSP	penicillin-resistant *Streptococcus pneumoniae*
q6h	every 6 hours
q8h	every 8 hours
qd	once daily
Shionogi	Shionogi & Co., Ltd.
TEAE	treatment-emergent adverse event
TOC	test-of-cure
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
WBC	white blood cell count

Definitions of Terms

Term	Definition of Term
Acute Physiology & Chronic Health Evaluation II (APACHE II)	The APACHE II is a severity of disease classification system that uses a point score based upon initial values of 12 routine physiological measurements, age, and previous health status to provide a general measure of disease severity and prediction of outcome.
$AUC_{0-\infty}$	Area under the curve from time zero to infinite time
Clinical Pulmonary Infection Score (CPIS)	This 5-item instrument was used to monitor signs and symptoms of pneumonia to determine a diagnosis of pneumonia in ventilated patients and to determine their clinical progress. The components included tracheal secretions, chest x-ray infiltrates, core/rectal temperature (°C), leukocytes (per mm^3), and arterial oxygen pressure (PaO_2)/fraction of inspired oxygen (FiO_2) (mmHg).
C_{max}	maximum concentration
Δ_{50}	Estimated 50% preservation of benefit over placebo: $C_{ll} - P_p) / 2$, C_{ll} by DerSimonian and Laird – weighted non-iterative estimates
MIC_{50}	minimum inhibitory concentration for 50% of strains
MIC_{90}	minimum inhibitory concentration for 90% of strains
P_c	Estimated proportion cured (cure rate) for comparator
PC	Pneumonia Clinical Definition: This was the same as the PS definition (see definition below) except that the diagnosis of an infiltrate was based only on the "chest X-ray" page of the case report form. Thus, for this definition, the investigator's interpretation over-ruled the radiologist's report, in the few cases where they were discrepant. In addition, other clinical and laboratory findings

ABBREVIATIONS AND DEFINITIONS OF TERMS (CONTINUED)

	(e.g., culture results) not stipulated in the inclusion criteria were considered in support of the diagnosis. The inclusion criteria for temperature and WBC count at screening were based on the case report form where inhouse source documentation was not available.
PS	Pneumonia Strict Definition: Patients had supporting data inhouse for all the inclusion criteria relevant to the diagnosis of pneumonia defined in the protocol, as described above. In particular, these patients had a independent radiologist's report (or equivalent), confirming the presence of pulmonary infiltrates consistent with pneumonia. This was required regardless of evidence from other sources, such as the investigator's interpretation of the X-ray and other clinical findings. Patients with missing radiology reports (except where these were routinely not produced) were excluded from this definition.
P_p	Estimated proportion cured (cure rate) for placebo
Treatment-Emergent Adverse Event (TEAE)	TEAEs were defined as those adverse events (AEs) that first occurred (or worsened) after the date and time of the start of administration of the first dose of i.v. study drug therapy and up to 30 days after the last dose of study drug therapy (i.v. or oral).
T>MIC	time above minimum inhibitory concentration
$t_{1/2}$	elimination half-life
V_{ss}	steady-state volume of distribution

ADVISORY COMMITTEE BRIEFING BOOK

1. EXECUTIVE SUMMARY

1.1. Introduction

The Food and Drug Administration (FDA) approved doripenem on 12 October 2007, under the tradename DORIBAX™, for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) for a variety of gram-positive and gram-negative pathogens (Section 2.1). Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD; the Sponsor) submitted a New Drug Application (NDA) on 5 June 2007 for the treatment of nosocomial pneumonia (NP), including ventilator associated pneumonia (VAP), which is the focus of this Advisory Committee meeting.

Nosocomial pneumonia is caused by a broad-range of bacteria, and is associated with a high risk of morbidity and mortality, especially in mechanically-ventilated patients. Resistant pathogens, and especially multidrug-resistant strains, can be associated with increased morbidity and mortality (Section 2.2).[1]

The carbapenems, such as imipenem and meropenem, are frequently used and highly regarded therapies for NP, although meropenem is not approved for use in NP.[1] Doripenem has many similarities to the other carbapenems, as well as some important differences, such as greater potency against *Pseudomonas aeruginosa* (Section 4.4). These characteristics suggest the agent will be useful in NP, particularly for patients in the intensive care unit (ICU), who have an increased risk for infection with *P. aeruginosa* and often have conditions with an increased increased risk for seizures, such as head trauma or intracranial hemorrhage. A number of preclinical studies suggest a reduced risk for seizures with doripenem in comparison to other carbapenems (Section 5.3.3.5).

1.2. Microbiology

Doripenem is a carbapenem that has broad antibacterial potency against aerobic and anaerobic gram-positive and gram-negative bacteria (Section 4). Doripenem shares the bactericidal mode of action of other β-lactam antibiotics by targeting penicillin-binding proteins (PBPs) to inhibit the biosynthesis of the bacterial cell wall. Doripenem is resistant to hydrolysis by most β-lactamases, including

penicillinases, cephalosporinases, and extended-spectrum β-lactamases (ESBLs). As is the case with other carbapenem antibiotics, doripenem is unstable against carbapenemases such as the KPC serine carbapenemases or the metallo-β-lactamases produced by *Stenotrophomonas maltophilia* and *P. aeruginosa*. The frequency of in vitro doripenem resistance selection in *P. aeruginosa* is lower than that of other anti-pseudomonal antibiotics; resistance profiles are similar to those seen with other anti-pseudomonal β-lactam antibiotics.

Doripenem exhibits time-dependent bactericidal activity against common pathogens and has a persistent in vitro and in vivo post-antibiotic effect (PAE). In vitro synergy tests with doripenem show limited potential to antagonize or be antagonized by other antibiotics (i.e., levofloxacin, amikacin, trimethoprim-sulfamethoxazole, daptomycin, linezolid, and vancomycin). Doripenem is effective in various animal models of infection including pulmonary models caused by both gram-positive and gram-negative bacteria. Time above the minimum inhibitory concentration (T>MIC) is the definitive pharmacodynamic index, as for other carbapenems. In the mouse neutropenic thigh model, the mean doripenem %T>MIC values for stasis ranged from 12% to 29%. To achieve a 1 or 2 $\log_{10}$ reduction of bacterial counts, mean doripenem mean %T>MIC values of 21% to 36% or 27% to 43%, respectively, were required (Table 3).

1.3. Preclinical

In vitro studies in human liver microsomes and hepatocytes indicate that doripenem does not inhibit or induce the major cytochrome P450 isoenzymes. Therefore, doripenem is not expected to affect the clearance of drugs that are metabolized by cytochrome P450 mediated pathways.

The toxicity of doripenem has been characterized in single- and repeat-dose intravenous (i.v.) toxicity studies, inhalation toxicity, genotoxicity, reproductive and developmental toxicity, and safety pharmacology studies. Additional information has been obtained from in vitro and in vivo studies designed to assess hepatotoxicity, phototoxicity, antigenic potential in mice and in guinea pigs, injection local tolerance in rabbits, in vitro and in vivo hemolytic potential (direct Coombs' test in human and dog red blood cells) and seizure potential in various in vitro and in vivo models.

Doripenem did not affect the central nervous, cardiovascular, gastrointestinal, autonomic nervous, smooth muscle or urinary systems. Doripenem also showed lower propensity to cause seizure and renal toxicity when compared to other cabapenems. In addition, doripenem showed no evidence of mutagenic, reproductive, developmental or liver toxicity, immunotoxicity, phototoxicity or local irritation.

1.4. Clinical Pharmacology

Doripenem exhibits linear and time-independent pharmacokinetics over a dose range of 500 mg to 1 g when intravenously infused over either 1 or 4 hours (Section 6). Doripenem is rapidly distributed in the extracellular fluid compartment of tissues. The major metabolite of doripenem is a microbiologically inactive β-lactam ring-opened compound (designated doripenem-M-1), which is likely formed by dehydropeptidase-I (DHP-I). The mean doripenem elimination half-life is approximately 1 hour. Doripenem is primarily eliminated unchanged by the kidneys, with approximately 70% and 15% of an administered 500 mg dose recovered in the urine as doripenem and doripenem-M-1, respectively.

1.5. Clinical

1.5.1. Phase 3 Study Designs

Two multicenter, prospective, randomized, open-label, active-controlled Phase 3 studies of the safety and efficacy of doripenem in patients with NP, DORI-09 and DORI-10, were conducted (Section 7). The patient populations enrolled in the 2 trials encompassed the broad range of patients seen in this indication. In both studies, patients were male or female, 18 years of age or older, with clinical, radiological and microbiological evidence of NP.

Placebo-controlled trials were not considered appropriate in this severely ill population due to ethical concerns of high rates of morbidity and mortality in untreated patients.[1] The decision to conduct Studies DORI-09 and DORI-10 as open-label studies was based on a number of barriers to blinding (discussed in detail in Section 7.2.4). Because the studies were open-label, the Sponsor employed several measures to ensure the objectivity of measurements and assessments, including in-house blinding of data in both studies. In addition, in DORI-09, an external blinded evaluation committee (BEC) evaluated the unblinded assessments made by the investigators. There was a high concordance rate (98%) between investigator and BEC outcome assessments.

In DORI-09, a total of 448 patients with NP who were not ventilated (non-VAP) or with early-onset VAP (ventilated <5 days) were randomized equally (1:1) to 1 of 2 treatment groups: 1) i.v. doripenem 500 mg every 8 hours (q8h) (1-hour infusion), or 2) i.v. piperacillin/tazobactam 4.5 g every six hours (q6h) (30 min infusion). In DORI-10, 531 patients with early- or late-onset VAP were randomized equally (1:1) to 1 of 2 treatment groups: 1) i.v. doripenem 500 mg q8h (4-hour infusion), or 2) i.v. imipenem 500 mg q6h (30 min infusion) or 1,000 mg q8h (1-hour infusion). The 4-hour doripenem infusion was used in DORI-10 because patients in this study were at higher risk for infection with less susceptible pathogens. As it was not possible to select 1 imipenem dosing regimen that would have been acceptable at all sites, investigators in DORI-10 were allowed to select from 2 dosage regimens based on the usual practice at their institution and per country-approved label or guidelines. The 2 imipenem dosing regimens used in DORI-10 are considered to be pharmacodynamically equivalent.[2] Adjunctive amikacin was generally recommended in DORI-09 but was optional in DORI-10 based on the risk for *P. eruginosa* infection. In both studies adjunctive vancomycin was allowed if MRSA was suspected.

Published experience in the patient populations that best approximated the population defined by the inclusion/exclusion criteria in the 2 pivotal studies was evaluated to estimate the benefit of comparators over placebo. A noninferiority margin of 20% in these studies was prespecified in the protocols. The primary efficacy analysis was the comparison of clinical cure (defined in Section 7.2.5) rates at the test-of-cure (TOC) visit (conducted 6 to 20 days after the completion of all study drug therapy, including oral levofloxacin in DORI-09) in clinically evaluable (CE) patients. The coprimary efficacy analysis was the comparison of clinical cure rates in the clinical modified intent-to-treat (cMITT) analysis set (defined in Section 7.3.1).

1.5.2. Results

Both Phase 3 studies met their primary objective, the establishment of noninferiority between doripenem and the respective comparator treatment in the clinical cure rate at the TOC visit in CE patients (Section 7.4). In DORI-09, the cure rate among non-VAP and early onset-VAP patients in the CE analysis set who received doripenem was 81.3% compared with 79.8% in those who received piperacillin/tazobactam. The corresponding treatment difference was 1.5% with a 2-sided 95% confidence interval (CI) of -9.1% to 12.1%. In DORI-10, the clinical cure rate among VAP patients in the CE analysis set who

received doripenem was 68.3%, while for those who received imipenem, the cure rate was 64.8%. The corresponding treatment difference was 3.5%, with a 2-sided 95% CI of -9.1% to 16.1%. The lower limits of both confidence intervals (-9.1%) were well within the prespecified noninferiority margin of 20%. Results in patients in the coprimary cMITT analysis set were consistent with those observed in CE patients, supporting the noninferiority conclusion.

Microbiological cure (eradication or presumed eradication) rates with doripenem at the TOC visit were high overall (78% [Table 35]) and against the major causative pathogens of NP (Table 39), including *Staphylococcus aureus*: 25 of 31, 80.6% (methicillin-susceptible strains); *Streptococcus pneumoniae*: 14 of 16, 87.5%; *P. aeruginosa*: 28 of 38, 73.7%; *Acinetobacter baumannii*: 11 of 13, 84.6%; *Haemophilus influenzae*: 33 of 40, 82.5%; *Klebsiella pneumoniae*: 23 of 29, 79.3%; *Enterobacter cloacae*: 23 of 27, 85.2%; *Escherichia coli*: 16 of 21, 76.2%. Rates of clinical (Table 35, overall rates; Table 39, per pathogen rates) and microbiological cure in gram-negative infections were higher for doripenem versus comparator, although these findings should be interpreted cautiously because of small sample sizes.

Generally, clinical cure rates with doripenem therapy were high against pathogens resistant to other antibacterial agents. In the pooled data, the clinical cure rate with doripenem was 83.3% against the 18 gram-negative bacilli not susceptible to piperacillin/tazobactam, including *A. baumannii*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae* and *P. aeruginosa*, and the clinical cure rate was 50% against the 6 imipenem-resistant strains of *P. aeruginosa* (Table 43). Emergent infections were infrequent in both DORI-09 (3%, doripenem; 6% piperacillin/tazobactam) and DORI-10 (8%, doripenem; 11% imipenem) (Tables 40 and 41). In DORI-09, the emergence of decreased susceptibility (≥4-fold increase in MIC) among baseline pathogens was observed in only 1 *P. aeruginosa* isolate in the doripenem arm, whereas 6 strains with decreased susceptibility (3 *P. aeruginosa* and 3 *K. pneumoniae* isolates) were isolated in the piperacillin/tazobactam arm. Among *P. aeruginosa* pathogens susceptible (MIC≤4 μg/mL) at baseline to study drug received in DORI-10, emergence of decreased susceptibility (≥4-fold increase in MIC) was observed in 10 (36%) of 28 and 10 (53%) of 19 patients in the doripenem and imipenem treatment arms, respectively. Most post-baseline *P. aeruginosa* strains with increased MICs were genotypically identical or closely related to the baseline strain; all 10 post-baseline strains with decreased susceptibility in the imipenem

arm had MICs ≥8 µg/mL, compared with 5 of 10 in the doripenem arm (Table 42).

The adverse event profile observed with doripenem was consistent with the known safety profile of doripenem in approved indications (cUTI, cIAI) and of carbapenems, in general, and was similar to the respective comparator arm in each study (Section 8.2). In addition, among the 969 patients in the ITT analysis set in the Phase 3 NP studies (DORI-09, DORI-10), the overall rate of treatment emergent seizures in the doripenem treatment group was low (6/485; 1.2%) compared with 3.8% (10/263) for imipenem (p=0.031, post hoc comparison using Fisher's Exact Test). Seizures occurred in 2.7% (6/221) of piperacillin/tazobactam-treated patients (difference not statistically significant [p=0.207]).

The results of Studies DORI-09 and DORI-10 support the efficacy and safety of doripenem for i.v. injection in patients 18 years or older with NP, including VAP, and show a favorable benefit to risk profile in this patient population (Section 9).

2. INTRODUCTION

2.1. Regulatory History

Shionogi originated the development of doripenem. On 25 July 2005, the Japanese Health Authority approved doripenem i.v. solution (250 mg twice daily up to a maximum of 1,500 mg/day) for the treatment of a variety of indications, including respiratory tract infections. Doripenem was launched in Japan on 16 September 2005 under the trade name FINIBAX®. Shionogi granted Peninsula Pharmaceuticals, Inc. (PPI) exclusive rights for the development and commercialization in North America and other regions. Peninsula Pharmaceuticals, Inc. initiated clinical development of doripenem for the treatment of moderate to severe bacterial infections under IND 64,416 in December 2002. A Phase 2a meeting was held on 15 December 2003, at which dose selection for the Phase 3 program was discussed. An End of Phase 2 meeting was held with the Division of Anti-Infective and Ophthalmologic Products on 3 May 2004, at which the clinical development program for the study of doripenem in NP, cIAI, and cUTI, including the open-label design and choice of comparators for the NP studies was discussed and agreed to.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., acquired PPI in June 2005. On 01 July 2005, PPI transferred the IND to J&JPRD and

J&JPRD accepted sponsor obligations and responsibility for the doripenem IND 64,416. Since that time J&JPRD has engaged in numerous discussions with the FDA regarding the doripenem NP clinical development program that PPI had initiated. Several of these discussions focused on the important aspects of the NP clinical studies (DORI-09 and DORI-10) design, conduct and/or analyses. The discussions resulted in the following FDA agreements:

- 13 December 2005 Type A Meeting: FDA agreed to use clinical response in the clinically evaluable population as the primary endpoint, rather than the microbiologically evaluable population as specified in the protocol. Further, the FDA noted that for a noninferiority trial, the clinical response in the clinically evaluable population serves as a co-primary endpoint with the clinical response in the intent-to-treat (ITT) population.
- 28 February 2006 Type C Meeting: The FDA indicated that it was amenable to a one-time sample size re-estimation based on the observed inhouse-blinded evaluability rate, provided that the sample size was increased by adding new patients from previous sites who were similar in terms of demographic and clinical characteristics to patients enrolled prior to the sample size increase and that the addition of patients did not increase the original sample size by more than twofold.
- 09 March 2006 Discussion Between the Sponsor and FDA: The FDA indicated agreement with the Sponsor's proposal for a one-time sample size re-estimation based on the observed inhouse-blinded evaluability rate. On the basis of this agreement, study sample sizes were increased from 300 to 440 patients and from 400 to 520 patients in Studies DORI-09 and DORI-10, respectively.

The FDA also provided written comments on the DORI-09 Amendment 2 (26 April 2006), DORI-10 Amendment 2 (31 July 2006) and the Statistical Analysis Plans for both NP studies (11 December 2006, 28 March 2007, and 16 May 2007). The pre-NDA meeting for the planned submission of the cIAI/cUTI and NP NDAs was held on 27 July 2006.

On 12 December 2006, J&JPRD filed NDA 22-106 for the use of doripenem for injection, 500 mg every 8 hours (q8h) by i.v. infusion administered over 1 hour, for the treatment of cIAI and cUTI, including pyelonephritis caused by susceptible isolates of the designated micro-organisms. The FDA granted approval for this application on 12 October 2007 under the tradename DORIBAX™ (doripenem for injection) (see Attachment 1 for approved label). This approval was based on 3 double-blind comparator studies (2 for cIAI and 1 for cUTI) and 1 large single-arm cUTI study. J&JPRD filed a second NDA, 22-171, for the treatment of NP, including VAP, on 5 June 2007. This

application cross-referred to NDA 22-106 for all information except for clinical data associated with NP.

In May 2008, the Committee for Medicinal Products for Human Use (CHMP) of the European Union issued a Positive Opinion for Doripenem for the treatment of NP, including VAP; cIAI; and cUTI.

This briefing book outlines information to be presented at the Anti-Infective Drugs Advisory Committee Meeting on 16 July 2008, the purpose of which is to discuss doripenem, a broad-spectrum carbapenem (β-lactam) antibacterial agent, for which J&JPRD submitted an application to support the use of doripenem for injection in the treatment of patients 18 years of age or older with:

- Nosocomial pneumonia, including ventilator-associated pneumonia, caused by *Staphylococcus aureus* (methicillin-susceptible strains only), *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Enterobacter cloacae*, *Escherichia coli, Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa.*

2.2. Background and Medical Need in NP

Nosocomial pneumonia is the second most common hospital-acquired infection, while VAP is the most common ICU-acquired infection.[3] Nosocomial pneumonia, which is caused by a broad range of bacteria, is associated with a high risk of morbidity, especially in mechanically-ventilated patients. Resistant pathogens, and especially multidrug-resistant strains, can be associated with increased morbidity and mortality.[1] Initial empiric treatment of NP with a broad-spectrum antibacterial regimen that provides coverage against both gram-positive and gram-negative respiratory pathogens started before lower respiratory tract (LRT) culture results are available, decreases morbidity, duration of hospitalization, and costs associated with prolonged hospitalization.[1] The pathogens most frequently encountered in NP include *S. aureus*, *P. aeruginosa*, *K. pneumoniae, E. coli*, *Acinetobacter* species, *H. influenzae*, and *S. pneumoniae*. Because the mortality rate and other complications (e.g., acute respiratory distress syndrome, empyema, and lung abscess) from NP can be high, effective management of these infections requires early diagnosis and treatment with an optimal antibacterial agent with a spectrum of activity broad enough to cover these pathogens. Carbapenems have the broadest spectrum of antibacterial activity among the antimicrobial classes available for the treatment of NP and have good activity against more resistant species, such as

P. eruginosa.[4] As described in the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) Guidelines for therapy of NP,[1] the carbapenems are suitable for monotherapy in this indication because of their broad spectrum of activity against the most common causative pathogens.

The carbapenems, such as imipenem and meropenem, are frequently used and highly regarded therapies for NP, although meropenem is not approved for use in NP. Doripenem has many similarities to the other carbapenems but some differences, such as greater potency against *P. aeruginosa*, which suggest this agent will be particularly useful in NP. Doripenem is active in vitro against the key pathogens associated with NP, including *S. aureus* (methicillin-susceptible *S. aureus* [MSSA]), *Enterobacteriaceae* (e.g., *K. pneumoniae*, *E. coli*, and Enterobacter spp.), *P. aeruginosa*, *A. baumannii*, *H. influenzae*, and *S. pneumoniae*. A detailed discussion of microbiology is found in Section 4. Furthermore, doripenem is highly effective in various animal bacterial infection models, including pneumonia and mouse sepsis protection models. Due to the broad spectrum of antibacterial activity against aerobic pathogens that cause NP, the Sponsor expected that doripenem would be effective in the treatment of NP, including infections caused by pathogens resistant to other antibacterial agents.

Preclinical data suggest that the risk for seizures associated with doripenem is less than that of other carbapenems and that doripenem may possess an improved safety profile, especially in comparison with imipenem, with respect to seizures and related CNS events (refer to Section 8.2.7).

3. OVERVIEW OF BIOPHARMACEUTICS

Doripenem for injection (500 mg) is provided as single-use vials containing 500 mg sterile powder for reconstitution. The drug product contains no inactive ingredients. It is intended for i.v. infusion after reconstitution into a solution. Therefore, no biopharmaceutics studies have been conducted. The drug product used in the Phase 3 clinical studies is identical to the proposed commercial product.

4. MICROBIOLOGY

Doripenem is a carbapenem with broad antibacterial potency against aerobic and anaerobic gram-positive and gram-negative bacteria. It is less potent than imipenem, but more potent than meropenem, against gram-positive bacteria. Against gram-negative bacteria, the activity of doripenem is similar to that of

meropenem and similar to, or more active than, imipenem. Doripenem is generally 2- to 4-fold more potent against *Pseudomonas* isolates than imipenem and meropenem.

Doripenem shares the bactericidal mode of action of other β-lactam antibiotics by targeting PBPs to inhibit the biosynthesis of the bacterial cell wall. It is resistant to hydrolysis by a variety of β-lactamases, including penicillinases, cephalosporinases, and ESBLs. As is the case with other carbapenems, doripenem can be hydrolyzed by serine carbapenemases or the metallo-β-lactamases. The frequency of in vitro resistance selection in *P. aeruginosa* to doripenem is lower than that of other anti-pseudomonal antibiotics.

Doripenem exhibits time-dependent bactericidal activity against common pathogens and exhibits a persistent in vitro and in vivo PAE. In vitro synergy tests with doripenem show doripenem to have little potential to antagonize or be antagonized by other antibiotics. Doripenem is efficacious against both gram-positive and gram-negative bacterial pathogens in multiple bacterial infection models.[5-12] The percentage of the dosing interval that the plasma concentration exceeds the MIC (%T>MIC) is the definitive pharmacodynamic index, as for other carbapenems.

4.1. Mechanism of Action

Doripenem, as a carbapenem, exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential PBPs resulting in subsequent cell death. Carbapenems have high affinity for the PBPs of many bacterial species, but not for methicillin-resistant *Staphylococcus aureus* (MRSA) (PBP2a).[13-15] Although there are some variations, the PBP-binding properties of doripenem are generally comparable to those of other carbapenems.[13-15] Doripenem has high affinities for PBP1, PBP2, and PBP4 of *S. aureus*, but its affinity to PBP2a (MecA) is low, which explains its reduced activity against MRSA. In *E. coli* and *P. aeruginosa*, doripenem binds to PBP2, which is involved in the maintenance of a spherical cell shape, as well as to PBP3 and PBP4. The binding affinity of doripenem to PBP2 of *P. aeruginosa* was stronger than that documented for most cephalosporins.[16]

4.2. Mechanism of Resistance

Bacterial resistance mechanisms that affect doripenem include drug inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired PBPs, decreased outer membrane permeability, and active efflux. Doripenem is stable to hydrolysis by most β-lactamases, including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, but not to carbapenem hydrolyzing β-lactamases.[14,17-20] Carbapenem-resistant strains of *P. aeruginosa*, *Acinetobacter* spp., and some localized *Enterobacteriaceae* isolates that produce metallo-β-lactamases or serine carbapenemases such as the KPC enzymes, or those bacteria that produce chromosomal carbapenemases such as *S. maltophilia* and *Bacillus* spp., have reduced susceptibility to doripenem as well as to the other carbapenems. Doripenem is active (MIC ≤0.5 μg/mL) against *Enterobacteriaceae* that harbor ESBLs, including enzymes in the CTX-M and SHV families collected during doripenem clinical trials.[19] Although cross-resistance with other β-lactams may occur, some isolates resistant to other carbapenems may be susceptible to doripenem .[14, 17-19]

4.3. In Vitro Assessment of Resistance

In studies of resistance development, the bacterial mutation rates leading to resistance for *P. aeruginosa* on exposure to doripenem were generally less than those of the comparator anti-pseudomonal antibiotics, including other carbapenems. Doripenem demonstrated the lowest mutation frequency among the anti-pseudomonal antibiotics tested and, unlike the other antibiotics tested, no resistant mutants could be identified at frequencies as low as $<10^{-9}$ colony forming units (CFU)/mL when organisms were exposed to 8 times the MIC or higher.[21] In addition, multiple passage studies with doripenem and comparators showed that, in general, the magnitude of resistance that developed with doripenem was similar to, or less than, that of imipenem or meropenem.[21,22]

4.4. In Vitro Antibacterial Activity

4.4.1. Antibacterial Spectrum and Minimum Inhibitory Concentrations

The activity of doripenem has been evaluated by many independent investigators against approximately 10,000 clinical isolates from North America, Japan, and Europe.[7,20,23-34]An additional 98,000 isolates have been collected through global surveillance programs (2003-2006) in North America, Latin America, and Europe[35-39] and, during 2005-2006, from the United States (12,581 isolates) and Europe (6,683 isolates)[38] Surveillance data have also been obtained from the

United Kingdom and Ireland during 2005 (2706 isolates).[40] A summary of doripenem's activity against select organisms in North America in 2004 is provided below (Table 1). In addition, the activities of carbapenems against a worldwide collection of multidrug-resistant gram-negative pathogens are presented in Table 2.

4.4.1.1. In Vitro Activity Against Surveillance Isolates

Prospective nonduplicate bacterial isolates deemed clinically relevant from a variety of body sites were collected during the JMI (Laboratories) global surveillance program that included North America, Latin America, and Europe, with approximately 20 sites per geographical region.[35-39] A summary of doripenem's activity during 2004 from the North American sites is provided in Table 1.

In Vitro Activity Against Gram-positive Organisms

For oxacillin-susceptible *S. aureus,* the doripenem MIC_{90} was 0.06 μg/mL (Table 1). The meropenem MIC_{90} value was 2-fold higher at 0.12 μg/mL, and the imipenem MIC_{90} was lower at ≤0.12 μg/mL (the lowest concentration tested).

Against *S. pneumoniae,* including penicillin-resistant pneumococci, doripenem and meropenem MIC_{90} values were 0.5 μg/mL. The corresponding imipenem MIC_{90} value was ≤0.12 μg/mL.

In Vitro Activity Against Gram-negative Organisms

With *Enterobacteriaceae*, generally low MIC values are observed for all carbapenems (Table 1). Against *E. coli,* the MIC_{90} value was 0.03 μg/mL for doripenem, ≤0.06 μg/mL for meropenem (the lowest concentration tested) and 0.25 μg/mL for imipenem. Against *Klebsiella spp.,* the doripenem MIC_{90} value was 0.06 μg/mL and the meropenem MIC_{90} value was ≤0.06 μg/mL with a corresponding higher imipenem MIC_{90} of 0.25 μg/mL. Doripenem and meropenem had similar potency against *Enterobacter* spp., with MIC_{90} values of 0.12 μg/mL, compared to the corresponding value of 1 μg/mL for imipenem. Against *P. mirabilis*, the MIC_{90} values were 0.25 μg/mL for doripenem, 0.12 μg/mL for meropenem and 2 μg/mL for imipenem.

MIC values for the carbapenems against non-fermenters were generally higher than for *Enterobacteriaceae*. For *P. aeruginosa* the doripenem MIC_{90} was

4 μg/mL, compared to the higher meropenem and imipenem MIC_{90} values of 8 μg/mL. For *Acinetobacter spp*., the MIC_{90} value was 16 μg/mL for doripenem and >8 μg/mL for meropenem (the highest concentrated tested), with imipenem the most potent carbapenem, having an MIC_{90} of 4 μg/mL.

Table 1: In Vitro Antibacterial Activity of Doripenem and Select Comparator Agents Against Isolates From North American Surveillance Conducted During 2004

Organism / Antimicrobial Agent	2004 MIC (μg/mL) 90%	2004 MIC (μg/mL) Range
Oxacillin-susceptible *S. aureus* (N=1232)		
Doripenem	0.06	0.016-0.5
Imipenem	≤0.12	≤0.12-1
Meropenem	0.12	≤0.06-1
Piperacillin-tazobactam	2	≤0.5-16
Streptococcus pneumoniae (N=685)		
Doripenem	0.5	≤0.008-2
Imipenem	≤0.12	≤0.12-0.5
Meropenem	0.5	≤0.03-2
Piperacillin-tazobactam	4	≤0.12-16
Escherichia coli (N=965)		
Doripenem	0.03	≤0.008-4
Imipenem	0.25	≤0.12-2
Meropenem	≤0.06	≤0.06-4
Piperacillin-tazobactam	4	≤0.5->64
Klebsiella spp.(N=495)		
Doripenem	0.06	0.016->16
Imipenem	0.25	≤0.12->8
Meropenem	≤0.06	≤0.06->8
Piperacillin-tazobactam	16	≤0.5->64
Enterobacter spp. (N=310)		
Doripenem	0.12	0.016-2
Imipenem	1	≤0.12-4
Meropenem	0.12	≤0.06-4
Piperacillin-tazobactam	64	≤0.5->64
Proteus mirabilis (N=114)		
Doripenem	0.25	0.03-2
Imipenem	2	≤0.12-4
Meropenem	0.12	≤0.06-0.5
Piperacillin-tazobactam	1	≤0.5-16

Note: Data are from the JMI global surveillance program for 2004

(continued)

Table 1: In Vitro Antibacterial Activity of Doripenem and Select Comparator Agents Against Isolates From North American Surveillance Conducted During 2004 (continued)

Organism Antimicrobial Agent	2004 MIC (μg/mL) 90%	 Range
Pseudomonas aeruginosa (N=594)		
Doripenem	4	0.016-16
Imipenem	8	≤0.12->8
Meropenem	8	≤0.06->8
Piperacillin-tazobactam	>64	≤0.5->64
Acinetobacter spp. (N=141)		
Doripenem	16	0.03->16
Imipenem	4	≤0.12->8
Meropenem	>8	≤0.06->8
Piperacillin-tazobactam	>64	≤0.5->64
Haemophilus influenzae (N=456)		
Doripenem	0.5	≤0.008-2
Imipenem	ND	0.25
Meropenem	0.12	≤0.03-0.25
Piperacillin-tazobactam	ND	ND

Key: ND=not determined
Note: Data are from the JMI global surveillance program for 2004

4.4.1.2. In Vitro Activity Against Collections of Resistant Gram Negative P. Aeruginosa and Enterobacteriaceae

Doripenem was tested against a worldwide collection of 394 drug-resistant isolates (Table 2).[23] Doripenem had MICs ≤4 μg/mL against 29.4% of the imipenem- or meropenem-resistant *P. aeruginosa* isolates. One meropenem and no imipenem MIC was ≤4 μg/mL. No carbapenem MIC was <16 μg/mL against the metallo-β-lactamase producing *P. aeruginosa* strains, with the exception of 1 isolate with a doripenem MIC <4 μg/mL. The carbapenems were active against ESBL producing *E. coli* and *K. pneumoniae*. Doripenem was the most active, with MIC_{90} values for *E. coli* of 0.03 μg/mL and *K. pneumoniae* of 0.06 μg/mL. Imipenem was least active, with an MIC_{90} of 0.5 and 0.25 μg/mL for *E. coli* and *K. pneumoniae*, respectively.

Table 2: Activities of Three Carbapenems Against Select Gram-negative Organisms Possessing Various Resistance Mechanisms

Organism (Resistance Mechanism) Carbapenem Tested	N	MIC in μg/mL MIC_{50}	MIC_{90}	% with MIC ≤4 μg/mL
P. aeruginosa (Carbapenem resistant[a])	34			
Doripenem		8	>32	29.4
Imipenem		>8	>8	0
Meropenem		>8	>8	2.9
P. aeruginosa (MβL resistant)[b]	15			
Doripenem		>32	>32	6.7
Imipenem		>8	>8	0
Meropenem		>8	>8	0
K. pneumoniae (ESBL-producing)	34			
Doripenem		0.03	0.06	100
Imipenem		0.12	0.25	100
Meropenem		≤ 0.06	0.12	100
E. coli (ESBL-producing)	29			
Doripenem		≤ 0.015	0.03	100
Imipenem		0.12	0.5	100
Meropenem		≤ 0.06	≤ 0.06	100

[a] Resistance to either imipenem or meropenem at >16 μg/mL
[b] Metallo-β-lactamase resistance due to IMP,VIM, or SPM enzymes

Doripenem and other agents were evaluated against a collection of 600 multidrug-resistant non-fermentative cystic fibrosis isolates.[31] Doripenem was the most active agent. The MIC_{50} for doripenem against 200 *P. aeruginosa* (mucoid), 200 *P. aeruginosa* (nonmucoid), and 200 *Burkholderia cepacia* isolates was 8 μg/mL, whereas the imipenem MIC_{50} was 32 μg/mL. The doripenem MIC_{90} ranged from 32-64 μg/mL and imipenem from 64 to128 μg/mL.

4.4.2. Supportive In Vitro Microbiology Studies

4.4.2.1. Bactericidal Activity

Doripenem is bactericidal for both gram-positive and gram-negative bacteria. Time-kill curves show non-concentration dependent in vitro bactericidal activity. At concentrations of 2 to 4 times the MIC or higher, a 3-log reduction in bacterial load is observed within 6 hours for *E. coli, S. aureus,* and *P. aeruginosa*.[41] Similar cidal activity is observed for *E. faecalis, S. pneumoniae, K. pneumoniae, E. cloacae,* and *Acinetobacter* spp.[42] Bacterial regrowth is prevented with higher drug concentrations (>2 times MIC). Bactericidal activity has also been demonstrated in studies that determined minimum bactericidal concentrations with over 100 clinical isolates, including β-lactamase positive *S. aureus* and *E. coli.*[42,43]

4.4.2.2. Synergy Studies

In vitro synergy tests with doripenem show doripenem has little potential to antagonize or be antagonized by other antibiotics (i.e., levofloxacin, amikacin, trimethoprim-sulfamethoxazole, daptomycin, linezolid, and vancomycin).[44]

4.4.2.3. Post-antibiotic Effects

Doripenem exhibits a species-dependent PAE. It has a moderate PAE (1.8 to 1.9 hours) against *S. aureus* and *P. aeruginosa*;[6] although 1 study demonstrated a relatively short in vitro PAE versus *P. aeruginosa* (0.79 hours).[45] As with other carbapenems, the PAE is typically short against species such as *E. coli* and *K. pneumoniae* (less than 1 hour). In contrast, in vivo, there is a prolonged (6 hour) PAE of doripenem against *P. aeruginosa*.[46] Prolonged in vivo PAE has also been confirmed in a neutropenic mouse thigh infection model with species of *S. aureus*, *S. pneumoniae, K. pneumoniae* and *P. aeruginosa*.[6,47] In *S. aureus* 29213, no PAE was noted with lower doses, although a PAE of 8.2 hours was observed with the higher dose of 37.5 mg/kg.

4.4.3. Animal Infection Models

4.4.3.1. Efficacy in Animal Models

Doripenem is efficacious against both gram-positive and gram-negative bacterial infections including *S. aureus, S. pyogenes, S. pneumoniae, E. faecalis, E. coli, K. pneumoniae, E. cloacae, P. aeruginosa* and *H. influenzae* in various animal models of bacterial infections, including sepsis and pulmonary infection.[5,6,7-12] In pulmonary infection models, doripenem was efficacious against *S. pneumoniae*, including penicillin-resistant *S. pneumoniae* (PRSP) and *P. aeruginosa*. For a penicillin-susceptible *S. pneumoniae* strain (TUH39), doripenem and imipenem

were equally effective and both were twice as effective as meropenem.[7] Against penicillin-resistant *S. pneumoniae* SR11031, doripenem displayed significant activity ($p<0.05$, Dunnet's test) at 3 and 10 mg/kg in reducing the number of viable colonies in mouse lungs. Imipenem showed increased efficacy compared to doripenem and meropenem in this study.[48] As expected, the carbapenems were more efficacious than ceftazidime or ampicillin at 10 mg/k ($p<0.05$, Tukey's test). In ceftazidime-resistant *P. aeruginosa* respiratory infections in neutropenic mice, doripenem, meropenem, and imipenem were equally effective in reducing the viable bacterial count in the lungs of the mice.[48] As expected with this ceftazidime-resistant strain, minimal in vivo activity was observed with ceftazidime.

4.4.3.2. Pharmacokinetics and Pharmacodynamics in Animal Models

The pharmacokinetic parameters and the pharmacodynamic effects of doripenem were characterized in neutropenic mice using the standard procedures established by Andes and Craig.[47]

Determination of the pharmacokinetic parameters revealed that the elimination half-life ($t_{1/2}$) ranged from 0.19 to 0.29 hours and was not dose-related. The $t_{1/2}$ for doses of 9.38, 37.5 and 150 mg/kg were 0.29, 0.19, and 0.22 hours, respectively. The maximum (plasma) concentration (C_{max}) values for these doses were 2.72, 31.9 and 96 µg/mL, respectively, and the areas under the concentration-time curve (AUC) were 1.65, 11.7 and 53.3 µg*h/mL, respectively. Doripenem was approximately 5% protein-bound in mouse plasma, as determined by ultrafiltration.

Multiple dosing regimens of doripenem were evaluated in the mouse neutropenic thigh model to determine the pharmacodynamic effect against selected strains of *S. pneumoniae*, *S. aureus*, *E. coli*, *K. pneumoniae*, *E. cloacae*, and a single strain of *P. aeruginosa.* The in vitro, in vivo, and pharmacodynamic results of doripenem against the tested organisms are found in Table 3.

Against *S. pneumoniae* (n=7), the mean percentages of the dosing interval required for doripenem plasma concentrations to be above the MIC (%T>MIC) to produce stasis, a 1 $\log_{10}$ kill, or a 2 $\log_{10}$ kill of inoculated bacteria were 12%, 21% and 27%, respectively. In 3 strains of *S. aureus*, the doripenem %T>MIC required for microbiologic effect was slightly higher than that needed for eradication of *S. pneumoniae,* with 29%, 32%, and 35% of the dosing interval

required to produce stasis, 1 $\log_{10}$ or 2 $\log_{10}$ decrease, respectively, in the *S. aureus* inoculum.

Doripenem was tested against 10 strains of gram-negative bacteria including *E. coli*, *K. pneumoniae*, *E. cloacae* and *P. aeruginosa*. The percentages of the dosing interval in which plasma concentrations of doripenem were required to be above the MIC to produce 1 $\log_{10}$ and 2 $\log_{10}$ decreases in the inoculum were slightly longer for gram-negative bacteria than for *S. aureus*. Mean values for all tested gram-negative strains were 29%, 36% and 43 % T>MIC to achieve stasis, a 1 $\log_{10}$ and 2 $\log_{10}$ decrease, respectively. The times above MIC required to achieve stasis, a 1 $\log_{10}$ decrease, and a 2 $\log_{10}$ decrease for *P. aeruginosa* were 23%, 28%, and 35% respectively.

In summary, the doripenem mean %T>MIC for stasis ranged from 12% to 29% for the organisms tested. To achieve a 1 or 2 $\log_{10}$ reduction of bacterial counts, doripenem mean %T>MIC values of 21% to 36% and 27% to 43% were needed, respectively.

Table 3: Doripenem In Vitro and In Vivo Activity in the Murine Thigh Infection Model

Organism	Number of Isolates	MIC (μg/mL)	Observed Effect	%T>MIC Mean ± SD[a]	%T>MIC Range
S. pneumoniae	7	0.004-0.50	Stasis	12.4 ± 6.2	2.3-21
			1 Log_{10} Kill	21.1 ± 8.9	10-34
			2 Log_{10} Kill	27.3 ± 11.9	12-47
S. aureus	3	0.015-4	Stasis	29 ± 5.3	25-35
			1 Log_{10} Kill	32.3 ± 6.7	28-40
			2 Log_{10} Kill	35.4 ± 5.0	31-41
Gram-negatives[b]	10	0.015-0.50	Stasis	29 ± 5.3	20-38
			1 Log_{10} Kill	36.1 ± 7.4	27-49
			2 Log_{10} Kill	43.3± 7.1	35-54

[a]Standard deviation
[b]3 *E. coli* , 4 *K. pneumoniae* , 2 *E. cloacae* , 1 *P. aeruginosa*

5. PRECLINICAL

5.1. Overview

A full preclinical package was submitted in support of the first NDA for doripenem, resulting in its approval for the treatment of cIAI/cUTI. Data from that submission, which are reflected in the current labeling (Attachment 1), are summarized below. No additional preclinical studies have been conducted to support the NP program.

All pivotal toxicology studies were performed in accordance with the Good Laboratory Practice (GLP) regulations of the country in which the study was conducted (US FDA, Organisation for Economic Co-operation and Development [OECD], or Japanese Ministry of Health and Welfare). Pharmacokinetic studies were conducted in accordance with Standard Operating Procedures that are in line with the recognized GLP standards of the country where the study was conducted. Pivotal toxicokinetic studies were also conducted in accordance with the principles of GLP.

5.2. Pharmacokinetics

Plasma protein binding of doripenem in animal species ranges from 6.1% to 35.2%, and is 8.1% in humans. The major metabolite of doripenem is a microbiologically inactive-lactam ring-opened compound (doripenem-M-1), which arises from the renal enzyme, DHP-I.

5.2.1. Drug-drug Interaction

In vitro studies in human liver microsomes and hepatocytes indicate that doripenem does not inhibit or induce the major cytochrome P450 isoenzymes. Therefore, doripenem is not expected to inhibit the clearance of drugs that are metabolized by these cytochrome P450 mediated metabolic pathways.

Doripenem is relatively metabolically stable in the presence of recombinant human DHP-I, with a stability much higher than that of imipenem and comparable to that of meropenem (Table 4). Hence, doripenem, as with meropenem and biapenem, can be administered as a monotherapy to humans without the need for coadministration of a DHP-I inhibitor, such as cilastatin.

Table 4: In Vitro Metabolic Stability of Doripenem to Human Renal DHP-I

	Proportion (%) of DHP-I Activity Remaining After Incubation for 90 Minutes		
Human Renal DHP-I (unit/mL)	Doripenem[a]	Meropenem[a]	Imipenem[a]
0.174	87.5	79.1	50.4
0.500	82.4	78.1	23.2

[a] Concentration of 100μg/mL
Note: Recombinant human renal dehydropeptidase-I (DHP-I) was obtained from COS1 cells

5.3. Toxicology

The toxicity of doripenem was characterized in single- and repeat-dose i.v. toxicity studies, inhalation toxicity, genotoxicity, reproductive and developmental toxicity, and safety pharmacology studies. Additional information was obtained from in vitro and in vivo studies designed to assess hepatotoxicity, phototoxicity, antigenic potential in mice and in guinea pigs, injection site local tolerance in rabbits, and in vitro and in vivo hemolytic potential (direct Coombs' test in human and dog red blood cells).

Doripenem did not affect the CNS, cardiovascular system, gastrointestinal system, autonomic nervous system or smooth muscle or urinary system. In addition, doripenem showed no evidence of mutagenic, reproductive, developmental or liver toxicity, immunotoxicity, or local irritation.

In a 1-month dog study with twice daily dosing, the no observed adverse effect level (NOAEL) was the high dose of 200 mg/kg per day. Doripenem at doses of 1 g/kg in rats and 100 mg/kg in dogs administered as once daily repeated i.v. doses for 3 months were nontoxic and, based on pathologic evaluations, there was no evidence of significant systemic toxicity. In dogs at daily i.v. doses of 250 mg/kg and higher, the gastrointestinal tract was the primary target organ (loose feces, diarrhea, mucoid/bloody feces, and erosion or ulceration in the gastrointestinal mucosa). A repeat-dose rabbit nephrotoxicity i.v. study demonstrated no effects at 200 mg/kg per day, while nephrotoxicity was observed in single-dose i.v. studies at 400 mg/kg in rabbits and 1 g/kg in dogs.

5.3.1. Genotoxicity

A series of genotoxicity studies (bacterial and mammalian cell mutation, chromosomal aberration, bone marrow micronucleus) showed no evidence of mutagenic or clastogenic activity at the tested doripenem concentrations or doses.

5.3.2. Carcinogenicity

Because of the short duration of treatment and intermittent clinical use, long-term carcinogenicity studies have not been conducted with doripenem.

5.3.3. Reproduction and Development

5.3.3.1. Fertility and Early Embryonic Development

Intravenous doses of doripenem as high as 1 g/kg per day had no adverse effects on general fertility of treated male and female rats, or on postnatal development and reproductive performance of the offspring.

5.3.3.2. Embryo-fetal Development

Doripenem had no effects on embryo-fetal development following i.v. administration during pregnancy (on gestation days 7 through 17 in rats and days 6 through 18 in rabbits), at doses as high as 1 g/kg per day in rats, and 50 mg/kg per day in rabbits. In the rat study, 1 female in the 1 g/kg/day group had abnormal delivery (all pups stillborn). These effects are considered to be unrelated to a direct effect of doripenem on parturition, and may have been related to the condition of the dams (i.e., maternal toxicity) at 1 g/kg/day.

5.3.3.3. Prenatal and Postnatal Development, Including Maternal Function

Pregnant female rats received i.v. doses of doripenem at 0.1, 0.3, 0.6, and 1 g/kg per day from Day 7 of gestation to Day 21 of lactation. Pups were observed for physical development, behavior, and reproductive plus other functions throughout the lactation and growth periods until sexual maturity. The NOAEL for this study was 1 g/kg per day based on the absence of toxic effects on maternal animals and their offspring.

5.3.3.4. Renal Toxicity

Increased Blood urea nitrogen and creatinine levels were noted in dogs treated with 1,000 and 2,000 mg/kg doses. The increased levels subsequently began to resolve, but the level remained elevated in the 2,000 mg/kg male as late as Day 20. Upon gross examination, renal pallor was evident. Histopathological examinations showed necrosis and regeneration of the cortical tubular epithelium in the male and female in the 2000 mg/kg group. A repeat-dose toxicity study comparing the effect of doripenem to other antibiotics was conducted in rabbits. Rabbits were intravenously treated for 5 days with meropenem, biapenem and imipenem/cilastatin and the cephem antibiotics cefazolin and cefmenoxime to compare the onset and severity of renal toxicity

among the drugs. Increases in serum urea nitrogen and creatinine and necrosis and regeneration of the tubular epithelium were noted in all animals in the cefmenoxime group, and necrosis of the tubular epithelium was noted in 1 of the 4 animals in the biapenem group and 2 of the 4 animals in the cefazolin group, but no findings suggesting renal toxicity were observed in any doripenem group or the meropenem and imipenem/cilastatin groups. The ranking of renal toxicity as concluded from this study is cefmenoxime >> CEZ= biapenem > imipenem/cilastatin = meropenem = doripenem.

5.3.3.5. Seizure-inducing Potential

Preclinical studies of secondary pharmacology, focusing on the convulsion-inducing effects of doripenem, were conducted in mice, rats, and dogs. In the mouse, the convulsion-inducing effect of doripenem was found to be markedly weaker than those of imipenem and panipenem (Table 5). Rats receiving an i.v. dose of 400 mg/kg of doripenem or meropenem exhibited little change in electroencephalographic findings or behavior. When doripenem, imipenem/cilastatin or meropenem was administered directly into the lateral ventricles of dogs, doripenem administration was not associated with any electroencephalographic changes suggestive of seizure activity or changes in animal behavior even at the highest dose tested (1,000 μg/dog) which was 10 times the dose of imipenem/cilastatin (100 μg/dog) and more than 3 times the dose of meropenem (300 μg/dog) that caused clonic convulsions.[49]

A study of the convulsive thresholds for electroshock or pentylenetetrazole (a proconvulsant that induces seizures) in rats and mice showed that doripenem did not cause, enhance or have an effect on seizures at the equivalent or higher doses that induced convulsions with imipenem/cilastatin or meropenem.[49]

Binding to GABA receptors, and thereby displacing GABA, is known to correlate closely to the induction of convulsions, so the concentrations resulting in 50% inhibition (IC_{50}) of GABA receptor binding by ^{3}H-muscimol (an avid binder of GABA) in mouse brain synaptic membrane samples were compared.[49] The IC_{50} values of imipenem and panipenem were estimated at 0.48 and 0.63 mM, while doripenem failed to inhibit GABA receptor binding by ^{3}H-muscimol even at the maximum concentration (C_{max}) of 10 mM (4,385 μg/mL) thus indicating that doripenem, unlike imipenem and panipenem, has little binding affinity for the GABA receptor.

In summary, no dose of doripenem evaluated, either administered systemically or directly into the CNS, was associated with seizures in animal studies.

Table 5: Inhibiting Action on GABA Receptor Binding by ^{3}H-muscimol

	Doripenem	Meropenem	Imipenem	Panipenem	Cefazolin
Binding inhibition effect of ^{3}H-muscimol (IC_{50}: mmol/L)	>10	>10	0.48	0.63	0.99

5.3.3.6. Hematology Changes

Hematology data showed a slight increase in total white blood cell (WBC) count resulting from an increase in lymphocytes in females in the 1,000 mg/kg group. Moreover, a trend toward a decrease in neutrophil count was seen in all male and female doripenem-treated groups. Treated males were unremarkable following recovery, however, in females, decreases in erythrocytes and neutrophils were observed at 1,000 mg/kg. Changes in lymphocyte and neutrophil counts were mild in severity and, were generally not considered biologically significant. The observed hematology changes were not considered toxicologically significant.

6. OVERVIEW OF CLINICAL PHARMACOLOGY

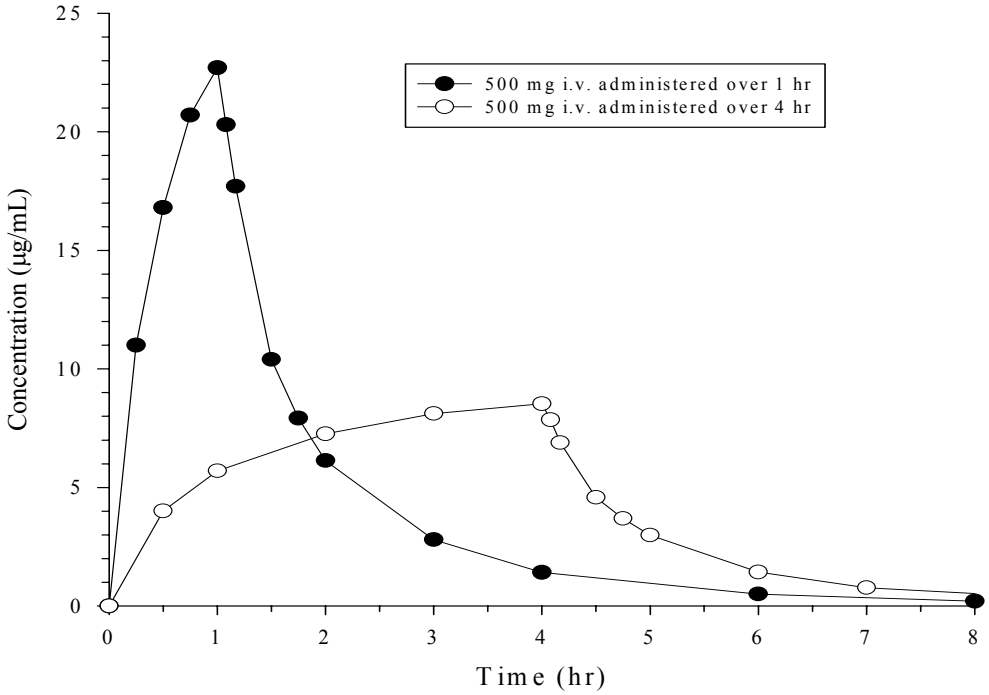
A full clinical pharmacology package was submitted in support of the first NDA for doripenem, resulting in its approval for the treatment of cIAI/cUTI. Data from that submission, which are reflected in the current labeling (Attachment 1), are summarized below. Additional clinical pharmacology data obtained in support of the NP NDA was limited to PK data from patients in the pivotal NP trials, which were included in the population PK and target attainment analysis. A summary of this information is included within this section (Section 6.5.1).

6.1. Pharmacokinetics

The single- and multiple-dose PK of i.v. doripenem was investigated in several studies in Western and Japanese populations. Doripenem exhibits linear and time-independent pharmacokinetics over a dose range of 500 mg to 1 g when intravenously infused over either 1 or 4 hours. The mean C_{max} and AUC from time zero to infinite time ($AUC_{0-\infty}$) of doripenem in healthy patients following administration of doripenem 500 mg over 1 hour are approximately 23 μg/mL and 36 μg.h/mL and following 500 mg over 4 hours are approximately 8 μg/mL and 34 μg.h/mL. Mean plasma concentration-time profiles following doripenem

500 mg 1-hour and 4-hour i.v. infusions to healthy patients are shown below in Figure 1.

Figure 1: Average Doripenem Plasma Concentrations Versus Time Following a Single 1-Hour and 4-Hour Intravenous Infusion of DORIBAX™ 500 mg in Healthy Patients (N=24)



6.2. Distribution, Metabolism, and Elimination

Doripenem binding to human plasma protein is minimal at approximately 8%. The median doripenem steady-state volume of distribution (V_{ss}) in healthy patients is 16.8 L. Doripenem penetrates into body fluids and tissues, including those at the site of infection for the approved indications. Although no data are available on penetration of doripenem into various lung compartments, other carbapenems[50-52] have been shown to achieve therapeutic concentrations in lung tissues and fluids, and the doripenem animal models and clinical studies provide evidence that therapeutic concentrations are achieved with doripenem 500 mg doses.

The predominant metabolite of doripenem, which is microbiologically inactive and is designated as doripenem-M-1, is formed via cleavage of its β-lactam ring, likely by DHP-I. Doripenem is primarily eliminated unchanged by the kidneys, with approximately 70% and 15% of an administered 500 mg dose recovered in the urine as doripenem and doripenem-M-1, respectively. Less than 3% of a

dose is eliminated in the urine as other minor metabolites. Biliary excretion is minimal at less than 1%. Doripenem has a mean elimination half-life of approximately 1 hour and a mean plasma clearance of approximately 15.9 L/hour.

6.3. Influence of Intrinsic Factors on Doripenem Pharmacokinetics

6.3.1. Renal Impairment

Following a single 500 mg dose of doripenem, AUC increases 1.6-fold, 2.8-fold, and 5.1-fold in patients with mild (creatinine clearance [CrCl] 51-79 mL/min), moderate (CrCl 31-50 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, compared to healthy patients with normal renal function (CrCl >80 mL/min). Dosage adjustment is necessary in patients with moderate and severe renal impairment. There is insufficient information to make dose adjustment recommendations in patients on any form of dialysis.

6.3.2. Hepatic Impairment

The pharmacokinetics of doripenem has not been studied specifically in patients with hepatic impairment. However, as doripenem does not undergo hepatic metabolism, the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment. No dosage adjustments are recommended for patients with hepatic impairment.

6.3.3. Age, Sex, and Race

Doripenem AUC increases 49% in elderly (66-84 years of age) adults relative to young adults. These changes are mainly attributed to age-related changes in renal function, and no dosage adjustment is necessary in elderly patients, except in cases of moderate to severe renal insufficiency.

Doripenem AUC is 13% higher in females compared to males. No dosage adjustment is recommended for race, sex, or age (see the approved label in Attachment 1).

6.4. Potential for Drug-drug Interactions

Doripenem does not inhibit or induce the major cytochrome P450 isoenzymes and, therefore, pharmacokinetic interactions of doripenem are not anticipated with drugs that induce, inhibit or are metabolized by cytochrome P450 or other liver enzyme systems.

As has been shown for other drugs, including carbapenems, that undergo active tubular secretion, coadministration of doripenem with probenecid decreases the renal clearance of doripenem.

A clinically significant reduction in serum valproic acid concentrations has been reported in patients receiving carbapenem antibiotics.[27] Although the mechanism of this interaction is not fully understood, data from *in vitro* and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis or increase formation of valproic acid glucuronide.[53] A drug-drug interaction study between doripenem and valproic acid is being conducted by the Sponsor.

6.5. Pharmacodynamics

For doripenem and other carbapenems, the time that the free serum drug concentration exceeds the MIC (T>MIC) for target organisms has been established as the PK/PD parameter that correlates best with the therapeutic efficacy. Extending the infusion time to 4 hours maximizes T>MIC for a given dose, and is the basis for the prolonged infusion in patients at risk for NP due to less susceptible pathogens**.** The development program of doripenem in NP sought to incorporate pharmacokinetic/pharmacodynamic (PK/PD) principles that have rarely been studied in large clinical trials.

6.5.1. Pharmacokinetic/Pharmacodynamic Target Attainment and Dose Selection

In the neutropenic mouse thigh infection model, bacteriostatic effects of doripenem are observed on average when free drug concentrations achieve a T>MIC of 30% of the dosing interval (DORI-M-002).[47] Although the magnitude of the %T>MIC required for clinical efficacy has not been definitively established for carbapenems, %T>MIC values of 25% to 35% are associated with maximal bacterial killing in neutropenic animals, and can be considered conservative targets for immunocompetent patients. Monte Carlo simulations, using the final population PK model (Table 6) predicted that doripenem 500-mg administered as a 4-hour infusion q8h regimen would provide activity against pathogens with higher MICs, thereby capturing a broader MIC distribution compared with the 500-mg q8h 1-hour infusion regimen.

Table 6: Percent of Patients With % T>MIC Higher Than PK/PD Target by MIC and PK/PD Targets From 25% to 35% in NP + cIAI + cUTI for a 500 mg Dose, q8h, 1-hour and 4-hour Infusion

	---------T>MIC 25% ----------		--------T>MIC 30% --------		-------T>MIC 35% -------	
MIC(ug/mL)	1-hour infusion	4-hour infusion	1-hour infusion	4-hour infusion	1-hour infusion	4-hour infusion
0.06	100	100	100	100	100	100
0.12	100	100	100	100	100	100
0.25	100	100	100	100	99.82	100
0.5	100	100	99.7	100	98.94	100
1	99.64	100	97.54	100	93.04	100
2	95.9	100	86.32	100	73.64	99.98
4	71.62	95.62	50.5	94.1	36.08	90.66
8	22.86	29.66	13.46	24.54	8.46	18.84
16	1.72	0.84	0.84	0.5	0.42	0.26

Based on the above simulations and the likely pathogens in NP, which generally have MICs ≤2 μg/mL, the dose of 500 mg q8h was expected to be effective in NP. The NP studies evaluated the same dose of doripenem (i.e., 500 mg q8h) administered over 2 different infusion durations. In DORI-09, the patient population was believed to be at low risk for pathogens with doripenem MICs >1 μg/mL and, thus, the 1-hour infusion was considered appropriate. For DORI-10, which enrolled only patients with VAP, a 4-hour infusion of doripenem was used and was predicted to cover organisms, especially *P. aeruginosa*, with higher MICs (up to 4 μg/mL), likely to be more prevalent in this patient population.

The results of the Monte Carlo simulations using the final population pharmacokinetic model and pathogen susceptibility data from Phase 3 studies indicated that for the metric %T>MIC, values of 90% and higher are achieved for NP across PK/PD targets of 25% to 35% T>MIC.

7. CLINICAL

7.1. Overview of Studies

The 2 Phase 3 studies conducted to support the indication of NP, including VAP (DORI-09 and DORI-10), were open-label, randomized, multi-center, adequately powered, active-controlled noninferiority studies, where the efficacy of doripenem therapy was compared to that of piperacillin/tazobactam (DORI-09) and imipenem (DORI-10). Although the 2 studies included many similar design elements, there were notable differences in study populations and some design features. When taken together, the studies represent a broad experience in NP. It was not appropriate to conduct placebo-controlled trials in

this severely ill population due to ethical concerns of high rates of morbidity and mortality in untreated patients.[1] Because blinding was not feasible (see complete discussion of the barriers to blinding the studies in Section 7.2.4), the clinical outcomes in DORI-09 were reviewed by an external, independent, BEC of expert clinicians. A total of 979 patients were enrolled into the 2 NP studies, 448 patients into DORI-09 and 531 patients into DORI-10. Critical aspects of the study design, such as the open-label nature of the trials, in-house blinding and use of a BEC in DORI-09, to mitigate potential bias, are discussed in Section 7.2.

Because NP occurs while patients are hospitalized for a variety of other conditions, e.g., trauma, medical or post-surgical settings, investigational sites were selected in various regions of the globe in an effort to capture the diversity of the disease under investigation and its associated comorbidities. Investigational sites in North America, South America, Europe, Australia, and South Africa were included (note: only North America and Europe participated in both studies). Both studies were in compliance with the guidelines of the FDA,[54] Committee for Proprietary Medicinal Products (CPMP) for antimicrobial drug development[55] and International Conference on Harmonization (ICH) guidelines for clinical trials.[56,57]

In both studies, central randomization was used to avoid selection bias in the assignment of patients to study drug therapy, to increase the likelihood that known and unknown patient attributes were evenly balanced between the 2 treatment arms, and to enhance the validity of statistical comparisons between treatment arms. Patients were randomly assigned (1:1) to either doripenem or comparator based on a computer-generated randomization code with permuted blocks that was prepared by the Sponsor. Prior to randomization, patients were stratified to achieve balance between the treatment arms with respect to factors that could impact outcome. Stratification factors included severity of illness, ventilation status, and region. A more detailed description of central randomization is given in Section 7.2.4.1.1.

The study population included male and female patients, 18 years of age or older, who required i.v. antibiotics, with clinical, radiological and microbiological evidence of NP, presumed to be caused by micro-organisms susceptible to both doripenem and comparators. The diagnosis of pneumonia and study inclusion/exclusion criteria are discussed in detail in Section 7.2.1.

Study procedures related to confirmation of the diagnosis of NP are discussed in Section 7.2.1.1.

In Study DORI-09, a 1-hour infusion of doripenem 500 mg (q8h) was compared to piperacillin/tazobactam (4.5 g [infused over 30 minutes q6h]) in patients with non-VAP or with early-onset VAP. In Study DORI-10, a 4-hour infusion of the same dosage of doripenem (q8h) was compared to imipenem (500 mg [infused over 30 minutes q6h] or 1 g [infused over 1 hour q8h]) in patients with VAP, including those at higher risk for less susceptible pathogens (such as patients with late-onset VAP). As it was not possible to select 1 dosing regimen that would have been acceptable at all sites, investigators in DORI-10 were allowed to select from 2 dosage regimens of imipenem that were approved in the U.S. per the usual practice at their institution or per country-approved labeling or guidelines. The rationale for the different doripenem infusion times in the 2 studies is provided in Section 6.5.1. In both studies patients were to be treated for a period of 7 to 14 days. Investigators in Study DORI-09 (only) had the option of switching patients to oral therapy (levofloxacin 750 mg q.d. or suitable alternative oral therapy) after at least 72 hours of i.v. study drug therapy (9 doses of doripenem or 12 doses of piperacillin/tazobactam, or an equivalent number of doses, if the dose was adjusted for renal impairment), if criteria for improvement, described in detail in Section 7.2.2.3, were met. There was no provision for an oral switch in Study DORI-10.

Efficacy was evaluated by clinical assessment of the improvement or resolution of signs and symptoms associated with NP, which included Clinical Pulmonary Infection Score (CPIS) determination (for intubated patients only), physical examination of the chest (for non-ventilated patients only), vital signs (including measurement of oral temperature [or equivalent]), WBC, ventilator needs, oxygenation status, and chest X-ray assessments at the end of i.v. therapy (EOT[i.v.]), TOC and late follow-up (LFU) visits. Microbiological efficacy (pathogen eradication or presumed eradication, described in Section 7.2.6) was also determined. The primary efficacy endpoints were the clinical cure rates (clinical cure is defined in Section 7.2.5) in the cMITT and CE at TOC analysis sets (see Section 7.3.1 for a definitions of the analysis sets).

The safety of doripenem was evaluated through the monitoring of treatment-emergent adverse events (referred to as adverse events throughout this report), measurement of vital signs, physical examination findings and the

systematic collection of blood and urine specimens analyzed in a central laboratory.

7.2. Critical Aspects of Study Design

7.2.1. Study Population

Patients in the NP studies were male or female, 18 years of age or older, with clinical, radiological and microbiological evidence (DORI-10 only) of NP, presumed to be caused by micro-organisms susceptible to both doripenem and comparators who required i.v. antibiotics. Patients were required to have evidence of pneumonia including the presence of a new or progressive infiltrate on chest radiograph and at least 1 of the following: fever or hypothermia; elevated total peripheral white blood cell (WBC) count (≥10,000/mm^3) or >15% immature neutrophils (bands), regardless of total peripheral WBC count, or leukopenia with a total peripheral WBC <4,500/mm^3 (caused by the infection). Post-study confirmation of the diagnosis of NP is detailed in Section 7.4.1.6.1. Patients with NP who had early-onset VAP or non-VAP and had been hospitalized for 48 hours or more, or had a prior hospital admission of at least 48 hours and were discharged within the last 7 days, were eligible for enrollment into Study DORI-09. Eligible patients included residents of chronic care facilities. In Study DORI-10 only patients with early- (<5 days) or late-onset (≥5 days) VAP were enrolled; patients were required to have received mechanical ventilation for at least 24 hours or to have been weaned from mechanical ventilation within the last 72 hours to qualify. All ventilated patients were required to have a baseline CPIS of ≥5. In DORI-09 nonventilated patients were required to have had at least 2 of 5 signs or symptoms of pneumonia (cough; new onset or production of purulent sputum or other respiratory secretions, or a change in the character of sputum; ausculatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation [dullness on percussion, bronchial breath sounds, or egophony]; dyspnea, tachypnea, or respiratory rate ≥30 per minute particularly if any or all of these were progressive in nature; hypoxemia with a PaO_2 <60 mmHg while on room air, as determined by arterial blood gas [or equivalent oxygen saturation by pulse oximetry]). Gram stains requirements for sputum specimens were not specified in the inclusion criteria in DORI-09, but were described in the procedures section of the protocol. In DORI-10, investigators were required to perform gram stain examinations of expectorated sputum in recently extubated patients; the criteria for acceptability of an appropriate specimen was

>25 polymorphonuclear cells and <10 squamous epithelial cells per low power field. Excluded from the studies were patients with pneumonia known to be caused solely by pathogen(s) resistant to either doripenem (meropenem was used as a surrogate) or comparator, APACHE II scores <8 or >29 (DORI 10) or >25 (DORI 09), an infection or complication requiring non-study systemic antibacterial therapy or prolonged antibacterial therapy for >14 days, structural lung disease (other than chronic obstructive pulmonary disease), severe acute respiratory distress syndrome, septic shock, end-stage renal failure (including any form of dialysis), cavitary lung disease, primary or secondary lung cancer, cystic fibrosis, *Pneumocystis jiroveci (carinii)* pneumonia, active tuberculosis, immunocompromising illness or chronic treatment with an immunosuppressive agent, any rapidly progressing disease or immediately life-threatening illness, or use of drotrecogin alpha (in DORI-10 only). Patients were also not eligible if they had received systemic antibiotic therapy for ≥24 hours in the 48 (DORI-10) or 72 (DORI-09) hours before randomization (unless they had failed prior therapy for NP), were considered unlikely to survive until the final study visit, or had an order against resuscitation. Patients with significant liver function abnormalities, severe neutropenia, or thrombocytopenia were excluded, as were those with a history of moderate or severe hypersensitivity to β-lactam antibiotics (both studies) or β-lactamase inhibitors (DORI-09 only).

The protocol inclusion/exclusion criteria for DORI-09 and DORI-10, taken verbatim from the protocols, is provided in Attachment 2.

7.2.1.1. Confirmation of Diagnosis of NP

The clinical diagnosis of NP is generally made using a combination of findings including fever, elevations or depressions of the WBC count with a left shift, radiologic abnormalities showing a new or progressive infiltrate and elevated CPIS. A full independent radiological report from the local radiologist was obtained when available. However, given the limitations of chest radiograph interpretation in the absence of the full clinical picture, investigators (or their clinical counterparts) were asked to provide their interpretation of the chest X-rays in the relevant case report form page, taking into account the clinical presentation of the patients, when appropriate. In addition to clinical diagnostic criteria, all patients were required to have an LRT specimen obtained at baseline. As a number of different methodologies for obtaining and interpreting specimens are available (e.g., bronchoscopic BAL, mini-BAL, tracheal aspirates, each with various quantification limits) and none has yet been established as the

standard,[58] investigators obtained and processed specimens using techniques and methods according to their standards.

In DORI-09, the BEC was provided with a comprehensive summary of relevant clinical findings, including the radiographic findings recorded in the case report form and the full radiology report, when available. As part of the evaluation by the BEC, diagnostic criteria, including the radiographic findings, were specifically reviewed and the final diagnosis of NP was confirmed (or refuted) by the BEC based on all the available data. The members of the BEC for DORI-09 were experienced, internationally renowned clinician-researchers who were very familiar with the diagnosis and evaluation of responses in NP and were involved in the conduct of the study. A list of BEC members and their affiliations is provided in Attachment 3. Two members of the BEC were provided with patient profiles extracted from the database, which included the investigator's interpretation of the chest X-ray findings (recorded on the case report form) and a copy of the original radiology report, when available. All relevant clinical data were also provided. In addition to an evaluation of outcome, they were asked specifically if the patient met the criteria for the diagnosis of pneumonia at baseline, based on clinical signs and symptoms, the radiology report, and relevant laboratory findings. If these 2 members disagreed in their outcome assessments, the full committee, requiring a quorum of 5 members, reviewed the entire case. If the full committee failed to reach a decision, the patient was considered nonevaluable. A BEC was not instituted in Study DORI-10 (see related discussion in Section 7.2.4.1.2).

After completion of the study and at the request of the FDA, the documentation that diagnostic criteria for pneumonia described in the protocols had been met was assessed and analyses were rerun in patients who met stringent definitions of all diagnostic criteria (see Section 7.4.1.6.1 for a complete discussion).

7.2.2. Study Treatments

7.2.2.1. Doripenem

The doripenem treatment regimen used in the NP studies is discussed in detail in Section 7.1.

7.2.2.2. Comparator Treatment

Piperacillin/tazobactam and imipenem were chosen as the comparators in DORI-09 and DORI-10, respectively, because they have a broad spectrum of antibacterial activity, are approved in participating countries for the treatment of

adults with LRT infections or NP and are widely used for these infections.[59,60] Imipenem was selected as the comparator in Study DORI-10 because carbapenems are widely used and recommended for VAP, particularly when multiple-drug-resistant bacteria are suspected.[1,4,60]

Two different dosing regimens of imipenem (500 mg q6h or 1 g q8h), both of which were approved in the U.S., were allowed in DORI-10 because it was not possible to select 1 dosing regimen that would have been acceptable at all sites. Both regimens are recommended per ATS/IDSA guidelines for the treatment of NP.[1] Furthermore, the allowance of 2 regimens would not be expected to affect the overall efficacy assessment of imipenem, as these regimens are pharmacodynamically equivalent.[2] The selection of an imipenem dosage regimen was at the discretion of the investigator and was based on the usual practice at his or her institution. Once selected, the regimen was to be used consistently throughout the study at that institution. Because of their broad antibacterial activity and proven favorable safety profile, the use of piperacillin/tazobactam or imipenem as the comparator in studies of NP could be regarded as stringent tests of the balance of the risk and benefit of an investigational agent.

7.2.2.3. Oral Switch Therapy

In DORI-09 a switch to oral therapy was allowed to facilitate hospital discharge, when possible, although investigators were encouraged to maintain i.v. study drug therapy for as long as feasible. Oral levofloxacin therapy (750 mg q.d.) or suitable alternative oral therapy was chosen as the oral switch agent because it is approved for the treatment of NP and has an acceptable anti-bacterial profile against most NP pathogens. Investigators had the option of switching patients to oral therapy after at least 72 hours of i.v. study drug therapy (9 doses of doripenem or 12 doses of piperacillin/tazobactam, or an equivalent number of doses, if dose was adjusted for renal impairment), if all of the following criteria for improvement were met: body temperature <38°C/100.4°F, without the influence of antipyretic agents; WBC ≤15,000 cells/mm^3 or that had decreased by 25% from peak (if increased at baseline); most of the symptoms of NP were absent or improved compared to Day 1 pre-dose; and improvement or lack of progression was evident upon chest X-ray. Levofloxacin susceptibility results were anticipated to be available by the time patients were to be switched to oral therapy. In Study DORI-10, only i.v. study therapy was allowed.

7.2.3. Adjunctive Therapy

As doripenem does not cover MRSA adequately and because combination therapy is often recommended for *Pseudomonas* pneumonia, concomitant vancomycin and/or amikacin therapies were recommended to be used, at the investigator's discretion, for suspected or proven MRSA or *P. aeruginosa* infections, respectively, in both studies. If MRSA was the only pathogen identified from the baseline LRT microbiological specimen, the investigator was advised to withdraw the patient from study drug therapy. If the respiratory specimen and blood culture were negative for MRSA, vancomycin therapy was to be discontinued after 48 hours, at the investigator's discretion. Alternatives to vancomycin therapy for MRSA (e.g., linezolid) were occasionally allowed, after discussion with the Sponsor. In DORI-09, amikacin, or suitable alternative aminoglycoside therapy, was to be started with the initiation of i.v. study drug therapy. This was necessitated by the labeling for piperacillin/tazobactam in some regions, including the U.S., which recommends that it be used concomitantly with an aminoglycoside for initial presumptive treatment of NP. For patients in the imipenem arm in DORI-10, adjunctive amikacin was allowed at the investigator's discretion, if *P. aeruginosa* pneumonia was suspected. In both studies amikacin was to be discontinued at the discretion of the investigator if *P. aeruginosa* infection was not confirmed (generally within 48 hours in DORI-10) at the discretion of the investigator, unless *P. aeruginosa* was isolated at baseline in the comparator arm, when it could be continued for approximately 5 days in DORI-09 and 5 to 7 days in DORI-10. Amikacin was to be discontinued, at the investigator's discretion, if a meropenem-susceptible *P. aeruginosa* was isolated in doripenem-treated patients. However, the protocols specified that if *P. aeruginosa* was isolated, patients in the doripenem treatment group were permitted to continue adjunctive therapy beyond 48 hours, at the discretion of the investigator. The different recommendations in the doripenem arm compared with the comparator arms reflect an attempt to limit the use of adjunctive therapy in doripenem-treated patients.

7.2.4. Open-label Design

The decision to conduct Studies DORI-09 and DORI-10 as open-label studies was based on a number of barriers to blinding. One important barrier was the difference in dosing intervals required for the administration of doripenem and piperacillin/tazobactam (q8h versus q6h, respectively) in Study DORI-09. Blinding would have required these critically-ill patients to receive a total of 7 i.v. infusions each day. Similarly, as discussed previously under the

comparator treatment subheading in this section, 2 imipenem regimens were allowed in DORI-10, which made blinding very difficult. Alternative comparators that might have facilitated blinding were considered inappropriate because of their narrower antibacterial spectrum (e.g., levofloxacin) or because they were not globally approved for the treatment of NP (e.g., meropenem, cefepime) and had different dosing adjustment schedules for patients with various degrees of renal impairment. Another important barrier to blinding the studies was the additional fluid administration that placebo infusion would have required. The additional fluid requirements were considered potentially detrimental because patients in these studies frequently had cardiac and renal co-morbidities, and by definition, varying degrees of pulmonary dysfunction. The potential of doripenem to cover pathogens resistant to the comparator agents could only be evaluated in an open-label study as a blinded study would need to exclude patients infected with strains resistant to either study drug (e.g., patients with ESBL-producing *Enterobacteriaceae* in DORI-09 and patients with imipenem-resistant *P. aeruginosa* in DORI-10).

Other barriers to blinding in both studies included differences in the requirement for the discontinuation of adjunctive amikacin therapy between doripenem and comparator in both studies, i.e., amikacin was to be discontinued, at the investigator's discretion, if *P. aeruginosa* was isolated in doripenem-treated patients, but it was to be continued in patients treated with comparator, to be consistent with standard practice (refer to a detailed discussion of adjunctive therapy with amikacin in Section 7.2.3).

The concern in open-label studies of potential bias in assigning patients to study drugs (selection bias) and in the assessment of patients' evaluability (assessment bias) were addressed via the utilization of a central randomization procedure and the establishment of the in-house blinding procedure and utilization of a BEC, respectively. These procedures are described in the 2 sections that follow.

7.2.4.1. Addressing the Potential for Selection Bias

In both DORI-09 and DORI-10, no specific procedures were implemented to ensure that investigators were blinded to treatment assignment. However, investigators were required to decide whether or not to enroll a patient prior to the assignment of study treatment. As discussed in detail in Section 7.2.4.1.1, treatment assignment was performed centrally by a computer-generated randomization code.

Early discontinuations from study treatment were carefully monitored to ensure that investigators were not biased for or against either doripenem or the comparator prior to starting study medication. In Study DORI-09 there was a total of 4 study drug discontinuations prior to the initiation of study drug, 1 due to an early death, 1 due to withdrawal of consent and 2 for inclusion or exclusion criteria not met that were discovered later. In Study DORI-10 there was a total of 6 study drug discontinuations prior to the initiation of study drug, 1 due to early death, 1 due to withdrawal of consent and 4 for inclusion or exclusion criteria not met that were discovered later. Given these small numbers, no systematic bias was detected either for or against either treatment group in either study. Treatment discontinuations and causes for these discontinuations within the first 4 days of study drug in Study DORI-09 are summarized in Attachments 4.1.1 and 4.1.2. Treatment discontinuations and causes for these discontinuations within the first 4 days of study drug in Study DORI-10 are summarized in Attachments 4.2.1 and 4.2.2.

7.2.4.1.1. Central Randomization

Central randomization was used to avoid selection bias in the assignment of patients to study drug therapy, to increase the likelihood that known and unknown patient attributes were evenly balanced between the 2 treatment arms, and to enhance the validity of statistical comparisons between treatment arms. Patients were randomly assigned (1:1) to either doripenem or comparator based on a computer-generated randomization code using permuted blocks that was prepared by the Sponsor. Prior to randomization, patients were stratified according to geographic region (DORI-09: North America, South America, Europe/Other; DORI-10: North America, Europe, and Other), either mechanical ventilation association (non-ventilator associated vs. early-onset VAP) for DORI-09 or duration of mechanical ventilation (less than 5 days vs. 5 or more days) for DORI-10, and severity of illness (APACHE II score ≤15 or >15). The patient number and study drug therapy (doripenem or comparator) were assigned from the computer-generated randomization code, after designated study site personnel called into the Interactive Voice Response System (IVRS). Investigators were required to decide whether or not to enroll a patient prior to the assignment of study treatment. The study site personnel could not predict the treatment assignment before the call to the IVRS system nor was it feasible that they could have assessed the likelihood of a particular treatment being assigned because blocks of randomization codes were grouped by region.

7.2.4.1.2. In-house Blinding and the Blinded Evaluation Committee

To address concerns with the open-label design of the NP studies, the Sponsor instituted in-house blinding procedures. In both studies, the Sponsor assessed patient evaluability for all analyses in a blinded fashion (i.e., without knowledge of treatment assignments). In addition, access to datasets that contained treatment assignments was not permitted for statistical, in-house data management, and medical teams before database lock.

To compensate for the unblinded assessments made by the investigators, an external BEC of expert clinicians determined final clinical outcomes in Study DORI-09 (note: the decision not to include a BEC in Study DORI-10 is discussed below). The 10 members selected for the BEC were physicians experienced in the diagnosis and management of NP, including pulmonologists, intensivists or infectious disease specialists, who were external to J&JPRD, who were not involved in the conduct of the study (i.e., did not enroll patients or follow the clinical progress of patients) and who were blinded to study treatment. A list of BEC members in DORI-09 and their affiliations is included in Attachment 3. The BEC was convened during the conduct of Study DORI-09 and before database closure. The BEC had a 3-fold focus: 1) the determination of whether patients met the study definition of pneumonia; 2) the determination of whether there were any factors (such as concomitant diseases and concomitant non-study antibiotic administration) that interfered with the TOC clinical outcome assessment, which might have rendered patients nonevaluable for the primary analysis; and 3) determination of the final clinical outcome at TOC in all patients who had received at least 48 hours of study drug therapy. In the event that the clinical outcome of the BEC differed from that of the investigator, the decision of the BEC over-ruled the investigator's assessment and was used in the primary analyses of efficacy.

As DORI-10 was also open-label, the Sponsor carefully considered instituting a BEC in that study. However, on the basis of discussions and guidance given by external experts, the Sponsor decided that the investigator, rather than an outside body, would be in the best position to make final outcome assessments because of the greater complexity of the patients and severity of the disease in these patients, who were treated in ICUs, and many of whom would have been expected to have highly complex clinical courses and numerous measures of progress. In addition, the complexity and volume of clinical information in

ICU patients precluded capturing sufficient details in the case report form or data listings. Furthermore, the high concordance (98%) between the investigator and the BEC outcome assessments in DORI-09 supports the reproducibility of the investigator's assessments.

7.2.4.2. Addressing the Potential for Assessment Bias

7.2.4.2.1. Objectivity of Measurements

The design of both NP studies included several measures to reduce the potential for either investigator or Sponsor bias in the assessment of clinical outcome. Investigators were required to use objective measurements, such as body temperature, WBC, oxygenation status, respiratory rate, and leukocyte count. In patients with VAP, in addition to various objective measures such as ventilatory requirements and oxygenation status, the predominant measure in monitoring clinical progress was a defined decrease in the CPIS.[61] (The CPIS is included in Attachment 5).Although the CPIS includes a somewhat subjective element in the estimation of tracheal secretions, it is considered a reproducible measure of the clinical outcome because all the other 4 of 5 parameters are objectively determined and all parameters in the score use a pre-defined point system.

Training sessions; regular monitoring of investigator's by Sponsor-designated personnel; instruction manuals; and data verification, cross-checking and data audits were performed to ensure the quality of all data. In addition, investigator meetings were performed to prepare investigators and other study personnel for appropriate collection of study data.

7.2.5. Clinical Outcomes

Clinical outcomes were defined as follows:

- Clinical cure: Complete resolution or marked improvement or return to baseline of all signs and symptoms of pneumonia and improvement or lack of progression of all chest X-ray abnormalities, such that no additional antibacterial therapy was required for the treatment of the current infection.
- Clinical failure: Patients were classified as a clinical failure after at least 48 hours of therapy based on:
  - persistence or worsening in signs or symptoms of pneumonia;
  - development of new signs or symptoms of pulmonary infection requiring antimicrobial therapy other than, or in addition to, study drug therapy;
  - progression of chest radiographic abnormalities related to pneumonia; or

  - death during the study period, if pneumonia was thought to be contributory toward or sole cause of death.

  Of note, patients who received non-study antibiotic therapy for ongoing signs or symptoms of pneumonia were considered failures.

- Relapse: Recurrence of signs or symptoms of pneumonia and new radiographic evidence of pneumonia in a patient assessed as cured at the TOC visit.
- Indeterminate: Study data were not available for evaluation of efficacy for any reason, including: treatment change in the first 48 hours; death at any time and the index infection was clearly noncontributory, or extenuating circumstances precluded classification as cure of failure.

The primary study endpoint, i.e., clinical outcome at TOC visit in the CE analysis set, was based on the BEC's assessment in DORI-09 (refer to Section 7.2.4.1.2 for a detailed discussion of the BEC) and the investigator's assessment in DORI-10, with the exception of evaluable patients who were discontinued due to a drug related adverse event and required additional antibacterial therapy (who were automatically counted as failures). Early failures (failures before the TOC visit) were carried forward to the TOC visit. Patients whose clinical response at the TOC visit was indeterminate or missing were excluded from the CE analysis set. Such patients were counted as failures in the cMITT analysis set.

7.2.6. Microbiological Outcomes

Per-pathogen microbiological outcome categories at TOC (or at the time of failure) were as follows:

- Eradication: Absence of original baseline pathogen from a LRT specimen culture or blood
- Presumed eradication: No source specimen to culture and patient assessed as clinical cure
- Persistence: Continued presence of the original baseline pathogen in culture of a LRT specimen
- Presumed persistence: No source specimen to culture in a patient who was judged to be a clinical failure
- Recurrence: Isolation of the original baseline pathogen from a culture of the LRT specimen, taken after the TOC visit and the TOC culture was negative or presumed eradicated (note: this outcome pertains to the LFU visit only).
- Indeterminate:
  - entry culture either not obtained or no growth;
  - assessment not possible because of protocol violation; or

- any other circumstance that made it impossible to define the microbiological response.

If more than one baseline pathogen was isolated, the per-patient microbiological response reflected the worst per-pathogen microbiological outcome of the baseline pathogens. Thus, for a favorable per-patient microbiological response, the microbiological outcome for each baseline pathogen must have been favorable (i.e., all baseline pathogens must have been eradicated or presumed eradicated at the TOC visit). If the microbiological outcome for any baseline pathogen was unfavorable (i.e., persistence or presumed persistence at TOC), the patient was determined to have had an unfavorable per-patient microbiological response.

7.2.7. Safety Assessments

All adverse events from the time of the first study-related procedure through the last study visit were captured on the case report form. The investigator reported his or her opinion regarding the severity of the adverse event, its relationship to study drug, the action taken with respect to administering study drug, the measures required for the management of the event, and the ultimate outcome of the event. In addition, adverse events that, in the opinion of the investigator, represented possible allergic reactions to study drug therapy or study drug intolerability were specifically noted as such in the case report form.

All adverse events discussed in this briefing book are treatment-emergent adverse events (e.g., adverse events that started at or after the start of infusion of the first dose of study drug) and are referred to simply as adverse events within this briefing book. For summary purposes only adverse events with an onset date up to 30 days after administration of the last dose of study drug are included.

In addition to assessing investigator-reported adverse events related to laboratory values, blood samples for serum chemistry and hematology evaluations, and urine samples for urinalysis were taken from all patients at protocol-specified times (baseline, end of i.v. therapy, early-follow-up and later follow-up) and analyzed in a central laboratory. Broadly, laboratory data were analyzed 2 ways: changes in mean values over time (i.e., population changes), and shifts in toxicity grade for each laboratory test at selected time points (i.e., individual patient changes). Evaluation of these results provided a more thorough profile of changes in laboratory values than evaluation of laboratory adverse events reported by the investigators.

Laboratory data were assessed using the toxicity grades defined by the Division of Microbiology and Infectious Diseases[62] which were modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values were not collected systematically in these studies. In addition, Grade 0 (representing normal range) was added so that shifts from normal could be analyzed. The modified toxicity grading scale used is included in Attachment 6.

To further examine the potential for severe hepatic injury, patients who met the criteria for Hy's High Risk (HHR) Classification were assessed; HHR was defined by an alanine aminotransferase >3 times upper limit of normal (ULN) and a total bilirubin >1.5 times ULN at the same time point, but without evidence of biliary obstruction (i.e., concurrent value of alkaline phosphatase >1.5 times ULN).[63]

In addition to causality as determined by the investigators, the Sponsor independently evaluated adverse events for causality and whether they qualified as doripenem adverse drug reactions (ADRs). The definition and identification of ADRs followed regulatory guidance.[64] An ADR was defined as an undesirable effect, reasonably associated with the use of doripenem that may have occurred as part of its pharmacological action or was unpredictable in its occurrence. Adverse drug reactions included only those adverse events for which there was some basis to believe that there was a causal relationship between doripenem and the occurrence of the adverse event. As ADR terms were derived from adverse events, these potentially included clinical syndromes, signs or symptoms, changes in clinical laboratory parameters, and changes in other measures of critical body functions (e.g., vital signs and electrocardiograms). All adverse events from Phase 1, 2 and 3 studies were evaluated for potential ADRs. Particular attention was given to safety issues potentially associated with β-lactams and especially with the carbapenem drug class, such as seizure, rash, anaphylactic and hypersensitivity reactions, *Clostridium difficile*-related colitis, and increases in hepatic enzymes. Adverse events with an incidence >10% in any indication were automatically considered ADRs. The identification of an ADR for doripenem was based on review of all events that occurred in all clinical studies (including Phase 1, 2, and 3); however, the rates reported were the frequencies of events (regardless of causality) occurring in the 5 controlled Phase 3 studies (1 in cUTI, 2 in cIAI, and 2 in NP).

7.3. Critical Aspects of Statistical Analyses

7.3.1. Analysis Sets

The primary analysis set was the CE at TOC analysis set. This included all randomized patients who met the protocol-specified disease definition of pneumonia, as described in each study (see Section 7.2), and who received a predefined acceptable duration of study drug therapy. In addition, sufficient information had to be available to determine the patient's clinical outcome at the TOC visit, and these patients had to have no confounding events that interfered with the assessment of those outcomes. If baseline LRT pathogens were isolated, at least 1 was susceptible to the i.v. study drug therapy received. In DORI-10 and in patients with VAP in DORI-09, patients had to have a positive baseline LRT culture if they had not received any broad spectrum antibacterial agent in the previous 24 hours to be included in the CE at TOC analysis set. The receipt of non-study antimicrobial therapy active against likely NP pathogens disqualified patients from the CE analysis set.

A co-primary analysis set, the cMITT analysis set, included all randomized patients who received any dose of i.v. study drug therapy, whether or not they met all study inclusion/exclusion criteria. Meeting the definition for a hospital-acquired infection was required for inclusion in the CE at TOC analysis set but was not necessary for inclusion in the cMITT analysis set. In addition to the presence of a new or progressive infiltrate on chest radiograph, at least 1 of the following was required for patients to be included in the cMITT or CE at TOC analysis sets: 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 (≥10,000/mm^3) or >15% immature forms (bands) regardless of total peripheral WBC; or leukopenia with total peripheral WBC <4,500/mm^3 (caused by the infection). Radiographic reports and investigator interpretation of radiographic findings were reviewed after completion of the study by the Sponsor in a blinded fashion. A more detailed discussion of the evaluation of baseline radiographic findings is found in Section 7.4.1.6.1.

Other analysis sets used in the efficacy analyses included:

- Microbiological Modified Intent-to-Treat (mMITT). This analysis set was a subset of the cMITT analysis set, consisting of patients who had at least 1 baseline bacterial LRT isolate identified, regardless of susceptibility to the i.v. study drug therapies.

- Microbiologically Evaluable at TOC (ME at TOC). This analysis set was a subset of the CE at TOC analysis set, consisting of clinically evaluable patients who had at least 1 LRT pathogen identified at baseline (via sputum, other respiratory specimen, or blood) that was susceptible to the i.v. study drug therapy received.
- Clinically Evaluable at LFU Analysis Set (CE at LFU). This analysis set was a subset of the CE at TOC analysis set, consisting of patients who were clinically cured at the TOC visit, had a LFU assessment, did not receive any systemic antibacterial therapy after the TOC visit, and did not have any other confounding events after the TOC visit.

Safety analyses were conducted on the safety analysis set (the ITT analysis set), which included all patients, regardless of diagnosis, who received any dose of study drug therapy.

7.3.2. Efficacy Endpoints

A summary of efficacy endpoints for both NP studies is provided in Table 7.

Table 7: Efficacy Endpoints
Studies: JNJ38174942-DORI-09 and DORI-10

Endpoints	Description	Analysis set
Per patient clinical response at TOC	• Proportion of patients who were clinically cured	CE at TOC (Primary) cMITT (Co-primary) ME at TOC mMITT
Per patient microbiological response at TOC	• Proportion of patients who were microbiologically cured	ME at TOC
Per pathogen microbiological outcome at TOC	• Proportion of pathogens with a favorable microbiological outcome (eradication or presumed eradication)	ME at TOC Expanded ME at TOC
Per pathogen clinical outcome at TOC	• Proportion of pathogens with a favorable clinical outcome (cure)	ME at TOC
Per patient clinical response at EOT(IV)	• Proportion of patients who were clinically cured/improved	CE at TOC
Per patient clinical response at LFU	• Proportion of patients with clinical relapse	CE at LFU

7.3.3. Sample Size

The final sample size determination in each study was based on the expected clinical cure rate at TOC in the CE at TOC analysis set.

After a discussion with the FDA, the final sample size for DORI-09 of 440 patients, in Amendment 3, was increased from 300 patients in the original protocol and in Amendments 1 and 2 on the basis of a preliminary evaluability rate of 60% from a blinded inhouse assessment of the first 80 patients enrolled

into the trial. Similarly, in DORI-10, the sample size of 520 patients in Amendment 2 was increased from 400 patients in the original protocol and in Amendment 1, to maintain the target number of 130 CE patients per treatment arm, on the basis of a preliminary evaluability rate of 50% from a blinded inhouse assessment.

Based on prior studies in NP,[65-68] the clinical cure rates for doripenem and comparator were expected to be 65% to 60% in DORI-09 and DORI-10, respectively. As such, a sample size of 130 evaluable patients per treatment arm was calculated to have approximately 90% power, using a noninferiority margin of 20% and a 1-tailed 2.5% significance level (refer to Section 7.3.4 for a discussion of the justification of the selection of the noninferiority margin). Therefore, assuming 60% evaluability in DORI-09 and 50% in DORI-10, approximately 440 patients in DORI-09 and 520 patients in DORI-10 were to be enrolled in each study.

7.3.4. Justification of Noninferiority Margin

During the design of the clinical trials, several factors such as historical data, clinical experience, review of guidances (ICH E-9[56] and E-10[57]) and previous regulatory precedent were utilized to determine the appropriate noninferiority margin for the NP trials. Based on these efforts a noninferiority margin of 20% was pre-specified in both studies (DORI-09 and DORI-10). However, during the conduct of the studies, but before database lock, and at the request of the FDA, the Sponsor undertook a comprehensive review of the published literature, reevaluating the noninferiority margin that would be appropriate in this indication. This re-evaluation is detailed below.

An extensive literature search was performed to identify all relevant publications containing the following information:

- Cure rates of piperacillin/tazobactam or imipenem in studies conducted in a population similar to that of patients diagnosed with NP.
- Spontaneous resolution rate (as a surrogate of the placebo response rate) for NP.

The sources used for both searches were: Medline, Derwent, Biosis, Embase, Adis Clinical Trials Insight, and Trial Trove.

Literature was reviewed with a focus on NP patients who had disease comparable to that studied in Studies DORI-09 and DORI-10.

No randomized placebo-controlled trials in NP were identified in the literature, which was not unexpected given that placebo would not be considered an appropriate comparator for various reasons discussed in Section 7.1. It was therefore necessary to extract 2 critical elements from the published literature to justify the noninferiority margin. The first critical element was the clinical cure rate and sample size for clinical trials involving NP patients treated with piperacillin/tazobactam (the comparator in Study DORI-09) or imipenem (the comparator in Study DORI-10). The second critical element was the estimated cure rate in NP patients treated with inadequate or inappropriate therapy. The second element was expected to approximate the placebo response rate and was, therefore, used as a surrogate of the placebo clinical cure rate, recognizing that it was likely to be an overestimate of the true placebo cure rate.

7.3.4.1. Estimation of the Comparator's Cure Rate

Clinical cure rates and sample sizes in studies similar to DORI-09 that were published between 1998 and 2006 are summarized in Table 8. Clinical cure rates and sample sizes in studies similar to DORI-10 that were published between 1994 and 2006 are summarized in Table 10. The constancy assumption in the noninferiority margin consideration[69] was evaluated. Since these studies were published between 1994 and 2006, the clinical setting and medical practice of these studies were similar to those in the doripenem studies. In addition, no time trend is apparent upon inspection of the historical data in Tables 8 and 10, and the patients in the historical studies were similar to those who participated in the respective doripenem study.

For each of the DORI-09 and DORI-10 study designs, a meta-analysis based on DerSimonian and Laird's method[70] of treating each study as a random effect was performed to obtain a point estimate and its 2-sided 95% CI of the comparator's clinical cure rates. The results of the meta-analyses are presented in Table 9 and Table 11, each of which is located just below the table summarizing the individual studies upon which it was based. The assessment of the normality assumption was limited by the small number of studies included in each meta-analysis.

Table 8: Historical Piperacillin/Tazobactam Data From NP Studies in VAP and Non-VAP Patients

Study ID	# Clinical Cure	Sample Size	Proportion Cure
Joshi (2006)	67	98	68.4%
Brun-Buisson (1998)	26	51	51.0%
Schmitt (2006)	64	107	59.8%

Note: data in this table were used to estimate cure rates for the active comparator in Study DORI-09

Table 9: Estimates of Cure Rates (P_C %) for Active Comparator Piperacillin/Tazobactam With Two-Sided 95% CIs From Historical Data

Estimates (Proportion Cured %)	DerSirmonian-Laird Weighted Non-iterative Estimates
P_c	60.8
Standard error of P_c	4.7
2-sided 95% CI (P_c)	(51.6, 69.9)

P_c=proportion cured for comparator

Table 10: Historical Imipenem Data From NP VAP+Non VAP Studies

Study ID	# Clinical Cure	Sample Size	Proportion Cure
Joshi (2006)	42	73	57.5%[a]
Shorr (2005)	70	111	63.1%
West (2003)	57	94	60.6%
Zanetti (2003)	75	101	74.3%
Fink (1994)	44	83	53.0%[b]
Schmitt (2006)	73	110	66.4%

[a] Ventilated patients
[b] Clinical response
Note: data in this table were used to estimate cure rates for the active comparator in Study DORI-10

Table 11: Estimates of Cure Rates (P_C %) for Active Comparator Imipenem With Two-Sided 95% CIs From Historical Data

Estimates (Proportion Cured %)	DerSimonian-Laird Weighted Non-iterative estimates
P_c	63.0
Standard error of P_c	3.1
2-sided 95% CI (P_c)	(57.0, 69.0)

P_c=proportion cured for comparator

7.3.4.2. Estimation of Putative Placebo Cure Rates

In the absence of a placebo-controlled trial, reports that contained outcomes of patients who had received inappropriate or delayed therapy for treatment of NP were used. Estimates from these studies will overestimate the putative placebo response, as the initial "inappropriate" therapy was likely to have some efficacy and patients were usually switched to effective therapy after variable periods. These reports used to estimate the putative placebo cure rates are summarized in Table 12.

The studies reported mortality rates and not cure rates, therefore, a direct estimate of the placebo cure rate was not possible. Instead, the Sponsor used an indirect approach based on all-cause mortality rate or pneumonia-related mortality rate included in these reports, and the point estimate of the comparator's cure rate was used. This approach assumes that the ratio of the mortality rates of inadequate treatment (a surrogate for placebo) over adequate treatment (a surrogate for comparator treatment) was the same as the ratio of clinical failure rates. Again, this approach would likely result in an overestimate of the placebo cure rates and the ratios because death was probably averted in many patients who received inadequate therapy by switching to a more appropriate therapy.

The mortality ratios of inadequate versus adequate therapy were 1.8, 2.2, 2.4, 2.4 (2.7 for VAP patients), and 3.0 (Table 12). To estimate the putative placebo cure rate, the low end (2.2) of the middle cluster of the mortality ratio was used as the ratio of the clinical failure rate of an inadequate therapy versus an adequate therapy.

The estimated putative placebo cure rates are given in Table 13.

Table 12: Summary of Outcomes From Select Reports of Inappropriate, Delayed, or Inadequate Therapy

Author	Type of Study	N	Type of Patients	Outcome Measure	Result: Proportion of deaths	Mortality ratio (inadequate therapy vs. adequate therapy)
Kollef and Ward (1998)	Prospective, single-center, cohort study	130 (60)	VAP (Mini-BAL culture positive VAP patients)	All-cause MR	Inadequate therapy : 60.8% Adequate therapy: 33.3%	1.8
Leone et al. (2007)	Prospective observational study during 36-month period	115	VAP Positive BAL or tracheal aspirate cultures	All-cause MR	Inadequate therapy: Overall: 47% (7/15) (Related to VAP 27% [4/15]) Adequate therapy: Overall: 20% (20/100) (Related to VAP: 10% [10/100])	2.4 (VAP: 2.7)
Luna et al. (2006)	Prospective observational cohort study	76	VAP	All-cause MR	Inadequate or delayed appropriate therapy: 63.5% (33/52) Adequate Therapy: 29.2% (7/24)	2.2
Celis et al. (1988)	Prospective, case-control study	118 (120 episodes)[a]	NP	All-cause MR	Inadequate therapy: 91.6% (11/12) Appropriate therapy: 30.5% (33/108)	3.0
Rello et al. (1997)	5-year retrospective case-control observational study	113	VAP	Pneumonia-related MR	Inadequate therapy: 37.0% (10/27) Adequate therapy : 15.6% (n's not specified)	2.4

Key: MR=mortality rate; NP=nosocomial pneumonia; VAP=ventilator-associated pneumonia

[a] Two patients had 2 episodes (total number of episodes was 120).

Table 13: Estimates of Placebo Cure Rates for Hypothetical Placebo-Controlled Studies of the Comparator Treatment Groups Assuming a Ratio of Failure Rate of 2.2

Comparator	Failure Rate for Comparator (q_c)	Failure Rate for Placebo (q_p)	Cure Rate for Placebo (p_p)
Piperacillin/tazobactam	39.2%	86.2%	13.8%
Imipenem	37.0%	81.4%	18.6%

7.3.4.3. Estimation of the Parameter (Δ_{50}) That Represents 50% of the Comparator Effect Over Placebo

The fixed margin approach[69] was used to estimate Δ_{50}, the noninferiority margin that represents the preservation of at least 50% of the active comparator effect over placebo. Estimated placebo cure rates described in Table 13, and estimated active comparator cure rates described in Tables 9 and 11, were used in the estimation. To be conservative, the lower bound of the 2-sided 95% CI for active comparator cure rate and a placebo cure rate of 20%, which is greater than the highest estimate (18.6%) in Table 13, were used. The results are presented in Table 14 by doripenem study.

Table 14: Estimate of Δ_{50} With Placebo Cure Rate at 20%

Study	Placebo Cure Rate (P_p)	Lower Limit of the 2-Sided 95% CI for Comparator Cure Rate (C_{ll})	50% Preservation of the Benefit Over Placebo (Δ_{50})
DORI-09	20%	51.6%	15.8%
DORI-10	20%	57.0%	18.5%

$\Delta_{50}=(C_{ll} - P_p) / 2$, C_{ll} by DerSimonian and Laird:[70] weighted non-iterative estimates.

7.3.4.4. Discussion

There are no direct estimates for placebo clinical cure rates in NP studies. Therefore, the Sponsor estimated the placebo clinical cure rate in NP studies using extrapolations from studies of all-cause mortality and pneumonia-associated mortality of appropriate versus inappropriate initial antibiotics. The placebo clinical cure rate used in this approach was assumed to be 20%, which is considered an overestimate in a population of very sick, hospitalized patients infected with organisms that are generally considered clinically lethal.

7.3.4.5. Conclusion

As noted previously, the pre-defined noninferiority margin was 20% when the study was initiated, however, after conducting a comprehensive review of the literature, the Sponsor defined a conservative estimate of Δ_{50} for the clinical cure rate of 15.8% and 18.5% for piperacillin/tazobactam and imipenem, respectively. Given the high mortality rate in this condition and the low anticipated placebo affect, and the need to have new agents to treat pathogens potentially resistant to existing therapies, the Sponsor considers these estimates to be clinically acceptable. Therefore, the conservative Δ_{50} estimates were considered when drawing conclusions from the results of the two studies.

7.3.5. Handling of Dropouts or Missing Data

Patients who discontinued before the TOC visit, or had a missing or indeterminate outcome at the TOC visit, were considered nonevaluable and were excluded from the CE at TOC analysis set. However, failures before the TOC visit were carried forward to the TOC visit and could be considered evlauable failures. If otherwise evaluable, such patients were included in the primary analysis (CE at TOC analysis set). The cMITT analysis accounted for all treated patients with NP, with the exception of patients whose clinical outcome was cure and it was assessed too soon (<6 days after the last dose of study drug). These patients were excluded from the cMITT analysis.

7.3.6. Statistical Analyses

In the individual studies, the primary efficacy endpoints included the clinical cure rate at TOC (6 to 20 days post-therapy) in the CE at TOC analysis set and the clinical cure rate in the cMITT analysis set. The noninferiority of doripenem to comparator was tested in the individual studies and was concluded when the lower bound of the 2-sided 95% CI for the treatment difference (doripenem minus comparator), in the proportion of patients who were classified as clinically cured, was not less than the prespecified lower bound of the noninferiority margin of -20%. The 2-sided 95% CI was obtained in both studies using normal approximation to the difference between 2 binomial distributions with a continuity correction. The rationale for the selection of this particular margin is discussed in detail in Section 7.3.4.

7.3.7. Pooled Data

The proof of efficacy in this indication was based on independently demonstrating noninferiority in the 2 Phase 3 studies, DORI-09 and DORI-10. Pooling data across the studies provided a broader experience, since the 2 studies were conducted at different investigational sites by different investigators, and encompassed different types of patients with pneumonia included under the broader category of NP (i.e., hospital-acquired pneumonia [HAP], other healthcare associated pneumonia, and VAP). Another advantage of pooling the data was to have larger sample sizes for individual subgroup analyses. The combined data for these studies represents a large cohort (~1,000 NP patients [Table 15]), including 650 patients with VAP, one of the largest experiences reported in this patient population.

7.4. Results

7.4.1. Study Patients

7.4.1.1. Patient Disposition

Overall, approximately 67% of patients in both groups completed the study through to the late follow-up visit (Table 15). Death was the most common reason for discontinuation overall (13%) and in the individual studies (between 12% and 15%).

In addition, the 2 treatment groups within each study did not differ notably from one another in terms of patients who completed and discontinued from the study, for the various reasons presented in.

Table 15: Study Completion and Discontinuation Information
(Studies: JNJ38174942-DORI-9 and DORI-10: All Randomized Patients Analysis Set)

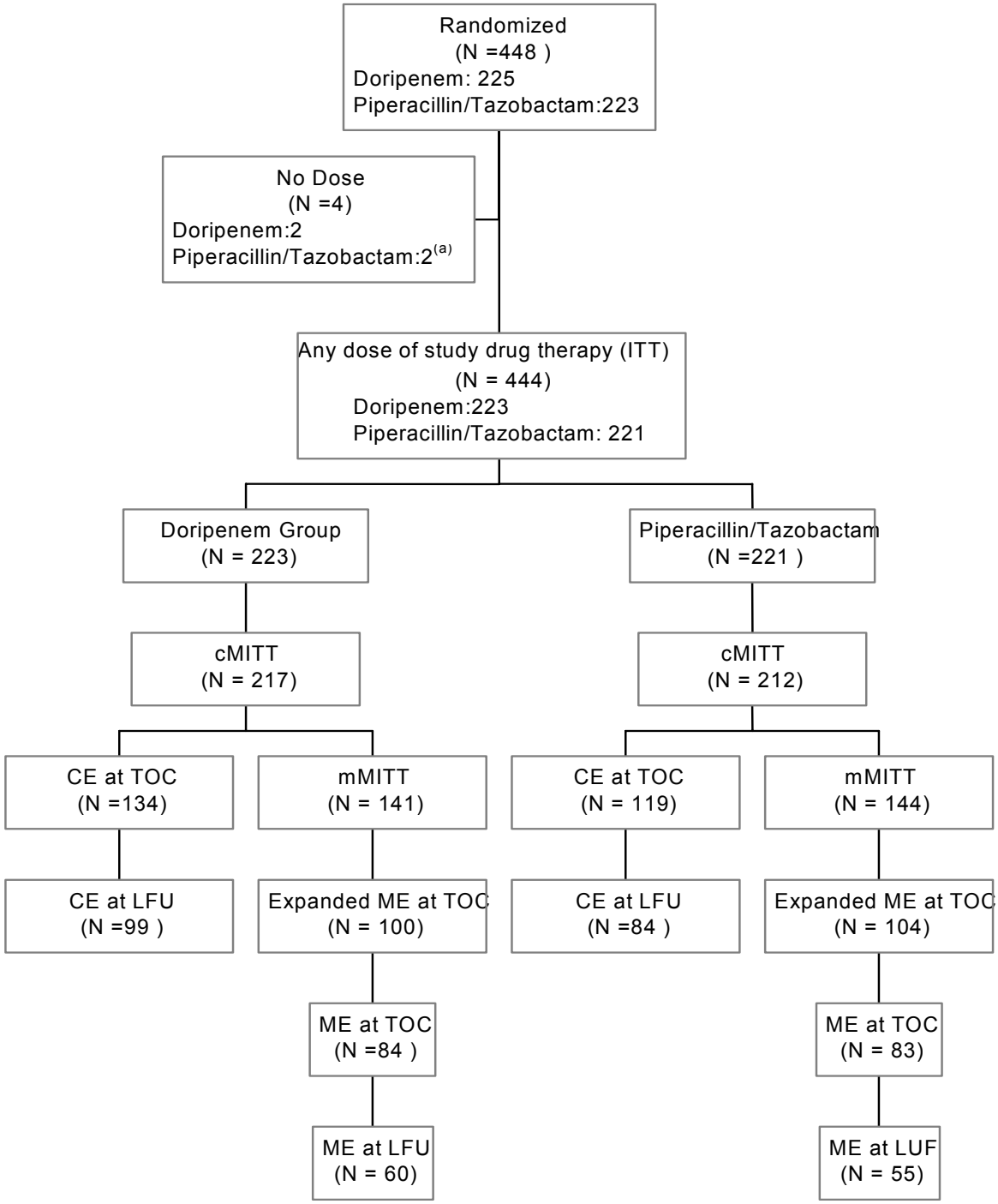
	DORI-09		DORI-10		Total	
	Doripenem (N=225) n (%)	Piperacillin/ tazobactam (N=223) n (%)	Doripenem (N=264) n (%)	Imipenem (N=267) n (%)	Doripenem [a] (N=489) n (%)	Comparators [b] (N=490) n (%)
Patient Completed [c] Study Per Protocol through Late Follow-up Visit	155 (68.9)	148 (66.4)	170 (64.4)	183 (68.5)	325 (66.5)	331 (67.6)
Patient Did Not Complete Study Per Protocol	70 (31.1)	75 (33.6)	94 (35.6)[d]	84 (31.5)	164 (33.5)	159 (32.4)
Adverse Event	6 (2.7)	6 (2.7)	11 (4.2)	9 (3.4)	17 (3.5)	15 (3.1)
At Request of Patient, Investigator, or Sponsor	3 (1.3)	2 (0.9)	2 (0.8)	0	5 (1.0)	2 (0.4)
Death	34 (15.1)	31 (13.9)	31 (11.7)	31 (11.6)	65 (13.3)	62 (12.7)
Lost to Follow Up	5 (2.2)	7 (3.1)	10 (3.8)	9 (3.4)	15 (3.1)	16 (3.3)
Need for Additional Antibacterial Therapy for An Infection Other Than Index Infection	1 (0.4)	3 (1.3)	5 (1.9)	9 (3.4)	6 (1.2)	12 (2.4)
Non-compliance	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)
Randomized but Study Drug Not Given	2 (0.9)	1 (0.4)	2 (0.8)	4 (1.5)	4 (0.8)	5 (1.0)
Treatment Failure[e]	16 (7.1)	19 (8.5)	15 (5.7)	9 (3.4)	31 (6.3)	28 (5.7)
Other	2 (0.9)	5 (2.2)	16 (6.1)	13 (4.9)	18 (3.7)	18 (3.7)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)
[b] Comparators refers to the combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)
[c] Patients were considered to have completed the study, as recorded on the case report form, if they had completed study drug therapy and all procedures through the late follow-up visit.
[d] One patient's reason for not completing the study was missing.
[e] Includes deaths due to pneumonia
Key: N=number of patients in the analysis set

7.4.1.2. Data Sets Analyzed and Exclusions From Analysis Sets

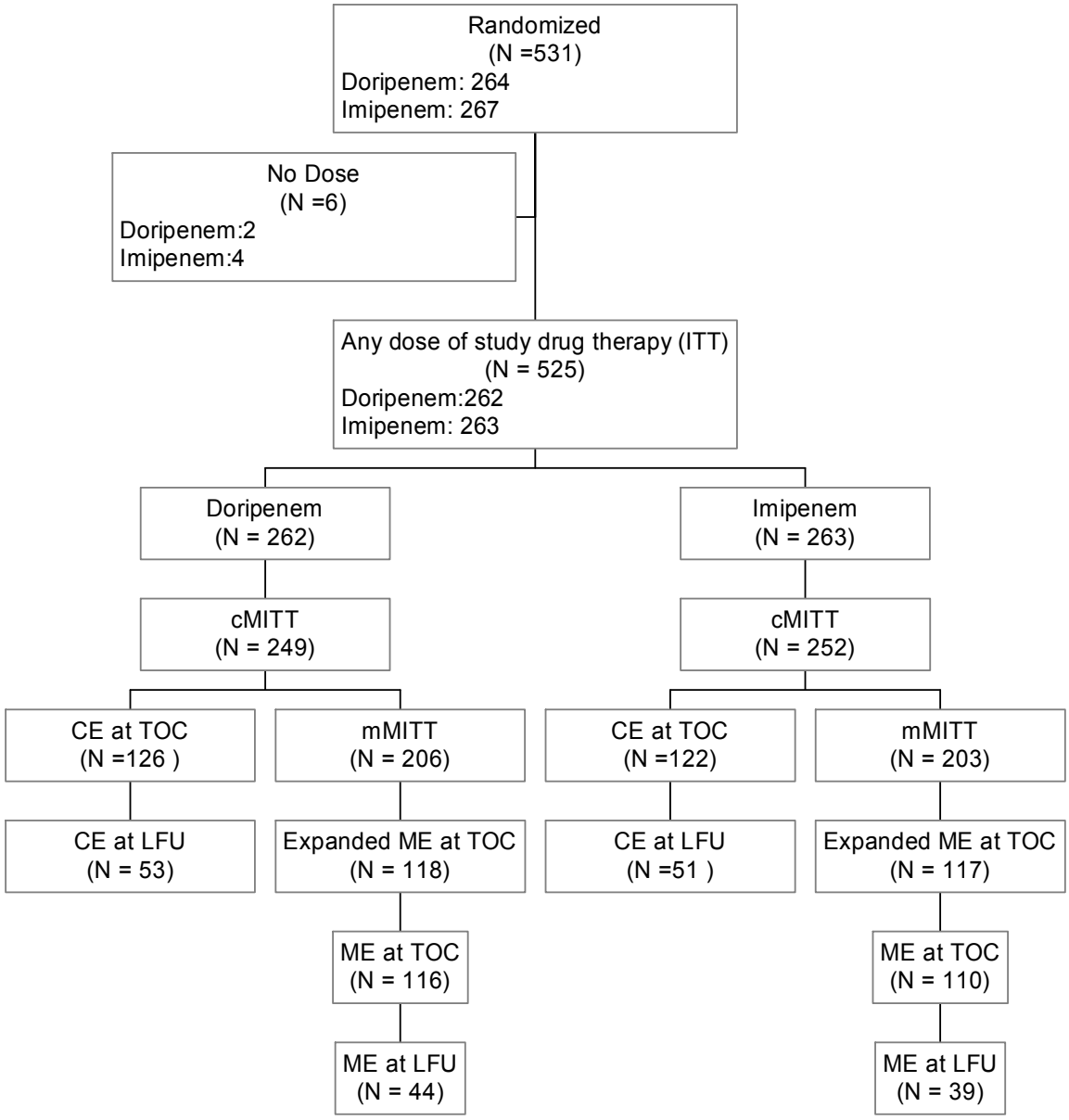
Schematic representations of the distribution of patients across the different analysis sets in Studies DORI-09 and DORI-10 are found in Figures 2 and 3, respectively.

Figure 2. Analysis Sets and Distribution of Patients
(Study DORI-09: All Randomized Patients)



Note: One subject was randomized to receive piperacillin/tazobactam but died prior to receiving any study drug.

Figure 3. Analysis Sets and Distribution of Patients
(Study DORI-10: All Randomized Patients)



There were no noteworthy differences in the number of patients randomized to treatment groups in the individual studies (Table 16). A higher percentage of patients in the comparator group (10%) than doripenem group (5%) were excluded from the CE at TOC analysis set because of resistant pathogen(s) isolated at baseline; otherwise, the overall percentages of patients excluded from the analysis sets for the various reasons

examined were generally comparable (Table 17). Lower evaluability was seen in Study DORI-10, illustrating the greater severity of disease in VAP, as evidenced by higher APACHE II scores at baseline (Table 19) and the greater likelihood of various complications in ICU hospitalized patients necessitating withdrawal from the study and changes in antimicrobial therapy (Table 17).

Table 16: Number of Patients Randomly Assigned to Treatment and Included in Each Analysis Set by Study and in the Pooled Data
(Studies JNJ38174942-DORI-09 and DORI-10: All Randomized Patients Analysis Set)

	---- Study DORI-09 ----		--- Study DORI-10 ----		----------Total ----------	
	Doripenem (N=225) n (%)	Piperacillin/ tazobactam (N=223) n (%)	Doripenem (N=264) n (%)	Imipenem (N=267) n (%)	Doripenem [a] (N=489) n (%)	Comparators[b] (N=490) n (%)
Clinical Modified Intent-to-Treat (cMITT)	217 (96.4)	212 (95.1)	249 (94.3)	252 (94.4)	466 (95.3)	464 (94.7)
Clinically Evaluable at TOC Visit (CE at TOC)	134 (59.6)	119 (53.4)	126 (47.7)	122 (45.7)	260 (53.2)	241 (49.2)
Clinically Evaluable at LFU Visit (CE at LFU)	99 (44.0)	84 (37.7)	53 (20.1)	51 (19.1)	152 (31.1)	135 (27.6)
Microbiological Modified Intent-to-Treat (mMITT)	141 (62.7)	144 (64.6)	206 (78.0)	203 (76.0)	347 (71.0)	347 (70.8)
Microbiologically Evaluable at TOC Visit (ME at TOC)	84 (37.3)	83 (37.2)	116 (43.9)	110 (41.2)	200 (40.9)	193 (39.4)
Expanded Microbiologically Evaluable at TOC[c] (Expanded ME at TOC)	100 (44.4)	104 (46.6)	118 (44.7)	117 (43.8)	218 (44.6)	221 (45.1)
Microbiologically Evaluable at LFU Visit (ME at LFU)	60 (26.7)	55 (24.7)	44 (16.7)	39 (14.6)	104 (21.3)	94 (19.2)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DOR-10)
[b] Comparators refers to the combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute infusion q6h or 1,000 mg 1-hour infusion q8h in DORI-10)
[c] Patients who are excluded from ME at TOC solely due to resistant baseline pathogen are included in the Expanded ME at TOC
Key: CE=clinically evaluable; cMITT=clinical modified intent-to-treat; LFU=late follow-up; ME=microbiologically evaluable; mMITT=microbiologic modified intent-to-treat; N=number of patients in the analysis set; TOC=test-of-cure

Table 17: Reasons for Exclusion From Analysis Sets for Each Study and the Pooled Data
(Studies: JNJ38174942-DORI-09 and DORI-10: All Randomized Patients Analysis Set)

	---- Study DORI-09 ----		----- Study DORI-10 -----		----------Total ----------	
Non-Evaluability Category	Doripenem (N=225)	Piperacillin/ tazobactam (N=223)	Doripenem (N=264)	Imipenem (N=267)	Doripenem [a] (N=489)	Comparators[b] (N=490)
Reason Not Evaluable	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Not cMITT Evaluable	8 (3.6)	11 (4.9)	15 (5.7)	15 (5.6)	23 (4.7)	26 (5.3)
Inadequate Evidence of Pneumonia	4 (1.8)	1 (0.4)	13 (4.9)	11 (4.1)	17 (3.5)	12 (2.4)
Patient Did Not Receive Any Dose of Study Therapy	2 (0.9)	2 (0.9)	2 (0.8)	4 (1.5)	4 (0.8)	6 (1.2)
Site 198[c]	2 (0.9)	7 (3.1)	0	0	2 (0.4)	7 (1.4)
Other	0	1 (0.4)	0	0	0	1 (0.2)
Not CE at TOC	91 (40.4)	104 (46.6)	138 (52.3)	145 (54.3)	229 (46.8)	249 (50.8)
Exclusion from the cMITT Analysis Set	8 (3.6)	11 (4.9)	15 (5.7)	15 (5.6)	23 (4.7)	26 (5.3)
Protocol-defined Disease Definition Not Met	12 (5.3)	7 (3.1)	13 (4.9)	12 (4.5)	25 (5.1)	19 (3.9)
Failure on Previous Antibacterial Therapy for HAP/VAP and Negative Baseline Respiratory Culture	8 (3.6)	8 (3.6)	12 (4.5)	13 (4.9)	20 (4.1)	21 (4.3)
If Ventilated, Negative Tracheal Aspirate & No Prior Antibacterial or No Change of Antibacterial Therapy	7 (3.1)	5 (2.2)	22 (8.3)	17 (6.4)	29 (5.9)	22 (4.5)
Inadequate/inappropriate Study Drug Therapy	17 (7.6)	22 (9.9)	41 (15.5)	31 (11.6)	58 (11.9)	53 (10.8)
Patient Received Both i.v. Study Medications Prior to Any Clinical Assessment	1 (0.4)	0	2 (0.8)	1 (0.4)	3 (0.6)	1 (0.2)
Prior Antibacterial Therapies Violation	4 (1.8)	1 (0.4)	0	0	4 (0.8)	1 (0.2)
Concomitant Antibacterial Therapies Violation	25 (11.1)	22 (9.9)	59 (22.3)	75 (28.1)	84 (17.2)	97 (19.8)
Confounding Baseline or Intercurrent Medical Event[d]	17 (7.6)	16 (7.2)	26 (9.8)	23 (8.6)	43 (8.8)	39 (8.0)
TOC Window Violation or "Indeterminate" Clinical Outcome Assessment at the TOC Visit	32 (14.2)	37 (16.6)	59 (22.3)	54 (20.2)	91 (18.6)	91 (18.6)
Only Baseline Resistant Pathogen(s) Isolated	19 (8.4)	32 (14.3)	5 (1.9)	15 (5.6)	24 (4.9)	47 (9.6)
Only Gram Positive LRT Pathogen and Treated with ≥ 24 Hours of Vancomycin	9 (4.0)	9 (4.0)	9 (3.4)	9 (3.4)	18 (3.7)	18 (3.7)
Other	0	0	0	1 (0.4)	0	1 (0.2)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DOR-10)
[b] Comparators refers to the combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute infusion q6h or 1,000 mg 1-hour infusion q8h in DORI-10)
[c] In Study DORI-09, 9 patients from European site 198 were excluded from all efficacy analyses because of serious noncompliance issues that were noted upon site monitoring
[d] Includes baseline conditions in the exclusion criteria (e.g., lung abscess, severe ARDS), deaths clearly unrelated to pneumonia (eg head trauma, subarachnoid hemorrhage) or events necessitating withdrawal (eg dialysis).
Key: CE=clinically evaluable; cMITT=clinical modified intent-to-treat; HAP=hospital-acquired pneumonia; LFU=late follow-up; LRT=lower respiratory tract; ME=microbiologically evaluable; mMITT=microbiologic modified intent-to-treat; N=number of patients in the analysis set; TOC=test-of-cure; VAP=ventilator-associated pneumonia
Note: Individual patients may have had more than 1 reason for exclusion from the analysis set

(continued)

Table 17: Reasons for Exclusion From Analysis Sets for Each Study and the Pooled Data
(Studies: JNJ38174942-DORI-09 and DORI-10: All Randomized Patients Analysis Set) (continued)

	---- Study DORI-09 ----		----- Study DORI-10 -----		----------Total ----------	
Non-Evaluability Category	Doripenem (N=225)	Piperacillin/ tazobactam (N=223)	Doripenem (N=264)	Imipenem (N=267)	Doripenem [a] (N=489)	Comparators[b] (N=490)
Reason Not Evaluable	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Not CE at LFU	126 (56.0)	139 (62.3)	211 (79.9)	216 (80.9)	337 (68.9)	355 (72.4)
Not Clinically Evaluable at TOC	91 (40.4)	104 (46.6)	138 (52.3)	145 (54.3)	229 (46.8)	249 (50.8)
Clinical Outcome Assessment at TOC Is Not "Clinical Cure"	74 (32.9)	75 (33.6)	108 (40.9)	115 (43.1)	182 (37.2)	190 (38.8)
Late Follow-up Window Violation or "Indeterminate" Clinical Outcome Assessment at LFU Visit	29 (12.9)	36 (16.1)	67 (25.4)	60 (22.5)	96 (19.6)	96 (19.6)
Concomitant Antibacterial Therapies Violation	17 (7.6)	11 (4.9)	59 (22.3)	71 (26.6)	76 (15.5)	82 (16.7)
Confounding Intercurrent Medical Event	6 (2.7)	9 (4.0)	8 (3.0)	6 (2.2)	14 (2.9)	15 (3.1)
Not Microbiological MITT Evaluable	84 (37.3)	79 (35.4)	58 (22.0)	64 (24.0)	142 (29.0)	143 (29.2)
Exclusion from the cMITT Analysis Set	8 (3.6)	11 (4.9)	15 (5.7)	15 (5.6)	23 (4.7)	26 (5.3)
No Qualifying Baseline Respiratory Pathogen Isolated	80 (35.6)	75 (33.6)	52 (19.7)	56 (21.0)	132 (27.0)	131 (26.7)
Not ME at TOC	141 (62.7)	140 (62.8)	148 (56.1)	157 (58.8)	289 (59.1)	297 (60.6)
Not Clinically Evaluable at TOC	91 (40.4)	104 (46.6)	138 (52.3)	145 (54.3)	229 (46.8)	249 (50.8)
No Qualifying Baseline Respiratory Pathogen Isolated	80 (35.6)	75 (33.6)	52 (19.7)	56 (21.0)	132 (27.0)	131 (26.7)
Other	1 (0.4)	1 (0.4)	3 (1.1)	2 (0.7)	4 (0.8)	3 (0.6)
Not ME at LFU	165 (73.3)	168 (75.3)	220 (83.3)	228 (85.4)	385 (78.7)	396 (80.8)
Not Microbiology Evaluable at TOC	141 (62.7)	140 (62.8)	148 (56.1)	157 (58.8)	289 (59.1)	297 (60.6)
Not Clinically Evaluable at LFU	126 (56.0)	139 (62.3)	211 (79.9)	216 (80.9)	337 (68.9)	355 (72.4)
Microbiological Response Was Not "Eradication" or "Presumed Eradication" at the TOC Visit	19 (8.4)	22 (9.9)	37 (14.0)	40 (15.0)	56 (11.5)	62 (12.7)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DOR-10)

[b] Comparators refers to the combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute infusion q6h or 1,000 mg 1-hour infusion q8h in DORI-10)

Key: CE=clinically evaluable; cMITT=clinical modified intent-to-treat; HAP=hospital-acquired pneumonia; LFU=late follow-up; LRT=lower respiratory tract; ME=microbiologically evaluable; mMITT=microbiologic modified intent-to-treat; N=number of patients in the analysis set; TOC=test-of-cure; VAP=ventilator-associated pneumonia

Note: Individual patients may have had more than 1 reason for exclusion from the analysis set

7.4.1.3. Baseline Characteristics

Demographic and Baseline Disease Characteristics

Overall, the demographic characteristics of patients in the CE at TOC analysis set were similar between treatment groups and were representative of the general patient population with NP suitable for treatment with doripenem and likely to be treated with this antibacterial agent[1] (Table 18). The demographic and baseline characteristics of patients in the pooled cMITT analysis set (including 466 doripenem-treated patients, 464 comparator-treated patients, as shown in Attachment 7), were generally similar to those of the pooled CE at TOC analysis set. Thus, the balance between treatment groups resulting from stratification and randomization was maintained in the CE at TOC analysis set.

Table 18: Demographic Characteristics for Each Study and the Pooled Data
(Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC Analysis Set)

	----- Study DORI-09 ------		----- Study DORI-10 -----		----------Total ----------	
	Doripenem (N=134)	Piperacillin/ tazobactam (N=119)	Doripenem (N=126)	Imipenem (N=122)	Doripenem[a] (N=260)	Comparators[b] (N=241)
Sex, n (%)						
N	134	119	126	122	260	241
Male	98 (73.1)	74 (62.2)	102 (81.0)	91 (74.6)	200 (76.9)	165 (68.5)
Female	36 (26.9)	45 (37.8)	24 (19.0)	31 (25.4)	60 (23.1)	76 (31.5)
Age						
N	134	119	126	122	260	241
Category, n (%)						
< 18	0	0	0	0	0	0
18 – 44	34 (25.4)	24 (20.2)	49 (38.9)	46 (37.7)	83 (31.9)	70 (29.0)
45 – 64	40 (29.9)	42 (35.3)	38 (30.2)	44 (36.1)	78 (30.0)	86 (35.7)
65 – 74	33 (24.6)	24 (20.2)	24 (19.0)	19 (15.6)	57 (21.9)	43 (17.8)
≥ 75	27 (20.1)	29 (24.4)	15 (11.9)	13 (10.7)	42 (16.2)	42 (17.4)
Mean (SD)	57.5 (19.17)	59.3 (18.87)	50.7 (19.63)	50.3 (19.02)	54.2 (19.66)	54.8 (19.44)
Median	58.5	62.0	52.0	49.5	56.0	57.0
Range	(19;94)	(18;97)	(18;86)	(18;86)	(18;94)	(18;97)
Age Category, n (%)						
N	134	119	126	122	260	241
<65	74 (55.2)	66 (55.5)	87 (69.0)	90 (73.8)	161 (61.9)	156 (64.7)
≥65	60 (44.8)	53 (44.5)	39 (31.0)	32 (26.2)	99 (38.1)	85 (35.3)
<75	107 (79.9)	90 (75.6)	111 (88.1)	109 (89.3)	218 (83.8)	199 (82.6)
≥75	27 (20.1)	29 (24.4)	15 (11.9)	13 (10.7)	42 (16.2)	42 (17.4)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)
[b] Comparators refers to the combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)
Key: N=number of patients in the analysis set; SD = standard deviation

(continued)

Table 18: Demographic Characteristics for Each Study and the Pooled Data
(Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC Analysis Set) (continued)

	----- Study DORI-09 ------		----- Study DORI-10 -----		----------Total ----------	
	Doripenem (N=134)	Piperacillin/ tazobactam (N=119)	Doripenem (N=126)	Imipenem (N=122)	Doripenem[a] (N=260)	Comparators[b] (N=241)
(Cont'd)						
Race, n (%)[c]						
N	134	119	126	122	260	241
American Indian or Alaskan Native	0	0	1 (0.8)	0	1 (0.4)	0
Asian	2 (1.5)	0	0	4 (3.3)	2 (0.8)	4 (1.7)
Black or African American	6 (4.5)	2 (1.7)	12 (9.5)	8 (6.6)	18 (6.9)	10 (4.1)
White	101 (75.4)	94 (79.0)	108 (85.7)	106 (86.9)	209 (80.4)	200 (83.0)
Native Hawaiian, Other Pacific Islander	0	0	0	0	0	0
Hispanic or Latino	23 (17.2)	23 (19.3)	5 (4.0)	4 (3.3)	28 (10.8)	27 (11.2)
Other	2 (1.5)	0	0	0	2 (0.8)	0
Region, n (%)[d]						
N	134	119	126	122	260	241
North America	19 (14.2)	17 (14.3)	53 (42.1)	50 (41.0)	72 (27.7)	67 (27.8)
USA	13 (9.7)	13 (10.9)	53 (42.1)	50 (41.0)	66 (25.4)	63 (26.1)
South America	41 (30.6)	37 (31.1)	0	0	41 (15.8)	37 (15.4)
Europe	70 (52.2)	62 (52.1)	47 (37.3)	47 (38.5)	117 (45.0)	109 (45.2)
Other	4 (3.0)	3 (2.5)	26 (20.6)	25 (20.5)	30 (11.5)	28 (11.6)

[c] Race was classified as other if the patient was not any of the stated race categories or more than 1 race was checked on the case report form.
[d] North America includes Canada and USA; South America includes Argentina, Brazil, and Chile; Europe includes Austria, Belarus, Belgium, Estonia, France, Georgia, Germany, Netherlands, Russia, Spain, and the Ukraine; Other includes Australia and S. Africa, Serbia, and Montenegro.
Key: N=number of patients in the analysis set; SD = standard deviation

A detailed breakdown of important prognostic factors and diagnostic criteria, as well as overall baseline microbiological features (i.e., baseline disease characteristics), is provided in Table 19. Patients in both DORI-09 and DORI-10 had indicators of severe disease. For example, the majority of patients in Study DORI-10 (51.6%) had an Acute Physiology and Chronic Health Evaluation II (APACHE II) score >15 compared with 25.3% of patients in DORI-09. However, the DORI-09 population was older and had considerable comorbidities. For example, a greater proportion of patients with renal failure at baseline were enrolled in DORI-09 than in DORI-10. Among the 303 patients with VAP, 49.8% (only patients in Study DORI-10) had late-onset VAP and 62.4% had a clinical pulmonary infection score (CPIS) ≥7. A greater proportion of patients in the comparator arm than in the doripenem arm in DORI-09 had bacteremia at baseline; however, the overall number of patients with bacteremia was small, bacteremia was not,

in general, associated with worse outcome, and the difference did not affect the comparative study results. The impact of adjunctive therapy is discussed in detail in Section 7.4.1.5.

Table 19: Baseline Disease Characteristics for Each Study and the Pooled Data
(Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC Analysis Set)

	----- Study DORI-09 ------		----- Study DORI-10 -----		----------Total ----------	
	Doripenem (N=134)	Piperacillin/ tazobactam (N=119)	Doripenem (N=126)	Imipenem (N=122)	Doripenem[a] (N=260)	Comparators[b] (N=241)
Ventilation Mode, n (%)						
N	134	119	126	122	260	241
Non-VAP	105 (78.4)	93 (78.2)	0	0	105 (40.4)	93 (38.6)
VAP	29 (21.6)	26 (21.8)	126 (100)	122 (100)	155 (59.6)	148 (61.4)
Early-onset VAP (<5 Days)	29 (100)	26 (100)	48 (38.1)	49 (40.2)	77 (49.7)	75 (50.7)
Late-onset (≥5 Days)	0	0	78 (61.9)	73 (59.8)	78 (50.3)	73 (49.3)
APACHE II Score, n (%)						
N	134	119	126	122	260	241
< 10	28 (20.9)	31 (26.1)	5 (4.0)	13 (10.7)	33 (12.7)	44 (18.3)
10-15	70 (52.2)	60 (50.4)	54 (42.9)	48 (39.3)	124 (47.7)	108 (44.8)
16-20	29 (21.6)	19 (16.0)	40 (31.7)	35 (28.7)	69 (26.5)	54 (22.4)
21-25	7 (5.2)	9 (7.6)	26 (20.6)	23 (18.9)	33 (12.7)	32 (13.3)
> 25	0	0	1 (0.8)	3 (2.5)	1 (0.4)	3 (1.2)
≤15	99 (73.9)	91 (76.5)	59 (46.8)	61 (50.0)	158 (60.8)	152 (63.1)
>15	35 (26.1)	28 (23.5)	67 (53.2)	61 (50.0)	102 (39.2)	89 (36.9)
Clinical Pulmonary Infection Score, n (%)[c]						
N	29	26	126	122	155	148
5	7 (24.1)	5 (19.2)	20 (15.9)	23 (18.9)	27 (17.4)	28 (18.9)
6	7 (24.1)	2 (7.7)	29 (23.0)	21 (17.2)	36 (23.2)	23 (15.5)
7	1 (3.4)	7 (26.9)	29 (23.0)	32 (26.2)	30 (19.4)	39 (26.4)
> 7	14 (48.3)	12 (46.2)	48 (38.1)	46 (37.7)	62 (40.0)	58 (39.2)
Baseline Creatinine Clearance Group, n (%)[d]						
N	134	119	126	122	260	241
Missing	2 (1.5)	5 (4.2)	0	1 (0.8)	2 (0.8)	6 (2.5)
Normal (≥80)	71 (53.0)	70 (58.8)	104 (82.5)	97 (79.5)	175 (67.3)	167 (69.3)
Mild Renal Failure (>50-<80)	35 (26.1)	33 (27.7)	9 (7.1)	16 (13.1)	44 (16.9)	49 (20.3)
Moderate Renal Failure (>30-≤50)	21 (15.7)	9 (7.6)	13 (10.3)	5 (4.1)	34 (13.1)	14 (5.8)
Severe Renal Failure (≤30)	5 (3.7)	2 (1.7)	0	3 (2.5)	5 (1.9)	5 (2.1)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)
[b] Comparators refers to the combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)
[c] Applicable to ventilated patients only
[d] Creatinine clearance was calculated using the patient's actual body weight, the serum creatinine level measured at the local laboratory and the Cockroft-Gault formula
Key: APACHE II=Acute Physiology and Chronic Health Evaluation II; n=number of patients; N=number of patients in the analysis set; SD=standard deviation; VAP=ventilator-associated pneumonia
Note: Baseline value was defined as the last available value before the start of i.v. infusion of the first dose of study drug therapy.
(continued)

Table 19: Baseline Disease Characteristics for Each Study and the Pooled Data (Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC Analysis Set) (continued)

	----- Study DORI-09 ------		----- Study DORI-10 -----		----------Total ----------	
	Doripenem (N=134)	Piperacillin/ tazobactam (N=119)	Doripenem (N=126)	Imipenem (N=122)	Doripenem[a] (N=260)	Comparators[b] (N=241)
Bacteremia, n (%)[e]						
N	134	119	126	122	260	241
No	126 (94.0)	102 (85.7)	113 (89.7)	111 (91.0)	239 (91.9)	213 (88.4)
Yes	8 (6.0)	17 (14.3)	13 (10.3)	11 (9.0)	21 (8.1)	28 (11.6)
With Same Pathogen Isolated From Both LRT and Blood, n	2	9	6	7	8	16
Any Adjunctive Therapy, n (%)						
N	134	119	126	122	260	241
No	25 (18.7)	16 (13.4)	79 (62.7)	74 (60.7)	104 (40.0)	90 (37.3)
Yes	109 (81.3)	103 (86.6)	47 (37.3)	48 (39.3)	156 (60.0)	151 (62.7)
Anti-MRSA Coverage, n (%)						
N	134	119	126	122	260	241
No	117 (87.3)	98 (82.4)	89 (70.6)	88 (72.1)	206 (79.2)	186 (77.2)
Yes	17 (12.7)	21 (17.6)	37 (29.4)	34 (27.9)	54 (20.8)	55 (22.8)
Anti-Pseudomonas Coverage, n (%)						
N	134	119	126	122	260	241
No	29 (21.6)	18 (15.1)	101 (80.2)	92 (75.4)	130 (50.0)	110 (45.6)
Yes	105 (78.4)	101 (84.9)	25 (19.8)	30 (24.6)	130 (50.0)	131 (54.4)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)
[b] Comparators refers to the combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)
[e] Bacteremia was defined as 1 positive blood culture if associated with a pathogenic organism, or 2 positive blood cultures if associated with organisms generally considered nonpathogenic.
Key: n=number of patients; N=number of patients in the analysis set; LRT=lower respiratory tract

In summary, demographic and baseline characteristics in the CE at TOC analysis set were generally similar between treatment arms within the individual studies, and were consistent with those of the general patient population with NP suitable for treatment with doripenem.[1] However, there were a few notable differences between studies, including a generally older population (45% versus 29% of patients ≥65 years of age, respectively) and a greater proportion of patients with moderate to severe renal dysfunction in DORI-09 than in DORI-10 (15% versus 8% of patients, respectively). The higher proportion of younger patients in DORI-10 was likely due to a greater proportion of patients with trauma admitted to the ICU. The lower rate of renal dysfunction in patients in DORI-10 may be related to the exclusion of patients requiring dialysis, including continuous renal replacement therapy (continuous hemofiltration), a

procedure commonly used in the ICU. As many more patients in DORI-10 were treated in the ICU this would have led to a differential exclusion for this reason. These between-study differences were unlikely to play a meaningful role in the comparative efficacy assessment for doripenem, because these and other demographic features within each study were similar between treatment groups.

The numbers of patients who were elderly or had high APACHE II scores or a high CPIS is evidence of the substantial proportion of high-risk patients enrolled in both of these studies.

7.4.1.4. Baseline Pathogens and Their Susceptibility Profiles

Lower Respiratory Tract Pathogens

Results from the DORI-09 study showed much higher resistance rates at baseline to piperacillin/tazobactam among *Enterobacteriaceae* than anticipated when the study was originally planned, reflecting the worldwide dissemination of ESBLs (Table 20). However, because adjunctive amikacin therapy was given to most patients (206/253, 81% of patients overall) in DORI-09 (Table 24), and most *Enterobacteriaceae* were susceptible to amikacin, most patients in the piperacillin/tazobactam arm did receive at least 1 appropriate empiric antibacterial agent.

In DORI-10, *Enterobacteriaceae* resistant to either carbapenem were not observed (Table 21). The data from the 2 studies indicate that while ESBLs appear to have disseminated widely, enteric carbapenemases remain rare in global terms. All baseline *P. aeruginosa* strains had doripenem MICs ≤4 µg/mL, whereas only 76% were susceptible (MIC ≤4 µg/mL) to imipenem in DORI-10. Susceptibility in *Acinetobacter* was similar between the 2 carbapenems evaluated in DORI-10.

A summary of susceptibility characteristics for all baseline LRT pathogens in both studies can be found in Attachment 8. The susceptibility profiles of baseline LRT pathogens confirmed the in vitro broad-spectrum activity of doripenem. Resistance (defined as an MIC of ≥16 µg/mL) to doripenem at baseline was rarely observed and was lower than resistance to the comparators. Overall, in both studies, the resistance of *P. aeruginosa* (4 of 105, 4%) to doripenem was notably lower than for comparator treatments (piperacillin/tazobactam: 19 of 105, 18%; imipenem: 15 of 105, 14%).

Table 20: Baseline LRT Pathogens and Susceptibility Characteristics to Study Drug Received
(Study JNJ-38174942-DORI-09: mMITT Analysis Set)

Pathogen Classification	---------- Doripenem ----------					---------- Piperacillin/tazobactam ----------				
Pathogen High Level Group	NI	---------- Susceptibility, n (%) ---------				NI	---------- Susceptibility, n (%) ---------			
Pathogen Name	n	S	I	R	Total	n	S	I	R	Total
Gram negative, aerobic	112	88	1	6	95	132	79	5	31	115
Non-Lactose Fermenters										
Acinetobacter baumannii	14	7 (58)	0	5 (42)	12	9	3 (33)	1 (11)	5 (56)	9
Pseudomonas aeruginosa	22	20(100)	0	0	20	32	21 (66)	0	11 (34)	32
Enterobacteriaceae	60	52(100)	0	0	52	64	40 (68)	4 (7)	15(25)	59
Enterobacter cloacae	12	11 100)	0	0	11	6	4 (80)	1 (20)	0	5
Escherichia coli	14	13(100)	0	0	13	11	7 (88)	1(13)	0	8
Klebsiella pneumoniae	20	17 100)	0	0	17	28	13 (46)	1 (4)	14(50)	28
Serratia marcescens	4	4 (100)	0	0	4	4	2 (50)	1 (25)	1 (25)	4
Haemophilus spp.	10	8 (100)	0	0	8	15	12(100)	0	0	12
Haemophilus influenzae	10	8 (100)	0	0	8	12	10(100)	0	0	10
Gram positive, aerobic	101	59	1	10	70	95	41	0	12	53
Staphylococcus aureus	61	41 (82)	1 (2)	8 (16)	50	55	41(80)	0	10 (20)	51
MRSA	18	9 (50)	1 (6)	8 (44)	18	15	5 (33)	0	10(67)	15
MSSA	32	32(100)	0	0	32	36	36(100)	0	0	36
Streptococcus pneumoniae	9	5 (100)	0	0	5	9	0	0	0	0
Streptococcus spp. other than *Streptococcus pneumoniae*	9	3 (100)	0	0	3	15	0	0	0	0
Enterococcus faecalis	11	6 (100)	0	0	6	8	0	0	0	0

Key: NI=the number of isolates; Total=the number of isolates with an interpretation of susceptibility results.
Note 1: The denominator for the percentage is Total.
Note 2: If multiple isolates were found for a given pathogen from the same patient, the isolate with the highest MIC value was used in the analysis.
Note 3: Only those pathogens with clinical and microbiological relevance were summarized in the table.
Note 4: For Doripenem, susceptibility definitions were Susceptible (S), Intermediate (I), or Resistant (R) if the MIC is ≤ 4µg/mL, = 8µg/mL or ≥ 16µg/mL, respectively. For Piperacillin/Tazobactam, the number Susceptible, Intermediate or Resistant is defined according to the Clinical and Laboratory Standards Institute (CLSI) recommendations.

Table 21: Baseline LRT Pathogens and Susceptibility Characteristics to Study Drug Received
(Study JNJ-38174942-DORI-10: mMITT Analysis Set)

Pathogen Classification	Doripenem					Imipenem				
Pathogen High Level Group	NI	Susceptibility, n (%)				NI	Susceptibility, n (%)			
Pathogen Name	n	S	I	R	Total	n	S	I	R	Total
Gram negative, aerobic	224	177	1	4	182	236	167	3	14	184
Non-Lactose Fermenters										
Acinetobacter baumannii	15	11 (85)	0	2 (15)	13	16	9 (82)	0	2 (18)	11
Pseudomonas aeruginosa	30	28 (100)	0	0	28	26	19 (76)	3 (12)	3 (12)	25
Enterobacteriaceae	116	103 (100)	0	0	103	117	94 (100)	0	0	94
Citrobacter koseri	4	2 (100)	0	0	2	5	4 (100)	0	0	4
Enterobacter aerogenes	11	11 (100)	0	0	11	8	7 (100)	0	0	7
Enterobacter cloacae	26	24 (100)	0	0	24	14	11 (100)	0	0	11
Escherichia coli	18	16 (100)	0	0	16	30	24 (100)	0	0	24
Klebsiella oxytoca	8	7 (100)	0	0	7	9	7 (100)	0	0	7
Klebsiella pneumoniae	26	24 (100)	0	0	24	22	20 (100)	0	0	20
Proteus mirabilis	6	6 (100)	0	0	6	8	6 (100)	0	0	6
Serratia marcescens	12	9 (100)	0	0	9	8	5 (100)	0	0	5
Haemophilus spp.	48	30 (100)	0	0	30	59	44 (100)	0	0	44
Haemophilus influenzae	47	30 (100)	0	0	30	55	42 (100)	0	0	42
Gram positive, aerobic	138	87	1	3	91	117	64	0	6	70
Staphylococcus aureus	74	58 (94)	1 (2)	3 (5)	62	76	55 (90)	0	6 (10)	61
MRSA	14	10 (71)	1 (7)	3 (21)	14	16	10 (63)	0	6 (38)	16
MSSA	48	48 (100)	0	0	48	45	45 (100)	0	0	45
Streptococcus pneumoniae	21	17 (100)	0	0	17	11	9 (100)	0	0	9
Streptococcus spp. other than *Streptococcus pneumoniae*	28	11 (100)	0	0	11	19	0	0	0	0
Enterococcus faecalis	1	1 (100)	0	0	1	2	0	0	0	0

Key: NI=the number of isolates; Total=the number of isolates with an interpretation of susceptibility results.
Note 1: The denominator for the percentage is Total.
Note 2: If multiple isolates were found for a given pathogen from the same patient, the isolate with the highest MIC value was used in the analysis.
Note 3: Only those pathogens with clinical and microbiological relevance were summarized in the table.
Note 4: For Doripenem, susceptibility definitions were Susceptible (S), Intermediate (I), or Resistant (R) if the MIC was ≤ 4µg/mL, = 8µg/mL or ≥ 16µg/mL, respectively. For Imipenem, the number Susceptible, Intermediate or Resistant was defined according to the Clinical and Laboratory Standards Institute (CLSI) recommendations.

Blood Pathogens

In DORI-09 19 patients in the ME at TOC analysis set had bacteremia at baseline. Of these, only 2 patients in the doripenem treatment arm and 9 patients in the piperacillin/tazobactam treatment arm had bacteremia with the same pathogen isolated from the LRT. A concomitant pathogen isolated from both LRT and blood is generally considered a confirmation of the organism(s) causing the LRT infection, but is likely to be a secondary bacteremia and, therefore not a sign of severity. [61]

In DORI-10, 23 patients in the ME at TOC analysis set had bacteremia at baseline. Of these, only 6 patients in the doripenem treatment arm and 7 patients in the imipenem treatment arm had bacteremia with the same pathogen isolated from the LRT.

Blood pathogens and their susceptibility in DORI-09 are shown in Table 22 and for DORI-10 in Table 23.

Table 22: Baseline Blood Isolates and Study Drug Therapy Susceptibility Characteristics
(Study JNJ-38174942-DORI-09: cMITT Analysis Set)

Pathogen Classification										
Pathogen High Level Group	---------- Doripenem ----------					---------- Piperacillin/Tazobactam ----------				
Pathogen High Level Subgroup	NI	-------- Susceptibility, n (%) -------				NI	-------- Susceptibility, n (%) -------			
Sponsor Pathogen Name	n	S	I	R	Total	n	S	I	R	Total
Gram negative, aerobic	7	6	0	0	6	16	10	0	3	13
Acinetobacter spp.	1	0	0	0	0	4	0	0	2 (100)	2
Acinetobacter spp.	1	0	0	0	0	4	0	0	2 (100)	2
Acinetobacter baumannii	0	0	0	0	0	3	0	0	2 (100)	2
Enterobacteriaceae	3	3 (100)	0	0	3	10	9 (100)	0	0	9
Enterobacter spp.	1	1 (100)	0	0	1	5	5 (100)	0	0	5
Enterobacter aerogenes	0	0	0	0	0	2	2 (100)	0	0	2
Enterobacter cloacae	1	1 (100)	0	0	1	2	2 (100)	0	0	2
Escherichia spp.	2	2 (100)	0	0	2	3	2 (100)	0	0	2
Escherichia coli	2	2 (100)	0	0	2	3	2 (100)	0	0	2
Haemophilus spp.	3	3 (100)	0	0	3	0	0	0	0	0
Haemophilus spp.	3	3 (100)	0	0	3	0	0	0	0	0
Haemophilus influenzae	2	2 (100)	0	0	2	0	0	0	0	0
Non-enterobacteriaceae	0	0	0	0	0	2	1 (50)	0	1 (50)	2

Key: NI=the number of isolates; Total=the number of isolates with an interpretation of susceptibility results.
Note 1: This table includes only pathogens that were isolated in >1 patient in any group
Note 2: The denominator for the percentage is Total.
Note 3: Isolates in the cMITT analysis set refer to both pathogenic and non-pathogenic organisms
Note 4: The denominator for the percentage is Total.
Note 5: For Doripenem, susceptibility definitions were Susceptible (S), Intermediate (I), or Resistant (R) if the MIC is = 4µg/ml, = 8µg/ml or = 16µg/ml, respectively. For Piperacillin/Tazobactam, the number Susceptible, Intermediate or Resistant is defined according to the Clinical and Laboratory Standards Institute (CLSI) recommendations.

(continued)

Table 22: Baseline Blood Isolates and Study Drug Therapy Susceptibility Characteristics
(Study JNJ-38174942-DORI-09: cMITT Analysis Set) (Continued)

Pathogen Classification										
Pathogen High Level Group	---------- Doripenem ----------					---------- Piperacillin/Tazobactam ----------				
Pathogen High Level Subgroup	NI	-------- Susceptibility, n (%) -------				NI	-------- Susceptibility, n (%) -------			
Sponsor Pathogen Name	n	S	I	R	Total	n	S	I	R	Total
Gram positive, aerobic	35	18	3	6	27	30	14	0	3	17
Enterococcus spp.	3	2 (100)	0	0	2	4	0	0	0	0
Enterococcus spp.	3	2 (100)	0	0	2	4	0	0	0	0
Enterococcus faecalis	2	1 (100)	0	0	1	4	0	0	0	0
Miscellaneous gram positive aerobes	1	0	0	0	0	4	0	0	1 (100)	1
Bacillus species (not speciated)	0	0	0	0	0	2	0	0	0	0
Staphylococcus spp.	31	16 (64)	3 (12)	6 (24)	25	20	14 (88)	0	2 (13)	16
Coagulase negative staphylococci	27	14 (67)	3 (14)	4 (19)	21	11	7 (88)	0	1 (13)	8
Staphylococcus epidermidis	6	2 (50)	1 (25)	1 (25)	4	2	2 (100)	0	0	2
Staphylococcus haemolyticus	4	1 (33)	1 (33)	1 (33)	3	2	1 (50)	0	1 (50)	2
Staphylococcus species (cns)	12	7 (78)	0	2 (22)	9	5	3 (100)	0	0	3
Staphylococcus warneri	2	2 (100)	0	0	2	1	1 (100)	0	0	1
Staphylococcus aureus	4	2 (50)	0	2 (50)	4	9	7 (88)	0	1 (13)	8
Staphylococcus aureus	4	2 (50)	0	2 (50)	4	9	7 (88)	0	1 (13)	8
Streptococcus pneumoniae	0	0	0	0	0	2	0	0	0	0
Streptococcus pneumoniae	0	0	0	0	0	2	0	0	0	0
Streptococcus pneumoniae	0	0	0	0	0	2	0	0	0	0

Refer to the first page of the table for footnotes

Table 23: Baseline Blood Isolates and Susceptibility Characteristics to the Study Drug Received
(Study JNJ-38174942-Dori-10: cMITT Analysis Set)

Pathogen Classification										
Pathogen High Level Group	---------- DORIPENEM ----------					---------- IMIPENEM ----------				
Pathogen High Level Subgroup	NI	-------- Susceptibility, n (%) -------				NI	-------- Susceptibility, n (%) -------			
Sponsor Pathogen Name	n	S	I	R	Total	n	S	I	R	Total
Gram negative, aerobic	16	9	0	0	9	15	13	0	1	14
*Acinetobacte*r spp.	3	3 (100)	0	0	3	1	1 (100)	0	0	1
Acinetobacter spp.	3	3 (100)	0	0	3	1	1 (100)	0	0	1
Acinetobacter baumannii	2	2 (100)	0	0	2	1	1 (100)	0	0	1
Enterobacteriaceae	9	5 (100)	0	0	5	11	10 (100)	0	0	10
Enterobacter spp.	4	3 (100)	0	0	3	3	3 (100)	0	0	3
Enterobacter cloacae	4	3 (100)	0	0	3	1	1 (100)	0	0	1
Klebsiella spp.	0	0	0	0	0	5	4 (100)	0	0	4
Non-enterobacteriaceae	2	1 (100)	0	0	1	2	1 (50)	0	1 (50)	2
Pseudomonas spp.	2	1 (100)	0	0	1	2	1 (50)	0	1 (50)	2
Pseudomonas aeruginosa	2	1 (100)	0	0	1	2	1 (50)	0	1 (50)	2
Gram positive, aerobic	44	26	2	0	28	40	22	1	2	25
Enterococcus spp.	4	2 (67)	1 (33)	0	3	1	0	0	0	0
Enterococcus spp.	4	2 (67)	1 (33)	0	3	1	0	0	0	0
Enterococcus faecalis	3	2 (100)	0	0	2	1	0	0	0	0

Key: NI=the number of isolates; Total=the number of isolates with an interpretation of susceptibility results.
Note 1: This table include only pathogens that were isolated in >1 patient in any group
Note 2: The denominator for the percentage is Total.
Note 3: Isolates in the cMITT analysis set refer to both pathogenic and non-pathogenic organisms
Note 4: The denominator for the percentage is Total.
Note 5: For Doripenem, susceptibility definitions were Susceptible (S), Intermediate (I), or Resistant (R) if the MIC is = 4µg/ml, = 8µg/ml or = 16µg/ml, respectively. For Piperacillin/Tazobactam, the number Susceptible, Intermediate or Resistant is defined according to the Clinical and Laboratory Standards Institute (CLSI) recommendations.

(continued)

Table 23: Baseline Blood Isolates and Susceptibility Characteristics to the Study Drug Received
(Study JNJ-38174942-Dori-10: Clinical Modified Intent-to-Treat Analysis Set) (Continued)

Pathogen Classification										
Pathogen High Level Group	---------- DORIPENEM ----------					---------- IMIPENEM ----------				
Pathogen High Level Subgroup	NI	-------- Susceptibility, n (%) -------				NI	-------- Susceptibility, n (%) -------			
Sponsor Pathogen Name	n	S	I	R	Total	n	S	I	R	Total
Gram positive, aerobic (continued)										
Staphylococcus spp.	35	21 (95)	1 (5)	0	22	35	22 (88)	1 (4)	2 (8)	25
Coagulase negative *staphylococci*	28	16 (94)	1 (6)	0	17	27	17 (89)	1 (5)	1 (5)	19
Staphylococcus capitis	2	1 (100)	0	0	1	1	0	0	0	0
Staphylococcus epidermidis	13	7 (100)	0	0	7	9	8 (89)	1 (11)	0	9
Coagulase negative *staphylococci*										
Staphylococcus sciuri	3	3 (100)	0	0	3	0	0	0	0	0
Staphylococcus simulans	2	2 (100)	0	0	2	1	1 (100)	0	0	1
Staphylococcus species (cns)	7	3 (75)	1 (25)	0	4	12	7 (100)	0	0	7
Staphylococcus aureus	7	5 (100)	0	0	5	8	5 (83)	0	1 (17)	6
Staphylococcus aureus	7	5 (100)	0	0	5	8	5 (83)	0	1 (17)	6
Streptococcus spp. other than *Streptococcus pneumoniae*	4	2 (100)	0	0	2	3	0	0	0	0
Streptococcus spp.	4	2 (100)	0	0	2	3	0	0	0	0
Streptococcus pyogenes	2	2 (100)	0	0	2	0	0	0	0	0

Refer to the first page of the table for footnotes

7.4.1.5. Adjunctive Therapy

Aminoglycosides are not recommended as monotherapy for NP; they are generally recommended as adjunctive therapy to β-lactams, for example, in order to broaden the spectrum of empiric coverage of organisms in NP to over 90%, especially when multi-drug resistant organisms are suspected.[1] In the doripenem studies, patients were not randomized to or stratified by adjunctive therapy.

The frequency of use of at least 1 dose of adjunctive amikacin or vancomycin is shown in Table 24 by study and by co-primary analysis set. In Study DORI-09, optional adjunctive therapy for potential MRSA was administered relatively infrequently (~15% in the CE at TOC analysis set); but as required by the protocol based on label provisions, the majority of patients (~80%) received adjunctive therapy (mostly with amikacin) for potential *P. aeruginosa*. In DORI-10 most patients received monotherapy, with less than 25% receiving amikacin and approximately 30% receiving vancomycin.

Table 24. Adjunctive Therapy by Indication
(Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC and cMITT Analysis Sets)

Study Received at Least 1 Dose of Adjunctive Therapy	**CE at TOC**			**cMITT**		
	Doripenem	**Piperacillin/ tazobactam**	**Total**	**Doripenem**	**Piperacillin/ tazobactam**	**Total**
DORI-09	**N=134**	**N=119**	**N=253**	**N=217**	**N=212**	**N=429**
Amikacin/Vancomycin	109 (81.3%)	103 (86.6%)	212 (83.8%)	180 (82.9%)	190 (89.6%)	370 (86.2%)
Amikacin	105 (78.4%)	101 (84.9%)	206 (81.4%)	166 (76.5%)	183 (86.3%)	349 (81.4%)
Vancomycin	17 (12.7%)	23 (19.3%)	40 (15.8%)	56 (25.8%)	63 (29.7%)	119 (27.7%)
	Doripenem	**Imipenem**	**Total**	**Doripenem**	**Imipenem**	**Total**
DORI-10	**N=126**	**N=122**	**N=248**	**N=249**	**N=252**	**N=501**
Amikacin/Vancomycin	51 (40.5%)	50 (41.0%)	101 (40.7%)	101 (40.6%)	118 (46.8%)	219 (43.7%)
Amikacin	27 (21.4%)	30 (24.6%)	57 (23.0%)	57 (22.9%)	66 (26.2%)	123 (24.6%)
Vancomycin	40 (31.7%)	37 (30.3%)	77 (31.0%)	78 (31.3%)	88 (34.9%)	166 (33.1%)

Adjunctive vancomycin was unlikely to have affected the clinical cure rates in the CE analysis set, as it was not administered to any patients with proven gram-positive pathogens, such as MSSA or *S. pneumoniae*, except 1 patient in DORI-09. Note, patients with only MRSA at baseline were not included in the CE analysis set.

The clinical cure rates with and without amikacin in DORI-09 in the 2 co-primary analysis populations are presented in Table 25.

Table 25: Clinical Cure Rate at TOC by Adjunctive Amikacin
(Study JNJ38174942-DORI-09: CE at TOC and cMITT Analysis Sets)

Analysis Set	Doripenem			Piperacillin/ Tazobactam		
CE at TOC	N	n	%	N	n	%
Adjunctive Amikacin	105	85	81.0	101	81	80.2
No Adjunctive Therapy	29	24	82.8	18	14	77.8
Clinical Modified Intent-to-Treat						
Adjunctive Amikacin	163	114	69.9	181	115	63.5
No Adjunctive Therapy	50	34	68.0	28	19	67.9

Key: N=the number of patients in the specific category; n=the number of patients who were clinically cured in the specified category

The clinical cure rates were similar between the doripenem treatment group and the piperacillin/tazobactam treatment group for both the CE at TOC and the cMITT populations, whether they received adjunctive amikacin or not. Thus any added benefit of the addition of amikacin could not be discerned.

The clinical cure rates in DORI-10 in the two co-primary analysis populations are presented in Table 26.

Table 26: Clinical Cure Rate at TOC by Adjunctive Amikacin
(Study JNJ38174942-DORI-10: CE at TOC and cMITT Analysis Sets)

Analysis Sets	Doripenem			Imipenem		
CE at TOC	N	n	%	N	n	%
Adjunctive Amikacin	27	20	74.1	30	14	46.7
No Adjunctive Amikacin	99	66	66.7	92	65	70.7
Clinical Modified Intent-to-Treat						
Adjunctive Amikacin	55	32	58.2	65	31	47.7
No Adjunctive Amikacin	189	112	59.3	184	113	61.4

Key: N=the number of patients in a specific category; n=the number of patients who were clinically cured in the category

The clinical cure rates were slightly higher for patients in the doripenem treatment group when they received adjunctive therapy than when they did not only in the CE at TOC analysis set and not in the cMITT analysis set. The clinical cure rate in patients in the imipenem treatment group was markedly lower when adjunctive amikacin was administered than when it was not in both co-primary analysis sets suggesting that the use of amikacin may be more of a marker of a sicker subpopulation. The differences between the treatment groups in some analyses likely reflect the variability observed when comparing small numbers in patients who received amikacin.

Although the influence of disease severity on outcomes in patients who received adjunctive therapy is difficult to quantify, the data presented do not allow discernment of any significant benefit of adjunctive therapy. If the premise that patients receiving adjunctive therapy are more likely to have severe disease is true, the generally higher cure rates with doripenem suggest that doripenem may be particularly useful in these patients.

7.4.1.6. Assessment of Compliance With Protocol

7.4.1.6.1. Confirmation of Compliance With the Protocol-Defined Definition of Diagnosis of Pneumonia

During the review of the NP NDA, the documentation that the inclusion criteria relating to the diagnosis of NP having been met was assessed. The primary study outcomes were reanalyzed in patients with an objectively documented diagnosis of NP. These reanalyses in both DORI-09 and DORI-10 included only patients who had substantial evidence supporting a baseline diagnosis of pneumonia (i.e., who met all of the protocol inclusion criteria related to the diagnosis of pneumonia, including appropriate chest radiograph findings, elevated leukocyte count or temperature, and stipulated clinical signs and symptoms). In the reassessment process only patient evaluability (based on confirmation of the baseline diagnosis) was reassessed; outcomes remained as originally recorded in the database.

In addition to the clinical re-evaluations, expectorated sputum gram stain results for patients in the modified mMITT analysis sets were interpreted for adequacy by the Sponsor to determine whether bacterial isolates were pathogens. Pathogens isolated from patients who met the protocol specified sputum gram stain criteria were included in revised per pathogen microbiologic outcome results.

A team of qualified Sponsor physicians (not involved in the conduct of the NP trials), who were blinded to treatment assignment as well as the original evaluability assessments, was convened by the Sponsor to rereview the DORI-09 and DORI-10 patients' chest X-ray findings and other baseline information relevant to the confirmation of the diagnosis of NP. Two sources of radiographic interpretation were available: the independent radiologist's report and the investigator's interpretation, as recorded on the case report form. Radiographic terms deemed acceptable and unacceptable descriptors of pneumonia were defined prior to the original study analyses. Each reviewer was provided with the independent radiology reports, radiographic interpretation, as

described by the investigator in the case report form, body temperature, blood WBC counts, CPIS and all other available clinical data in order to make assessments. Inclusion criteria required by the protocol for the diagnosis of NP included new or progressive infiltrates on chest X-ray, elevated oral temperature (>38^{o}C), and/or elevated WBC count or a left shift (bands) on the differential, CPIS ≥5 (without microbiology for intubated patients), clinical symptoms and physical signs of lung consolidation, and the presence of visible respiratory secretion purulence, as recorded in the CPIS in intubated patients. Although not a specifically required inclusion criterion, LRT specimen culture results were also considered.

Confirmation of the baseline WBC count was based on central laboratory data, but when these were not available or did not meet the protocol-specified inclusion criteria, locally obtained results were reviewed.

Patients were classified as having met the criteria for a diagnosis of pneumonia based on the following definitions:

- Pneumonia Strict (PS) Definition: Patients had supporting data inhouse for all the inclusion criteria relevant to the diagnosis of pneumonia defined in the protocol, as described above. In particular, these patients had a independent radiologist's report (or equivalent), confirming the presence of pulmonary infiltrates consistent with pneumonia. This was required regardless of evidence from other sources, such as the investigator's interpretation of the X-ray and other clinical findings. Patients with missing radiology reports (except where these were routinely not produced) were excluded from this definition.
- Pneumonia Clinical (PC) Definition: This was the same as the PS definition except that the diagnosis of an infiltrate was based only on the "chest X-ray" page of the case report form. Thus, for this definition, the investigator's interpretation over-ruled the radiologist's report, in the few cases where they were discrepant. In addition, other clinical and laboratory findings (e.g., culture results) not stipulated in the inclusion criteria were considered in support of the diagnosis. The inclusion criteria for temperature and WBC count at screening were based on the case report form where inhouse source documentation was not available.

The PS definition might be regarded as more objective since the radiographic interpretation was based on an independent radiology report. However, clinical practice is better reflected by the PC definition, where radiographic changes were interpreted by the clinicians treating the patient and were supported by

additional clinical or laboratory findings. Data were analyzed using both definitions.

In addition to the clinical definition of pneumonia, sputum gram stain smear results were evaluated based on copies of original microbiology laboratory reports. The sputum specimens were considered adequate if the WBC was >25 and the SEC <10 cells per low power field.

The results of reassessment of the diagnosis of pneumonia in the CE at TOC and the cMITT analysis sets meeting the PS and PC definitions of pneumonia at screening in Study DORI-09 are provided in Table 27.

Among patients in the CE at TOC analysis set in Study DORI-09, 97% and >99% met the PS and PC definitions of pneumonia, respectively. For patients in the cMITT analysis set, similar results were noted (95% and 99% for PS and PC definitions, respectively).

Table 27: Summary of Patients Meeting the Strict (PS) and the Clinical (PC) Definitions of Pneumonia (Study JNJ38174942-DORI-09)

Analysis Set	Doripenem n (%)	Piperacillin/ Tazobactam n (%)	Total n (%)
CE at TOC (Original NP NDA)	(N=134)	(N=119)	(N=253)
PS Definition	131 (98)	115 (97)	246 (97)
PC Definition	134 (100)	118 (99)	252 (>99)
cMITT	(N=213)	(N=209)	(N=422)
PS Definition	201 (94)	201 (96)	402 (95)
PC Definition	211 (99)	208 (>99)	419 (99)

Note: Percentages were calculated with the number of patients in each group as denominator.

The clinical efficacy of doripenem and piperacillin/tazobactam, based on the PS and PC subgroups in DORI-09 in the CE at TOC, cMITT, and mMITT analysis sets, is provided in Table 28. The nonferiority of doripenem to piperacillin/tazobactam in patients meeting PS and PC definitions of pneumonia was confirmed in all analysis sets.

This review and reanalysis of patients in DORI-09 supports the evaluation of the diagnosis of pneumonia made by the BEC.

Table 28: Clinical Cure Rates in Patients Meeting the Strict Definition of Pneumonia (PS) and Meeting the Clinical Definition of Pneumonia (PC)
(Study JNJ38174942-DORI-09)

	Doripenem 500 mg 1-h inf			Piperacillin/ Tazobactam			Diff[a]	
Analysis Set	N	n	%	N	n	%	(%)	95% CI[b]
Meeting PS Definition								
CE at TOC	131	106	80.9	115	91	79.1	1.8	(-9.1; 12.6)
cMITT	201	141	70.1	201	127	63.2	7.0	(-2.7; 16.7)
mMITT[c]	118	81	68.6	121	79	65.3	3.4	(-9.4; 16.1)
Meeting PC Definition								
CE at TOC	134	109	81.3	118	94	79.7	1.7	(-8.9; 12.3)
cMITT	211	147	69.7	208	133	63.9	5.7	(-3.8; 15.2)
mMITT[c]	123	84	68.3	125	83	66.4	1.9	(-10.6; 14.4)

[a] Diff=difference between doripenem minus piperacillin/tazobactam
[b] 2-sided 95% CI is based on the normal approximation to the difference of two binomial proportions with continuity correction.
[C] Patients with inadequate sputum specimens were excluded from the mMITT
Key: N=the number of patients in each treatment group.

The results of reassessment of the diagnosis of pneumonia in the CE at TOC and the cMITT analysis sets meeting the PS and PC definitions of pneumonia at screening in Study DORI-10 are given in Table 29. Among patients in the CE at TOC analysis set in Study DORI-10, 90% and 98% of patients met the PS and PC definitions of pneumonia, respectively. For patients in the cMITT analysis set, similar results were noted (91% and 98% for PS and PC definitions, respectively).

Table 29: Summary of Patients Meeting the PS and PC Definitions of Pneumonia
(Study JNJ38174942-DORI-10)

Analysis Set	Doripenem n (%)	Imipenem n (%)	Total n (%)
CE at TOC (Original NP NDA)	(N=126)	(N=122)	(N=248)
PS Definition	115 (91)	109 (89)	224 (90)
PC Definition	123 (98)	120 (98)	243 (98)
cMITT (Original NP NDA)	(N=244)	(N=249)	(N=493)
PS Definition	224 (92)	226 (91)	450 (91)
PC Definition	237 (97)	244 (98)	481 (98)

Note: Percentages calculated with the number of patients in each group as denominator.

The clinical efficacy of doripenem and imipenem, based on the PS and PC subgroups in DORI-10 in the CE at TOC, cMITT, and mMITT analysis sets, is provided in Table 30. The noninferiority of doripenem to imipenem in patients

meeting PS and PC definitions of pneumonia was supported in all of the analysis sets.

This rereview and reanalysis supports the investigator's assessment of the clinical diagnosis of pneumonia in the vast majority of these complex patients. In all but a few cases, the clinical diagnosis was confirmed by the objective findings.

Table 30: Clinical Cure Rates in Patients Meeting the Strict Definition of Pneumonia (PS) and Meeting the Clinical Definition of Pneumonia (PC)
(Study JNJ38174942-DORI-10)

	Doripenem 500 mg 4-h inf			Imipenem			Diff[a]	
	N	n	%	N	n	%	(%)	95% CI[b]
PS Definition								
CE at TOC	115	78	67.8	109	71	65.1	2.7	(-10.6; 15.9)
cMITT	224	129	57.6	226	131	58.0	-0.4	(-9.9; 9.2)
mMITT	183	103	56.3	180	107	59.4	-3.2	(-13.9; 7.5)
PC Definition								
CE at TOC	123	84	68.3	120	77	64.2	4.1	(-8.6; 16.8)
cMITT	237	139	58.6	244	140	57.4	1.3	(-8.0; 10.5)
mMITT	194	111	57.2	196	114	58.2	-0.9	(-11.3; 9.4)

Key: CI=confidence interval; N=the number of patients in each treatment group.
[a] Diff=Doripenem minus imipenem.
[b] 2-sided 95% CI is based on the normal approximation to the difference of two binomial proportions with continuity correction.

The number of acceptable expectorated sputum specimens from gram stain reports (WBCs >25 and SECs <10) reviewed is provided in Table 31. The table also includes, for interest, those patients with low SEC counts, regardless of WBCs, as this could be considered sufficient evidence to exclude a grossly contaminated specimen and hence suitability for culture (this latter group is however not included in the analyses).

The majority of expectorated sputum specimens with available gram stain results in DORI-09 (100/129, 77.5% in the mMITT analysis set) were considered acceptable (WBCs >25 and SECs <10). All but a few patients in DORI-10 were intubated, and thus the number of expectorated sputum specimens was small (<2.0% overall). A total of 134 of 284 patients in DORI-09 had sputum specimens taken at baseline and 129 (96%) of these patients had gram stain results available. In DORI-10, which allowed recently extubated patients to be enrolled, only 6 of 409 patients were not intubated at baseline and had sputum samples obtained, and all 6 of these patients had gram stain results available.

Table 31: Results of the Sputum Gram Stain Reports
(Study JNJ38174942 DORI-09 and DORI-10: mMITT Analysis Set [Original NP NDA])

	DORI-09 (N=284) n (%)	DORI-10 (N=409) n (%)
Patients with sputum specimens taken at baseline	134 (47.2)	6 (1.5)
Patients with Gram stain results for sputum specimens	129 (96.3 [a])	6 (100 [a])
SECs <10	118 (88.1[a])	4 (66.7 [a])
WBCs >25 AND SECs <10	100 (74.6 [a])	1 (16.7 [a])

[a] Among patients with sputum specimens.

The favorable per pathogen microbiologic outcomes for baseline LRT pathogens in patients meeting the PS definition are provided in Table 32. This table includes all patients with acceptable expectorated sputum as well as those with non-sputum LRT specimens.

The favorable per pathogen outcomes for baseline LRT pathogens in patients in the ME analysis set (excluding those with inadequate sputum specimens) meeting the PS definition were similar to those in the original ME population (Table 39) and showed that doripenem was microbiologically effective against the major causative pathogens of NP, including *S. aureus* (methicillin susceptible strains), *S. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *H. influenzae* and Enterobacteriaceae (*E. cloacae*, *E. coli*, *K. pneumoniae*).

Table 32: Favorable Per Pathogen Microbiological Outcomes for Common Baseline LRT Pathogens (mMITT) in Acceptable Expectorated Sputum or Non-Sputum LRT Specimens in the Pooled Data (Studies JNJ38174942-DORI-09 and DORI-10, PS Subset of ME at TOC Analysis Set)

Baseline Pathogen Classification:	-- Doripenem 500 mg --			--- Comparator ---				
Gram positive, aerobic	N	n	%	N	n	%	Diff[a] (%)	95% CI[b]
Staphylococcus aureus (MSSA)	26	20	76.9	27	23	85.2	-8.3	
Streptococcus pneumoniae	15	13	86.7	12	11	91.7	-5.0	
Acinetobacter baumannii	13	11	84.6	8	6	75.0	9.6	
Enterobacter cloacae	24	22	91.7	15	11	73.3	18.3	
Escherichia coli	18	15	83.3	22	15	68.2	15.2	
Klebsiella pneumoniae	23	18	78.3	15	9	60.0	18.3	
Haemophilus influenzae	37	31	83.8	44	35	79.5	4.2	(-15.1; 23.6)
Pseudomonas aeruginosa	33	23	69.7	27	16	59.3	10.4	

Common baseline pathogens were bacterial pathogens isolated in 10 or more Doripenem patients in the analysis set
"Favorable per pathogen microbiological outcomes" was defined as microbiological outcome of eradication or presumed eradication
[a] Diff= doripenem minus comparator;
[b] The 2-sided 95% CI is based on the normal approximation to the difference of 2 binomial proportions with continuity correction. The confidence interval is provided only if the number of patients with the pathogen is 30 or more in each of treatment arm.
Key: N=the number of patients who had the specific baseline pathogen; n=the number of patients who had favorable microbiological outcome for the specified pathogen.

In summary, the Sponsor confirmed that objective data were available to show that the diagnostic criteria for pneumonia were met in both studies in the vast majority of patients. The sensitivity analyses using the most stringent definition of pneumonia, shown above, were consistent with the results of the analysis of all patients submitted in the original NP NDA and support the conclusion that doripenem is noninferior to comparators for clinical and microbiologic outcomes.

7.4.1.6.2. Other Assessments of Compliance

The numbers of patients for whom selected important study procedures were not followed are shown in Tables 33 and 34. In general, high compliance rates with study procedures were observed in both studies. Only small numbers of patients did not have the TOC assessed in the 7 to 14 day post therapy period specified in the protocol. The majority of patients who switched to oral therapy met all of the specified criteria for the oral switch in DORI-09. Chest X-rays were not obtained in a small proportion of patients in both studies at the TOC visit, as required in the protocol, probably because these were not deemed to be warranted based on the patient's improved clinical condition.

Table 33. Other Assessments of Compliance: TOC Visit, Duration of Therapy, Dose Adjustments for Renal Impairment, Oral Switch, Chest X-ray at TOC
(JNJ38174942-DORI-09: Safety Analysis Set)

	Doripenem	Pipericillin/Tazobactam	Total
TOC not within 7 – 14 days after the last dose of therapy[a]	4	4	8
Oral switch was done but the eligibility cannot be confirmed[c]			
Temperature >38.5ºC	0	2	2
WBC abnormal at TOC	9	5	14
No chest X-ray at TOC[b]	7	10	17

[a] Failure could occur before the 7 – 14 days window
[b] Only patients who were assessed as cure at TOC are counted
[c] N = 182 subjects who switched to oral therapy

Table 34. Other Assessments of Compliance: TOC Visit, Duration of Therapy, Dose Adjustments for Renal Impairment, Chest X-ray at TOC
JNJ38174942-DORI-10: Safety Analysis Set

	Doripenem	Imipenem	Total
TOC not within 7 – 14 days after the last dose of therapy[a]	7	8	15
No chest X-ray at TOC[b]	22	16	38

[a] Failure could occur before the 7 – 14 days window
[b]Only patients who were assessed as cure at TOC are counted

7.4.2. Comparative Efficacy

7.4.2.1. Per-patient Clinical and Microbiological Response

Clinical and microbiological cure rates are presented for DORI-09 and DORI-10 by study and for the pooled data in Table 35. The confidence intervals for the difference between doripenem and comparator in clinical cure rates at TOC in the primary and co-primary analysis sets in both studies are summarized in Figure 4.

The lower bound of the 2-sided 95% CI of the treatment difference in clinical cure rate in the primary analysis set (CE at TOC, defined in Section 7.3.1) for both Study DORI-09 and Study DORI-10 were well above the protocol-specified –20% and the conservative margin estimates from the noninferiority margin justification after the study completion (-15.8% for DORI-09 and -18.5% for DORI-10 (refer to Section 7.3.4 for a discussion of the noninferiority margin justification). In addition, the between-group comparison of clinical cure rates in the co-primary (cMITT) analysis set were consistent with those of the primary analysis set. It is noteworthy that the lower bound of the 95% confidence interval for the treatment difference in clinical cure rate ranged from –11.4 to –4.1 across all analysis sets and both studies. These estimates are all well above the protocol-specified noninferiority margin of -20% and the conservative margin estimates (-15.8% and –18.5%, for DORI-09 and DORI-10, respectively), providing clear evidence that the clinical efficacy of doripenem in the treatment of NP was non-inferior to that of piperacillin/tazobactam and imipenem.

The overall lower clinical cure rates in DORI-10 were expected due to the exclusive enrollment of VAP patients, who had more severe illness (e.g., APACHE II scores >15, as shown in Table 19). A subgroup analysis conducted on the pooled data (Section 7.4.2.5) revealed lower cure rates for patients with VAP than patients with non-VAP (Table 45; 64% to 68% for VAP and 85% to 86% for non-VAP).

Table 35: Microbiological and Clinical Cure Rates for Nosocomial Pneumonia for Each Study and the Pooled Data (Studies JNJ38174942-DORI-09 and DORI-10)

	----Doripenem[a] ---			-- Comparators[b] --			Diff[c]	95%
	N	n	(%)	N	n	(%)	(%)	CI[d]
Study –DORI-09								
Clinical Cure at TOC/CE at TOC	134	109	(81.3)	119	95	(79.8)	1.5	(-9.1; 12.1)
Clinical Cure/cMITT[e]	213	148	(69.5)	209	134	(64.1)	5.4	(-4.1; 14.8)
Clinical Cure at TOC/ME at TOC[e]	84	69	(82.1)	83	65	(78.3)	3.8	(-9.4; 17.1)
Clinical Cure/mMITT[e]	139	94	(67.6)	144	97	(67.4)	0.3	(-11.4; 11.9)
Microbiological Cure at TOC/ME at TOC	84	71	(84.5)	83	67	(80.7)	3.8	(-8.9; 16.5)
Study –DORI-10								
Clinical Cure at TOC/CE at TOC	126	86	(68.3)	122	79	(64.8)	3.5	(-9.1; 16.1)
Clinical Cure/cMITT[e]	244	144	(59.0)	249	144	(57.8)	1.2	(-7.9; 10.3)
Clinical Cure at TOC/ME at TOC	116	80	(69.0)	110	71	(64.5)	4.4	(-8.7; 17.6)
Clinical Cure/mMITT[e]	202	117	(57.9)	201	118	(58.7)	-0.8	(-10.9; 9.3)
Microbiological Cure at TOC/ME at TOC	116	85	(73.3)	110	74	(67.3)	6.0	(-6.8; 18.8)
Pooled Data from Studies DORI-09 and DORI-10								
Clinical Cure at TOC/CE at TOC	260	195	(75.0)	241	174	(72.2)	2.8	(-5.3; 10.9)
Clinical Cure/cMITT[e]	457	292	(63.9)	458	278	(60.7)	3.2	(-3.3; 9.7)
Clinical Cure at TOC/ME at TOC	200	149	(74.5)	193	136	(70.5)	4.0	(-5.3; 13.4)
Clinical Cure/mMITT[e]	341	211	(61.9)	345	215	(62.3)	-0.4	(-8.0; 7.1)
Microbiological Cure at TOC/ME at TOC	200	156	(78.0)	193	141	(73.1)	4.9	(-4.1; 13.9)

[a] Doripenem 500 mg 1-hour infusion q8h in DORI-09 and doripenem 500 mg 4-hour infusion q8h in DORI-10

[b] Piperacillin/tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10

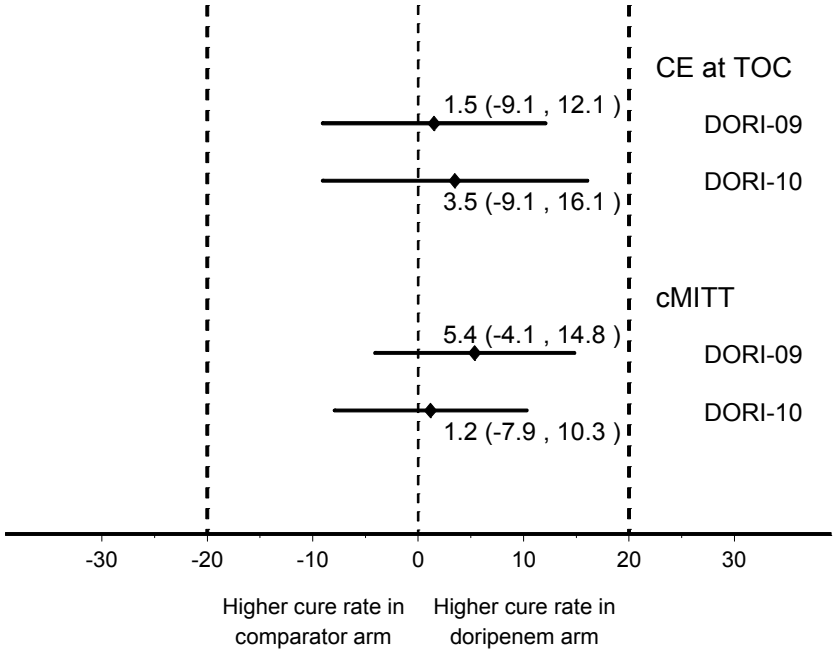
[c] Difference= doripenem group minus comparator group

[d] The 2-sided 95% CI was based on the normal approximation to the difference of two binomial proportions with continuity correction

[e] Patients who were clinically cured and had a TOC visit within 5 days after the end of study drug therapy were not included per FDA comment.

Key: CE=clinically evaluable; cMITT=clinical modified intent-to-treat; Diff=difference; ME=microbiologically evaluable; Microbiological cure=eradication or presumed eradication of all baseline pathogens; mMITT=microbiological modified intent-to-treat N=all patients in the analysis set at that time point; TOC=test-of-cure

Figure 4: The 2-sided 95% Confidence Intervals for the Difference Between Doripenem and Comparator Clinical Cure Rates



Outcomes were also assessed at the EOT[i.v.] visit (Table 36). Clinical cure/improvement rates for the pooled data in the CE at TOC analysis set at EOT(i.v.) visit were 83.8% in the doripenem arm and 84.2% in the comparator arm. These high cure/improvement rates are indicative of the efficacy of the i.v. portion of the study therapy regimens (note: as discussed in detail in Section 7.2.2.3, investigators in Study DORI-09 [only] had the option of switching patients to oral therapy after at least 72 hours of i.v. study drug therapy).

Table 36: Clinical Cure/Improvement Rate at EOT(i.v.) in the Individual Studies and Pooled Data (Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC Analysis Set)

	-- Doripenem[a] ---			-Comparators[b] --				
	N	n	%	N	n	%	Diff[c](%)	95% CI[d]
Study DORI-09	134	117	87.3	119	103	86.6	0.8	(-8.4; 9.9)
Study DORI-10	126	101	80.2	122	100	82.0	-1.8	(-12.4; 8.7)
Studies DORI-09 and DORI-10	260	218	83.8	241	203	84.2	-0.4	(-7.2; 6.4)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)
[b] Combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)
[c] Diff=Difference: doripenem combined group minus combined comparator group
[d] The 2-sided 95% CI was based on the normal approximation to the difference of two binomial proportions with continuity correction;
Key: CI=confidence interval; n=number of patients who had a favorable clinical response at that time point in the analysis set; N=all patients in the analysis set at that time point.

7.4.2.2. Per-pathogen Clinical and Microbiological Cure Rate

The per pathogen microbiological cure rates at the TOC visit by pathogen species for all patients in the individual studies in the ME at TOC analysis set are presented for pathogens isolated in ≥10 patients in the doripenem group in Studies DORI-09 and DORI-10 in Tables 37 and 38, respectively. A similar summary for the pooled data that includes clinical cure rates is presented for pathogens isolated in ≥10 patients in the doripenem group in the ME at TOC analysis set in Table 39. Doripenem was associated with high clinical cure rates at the TOC visit against the major causative pathogens of NP, including *S. aureus* (methicillin-susceptible strains), *S. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *H. influenzae*, and *Enterobacteriaceae* (*K. pneumoniae, E. cloacae*, *E. coli).* Consistent with clinical outcomes, the rate of microbiological cure (eradication or presumed eradication) in gram-negative infections was higher for doripenem versus comparator in gram-negative infections, although these findings should be interpreted cautiously because of small sample sizes. Of note, the 2-sided 95% CI around the difference in the clinical cure rate for *P. aeruginosa* for the pooled studies did not include zero. The clinical cure rates for *S. pneumoniae* appeared lower in patients treated with doripenem. However, because sample sizes were small, this difference should be interpreted cautiously. Of note, microbiological cure rates in the doripenem arm were higher than clinical cure rates for *S. pneumoniae*, indicating that clinical failures were usually not associated with failure to eradicate the pathogen, but was due to new infections. The lower clinical response rate is believed to be attributable to host factors or the presence of more than 1 pathogen.

Table 37: Per-pathogen Microbiological Cure Rates at the TOC Visit by Common Baseline Pathogen
(Study JNJ-38174942-DORI-09: ME at TOC Analysis Set)

Baseline Pathogen Classification	Doripenem N	Doripenem n	Doripenem %	Piperacillin/ Tazobactam N	Piperacillin/ Tazobactam n	Piperacillin/ Tazobactam %	Diff[a](%)	95% CI[b]
Gram positive, aerobic								
Staphylococcus spp.								
Staphylococcus aureus								
Staphylococcus aureus	17	14	82.4	15	15	100.0	-17.6	
MSSA	14	13	92.9	15	15	100.0	-7.1	
Gram negative, aerobic								
Enterobacteriaceae								
Enterobacter spp.								
Enterobacter cloacae	11	11	100.0	6	5	83.3	16.7	
Klebsiella spp.								
Klebsiella pneumoniae	14	11	78.6	11	7	63.6	14.9	
Non-enterobacteriaceae								
Pseudomonas spp.								
Pseudomonas aeruginosa	18	15	83.3	17	12	70.6	12.7	

[a] Doripenem minus piperacillin/tazobactam

[b] The 2-sided 95% CI is based on the normal approximation to the difference of 2 binomial proportions with continuity correction. The confidence interval is provided only if the number of patients with the pathogen is 30 or more in each of treatment arm.

Key: N=the number of patients who had the specific baseline pathogen; n=the number of patients who had favorable microbiological outcome for the specified pathogen.

Note 1: A per-pathogen microbiological outcome is favorable if the outcome is eradication or presumed eradication for the specific pathogen.

Note 2: Common baseline pathogens are bacterial pathogens isolated in 10 or more ME at TOC patients in the doripenem group at baseline.

Table 38: Per-Pathogen Microbiological Cure Rates at the TOC Visit by Common Baseline Pathogen (Study JNJ-38174942-DORI-10: ME at TOC Analysis Set)

Baseline pathogen classification	---- Doripenem ---			---- Imipenem ----				
Gram positive, aerobic	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Staphylococcus spp.								
Staphylococcus aureus								
MSSA	17	12	70.6	21	15	71.4	-0.8	
Enterobacteriaceae								
Enterobacter spp.								
Enterobacter cloacae	16	12	75.0	10	7	70.0	5.0	
Escherichia spp.								
Escherichia coli	12	9	75.0	17	10	58.8	16.2	
Klebsiella spp.								
Klebsiella pneumoniae	15	12	80.0	10	6	60.0	20.0	
Haemophilus spp.								
Haemophilus spp.								
Haemophilus influenzae	32	25	78.1	37	30	81.1	-3.0	(-25.0; 19.0)
Non-enterobacteriaceae								
Pseudomonas spp.								
Pseudomonas aeruginosa	20	13	65.0	14	5	35.7	29.3	

[a] Doripenem minus Imipenem

[b] The 2-sided 95% CI is based on the normal approximation to the difference of two binomial proportions with continuity correction. The confidence interval is provided only if the number of patients with the pathogen is 30 or more in each of treatment arm.

Key: N=the number of patients who had the specific baseline pathogen; n=the number of patients who had a favorable microbiological outcome for the specified pathogen.

Note 1: A per-pathogen microbiological outcome was favorable if the outcome was eradication or presumed eradication for the specific pathogen.

Note 2: Only bacterial pathogens isolated in 10 or more ME at TOC patients in the doripenem group at baseline are included.

Table 39: Per Pathogen Clinical and Microbiological Cure Rates at the TOC Visit by Common Baseline Pathogen (Studies JNJ38174942-DORI-09 and DORI-10: Pooled ME at TOC Analysis Set)

	Doripenem 500 mg[a]			Comparator[b]				
	N	n	%	N	n	%	Diff[c](%)	95% CI[d]
Clinical Cure Rates								
Gram positive, aerobic								
Staphylococcus aureus	37	24	64.9	38	29	76.3	-11.5	(-34.6; 11.7)
MSSA	31	20	64.5	36	27	75.0	-10.5	(-35.5; 14.5)
Streptococcus pneumoniae	16	10	62.5	13	12	92.3	-29.8	
Gram negative, aerobic								
Acinetobacter baumannii	13	11	84.6	10	7	70.0	14.6	
Enterobacter cloacae	27	21	77.8	16	12	75.0	2.8	
Escherichia coli	21	16	76.2	25	16	64.0	12.2	
Klebsiella pneumoniae	29	22	75.9	21	12	57.1	18.7	
Haemophilus influenzae	40	29	72.5	47	33	70.2	2.3	(-19.1; 23.6)
Pseudomonas aeruginosa	38	31	81.6	31	17	54.8	26.7	(2.4; 51.1)
Microbiological Cure Rates[e]								
Gram positive, aerobic								
Staphylococcus aureus	37	29	78.4	38	32	84.2	-5.8	(-26.1; 14.5)
MSSA	31	25	80.6	36	30	83.3	-2.7	(-24.2; 18.8)
Streptococcus pneumoniae	16	14	87.5	13	12	92.3	-4.8	
Gram negative, aerobic								
Acinetobacter baumannii	13	11	84.6	10	7	70.0	14.6	
Enterobacter cloacae	27	23	85.2	16	12	75.0	10.2	
Escherichia coli	21	16	76.2	25	17	68.0	8.2	
Klebsiella pneumoniae	29	23	79.3	21	13	61.9	17.4	
Haemophilus influenzae	40	33	82.5	47	38	80.9	1.6	(-16.9; 20.2)
Pseudomonas aeruginosa	38	28	73.7	31	17	54.8	18.8	(-6.5; 44.2)

[a] Doripenem combined group (doripenem 500 mg 1-hour infusion q8h in DORI-09 and doripenem 500 mg 4-hour infusion q8h in DORI-10)

[b] Combined comparator group (piperacillin/tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)

[c] Difference=doripenem combined group minus combined comparator group

[d] The 2-sided 95% CI was based on the normal approximation to the difference of two binomial proportions with continuity correction. The confidence interval is provided only if the number of patients with the pathogen is 30 or more in each of treatment arm.

[e] Microbiological cure=eradication or presumed eradication

Key: N=number of patients with specified baseline pathogens; n= number of patients who were clinically (or microbiologically) cured.

Note: This table includes only those baseline bacterial pathogens that were isolated in ≥10 patients in the doripenem treatment arm.

7.4.2.3. Emergent Pathogens and Persistent Infections With Altered Susceptibility

Emergent Pathogens

Emergent (i.e., non-baseline) pathogens were considered separately from baseline pathogens, and did not affect the per-patient microbiological response (but did affect the clinical response assessments). Emergent pathogens were categorized as either superinfection (occurring during the study therapy period) or new infection (occurring after discontinuation of study therapy).

In the cMITT analysis set, emergent infections were infrequent in both DORI-09 (3% with doripenem and 6% with piperacillin/tazobactam) and DORI-10 (8% with doripenem and 11% with imipenem) (Tables 40 and 41, respectively). In the combined studies, emergent LRT infections resistant to study therapy received (i.e., MIC ≥16 μg/mL for doripenem and according to Clinical and Laboratory Standards Institute [CLSI] definitions for comparators) were rare in the doripenem group (9/466; 1.9%) and slightly more common in the comparator group (16/464; 3.4%).

Table 40: Patients With Emergent LRT Infections
(Study DORI-09: cMITT Analysis Set)

	-----Doripenem -----			Piperacillin/tazobactam		
	N	n	%	N	n	%
Emergent infections						
Emergent LRT infections	214	7	3.3	208	13	6.3
Superinfection during study drug therapy	214	6	2.8	208	10	4.8
New infection after the completion of study drug therapy	214	1	0.5	208	3	1.4

Key: N=the number of patients in each analysis set, n=the number of patients who had emergent infections

Table 41: Patients With Emergent LRT Infections
(Study DORI-10: cMITT Analysis Set)

	----- Doripenem ----			Imipenem		
	N	n	%	N	n	%
Emergent infections						
Emergent LRT infections	248	20	8.1	251	28	11.2
Superinfection during study drug therapy	248	11	4.4	251	15	6.0
New infection after the completion of study drug therapy	248	9	3.6	251	13	5.2

Key: N=the number of patients in the analysis set; n=the number of patients who had emergent infections

In DORI-09, the emergence of decreased susceptibility (≥4-fold increase in MIC) among gram-negative baseline pathogens was rare in the doripenem arm (occurring in only 1 *P. aeruginosa* isolate); whereas, 6 isolates in the piperacillin/tazobactam arm developed decreased susceptibility (3 *P. aeruginosa* and 3 *K. pneumoniae* isolates).

In DORI-10, a methodical evaluation of changes in susceptibility in *P. aeruginosa* was undertaken; tracheal aspirates were obtained for culture at regular intervals while patients were intubated (i.e., baseline, approximately every 3 days while on i.v. therapy, at the end of i.v. therapy, at the TOC and late follow-up visits). These specimens were obtained regardless of clinical response. Among *P. aeruginosa* susceptible at baseline (MIC ≤4 μg/mL), emergence of decreased susceptibility was observed in 10 (36%) of 28 and 10 (53%) of 19 patients in the doripenem and imipenem treatment arms, respectively (Table 42). Most post baseline *P. aeruginosa* strains with

increased MICs were genotypically identical or closely related to the baseline strain and all 10 post-baseline strains with decreased susceptibility in the imipenem arm had MICs ≥8 µg/mL, compared with 5 of 10 in the doripenem arm. In addition to the emergence of resistance on therapy, 6 additional *P. aeruginosa* strains in the imipenem arm were intermediate or resistant to imipenem at baseline (Table 21). Of note, there were few isolates that demonstrated resistance development during or after doripenem treatment in the Phase 3 studies in the cUTI and cIAI registration trials.

Table 42: Proportion of Patients With Observed Decreased Susceptibility to Study Drug Received in *P. Aeruginosa* Strains Isolated From Baseline LRT Culture Specimens (Study JNJ-38174942-DORI-10: mMITT Analysis Set)

	--Doripenem --		----- Imipenem -----		P-value[a]
Patients with *P. aeruginosa* strains	n/N	%	n/N	%	
Isolated at baseline/total population	30/206	15	26/203	13	
With baseline MIC value available	28		25		
Baseline MIC <8 µg/mL	28/28	100	19/25	76	
Repeat isolates ≥4 x baseline MIC	10/28	36	10/19	53	0.368
Repeat isolates with MIC ≥8 µg/mL	5/28	18	10/19	53	0.024
Baseline or emergence of MIC ≥8 µg/mL	5/28	18	16/25	64	<0.001

[a]Fisher's Exact Test

Key: N=the number of patients in the subgroup set with *P. aeruginosa* isolated at baseline; n=the number of patients in the subgroup

Note: Decreased susceptibility in *P. aeruginosa* was defined as a ≥4-fold increase of the baseline MIC at any post-baseline visit. MICs were determined using the CLSI broth microdilution method.

Molecular Analysis of Emergent Resistance

Isolates from the doripenem clinical trials that demonstrated a ≥4-fold increase in doripenem MIC values during treatment were analyzed for resistance mechanisms.

Twenty pairs of *P. aeruginosa* isolates with 4-fold increases in MIC values (10 in each arm [doripenem and imipenem]) were evaluated.

The *P. aeruginosa* isolates produced chromosomal AmpC-type β-lactamases, which were expressed at different levels that did not strongly correlate with the doripenem MIC values. Changes in the expression of outer membrane proteins were observed between screening and post-treatment *P. aeruginosa* isolates.

Clinical Cure Rates In Doripenem-Treated Patients With Pathogens Resistant to Comparators

Although patients with baseline pathogens resistant to study drug received were excluded from the ME at TOC analysis set, strains resistant to comparator were included in the doripenem group if they were doripenem susceptible. The doripenem group included a few patients with such pathogens. Generally, clinical cure rates were high against these resistant pathogens. The clinical cure rate was 83.3% against the 18 gram-negative bacilli resistant or intermediate to piperacillin/tazobactam, including *A. baumannii*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae* and *P. aeruginosa*, and 50% against the 6 imipenem-resistant strains of *P. aeruginosa* (Table 43).

Table 43: Clinical Cure Rates for Doripenem Patients With Baseline LRT Pathogens That Were Resistant or Intermediate to Comparators
(Studies DORI-09 and DORI-10: ME at TOC Analysis Set)

	---------- Pathogens Resistant or Immediate to ----------					
	Piperacillin/tazobactam			Imipenem		
Baseline Pathogen Classification	N	n	%	N	n	%
Gram positive aerobic	0	0		2	2	100.0
Gram negative aerobic	18	15	83.3	6[a]	3	50.0

[a]All were *P. aeruginosa*

Key: N=number of baseline pathogens in doripenem-treated patients that were intermediate or resistant to the respective comparator; n=number of pathogens from N with a favorable outcome (i.e., patients who were assessed as clinical cures)

7.4.2.4. Relapse Rates

Relatively low and comparable clinical relapse (a recurrence of signs or symptoms of pneumonia or new radiographic evidence of pneumonia in a patient assessed as cured at the TOC visit) rates were observed in the pooled CE at LFU analysis set (4.6% and 5.2% for doripenem and comparator arms, respectively) (Table 44).

Table 44: Clinical Relapse Rate at the Late Follow-up Visit in the Individual Studies and Pooled Data
(Studies JNJ38174942-DORI-09 and DORI-10: CE at LFU Analysis Set)

	------- Doripenem[a] -------			---- Comparators[b] ----		
	N	n	%	N	n	%
Study DORI-09	99	3	3.0	84	3	3.6
Study DORI-10	53	4	7.5	51	4	7.8
Studies DORI-09 and DORI-10 Combined	152	7	4.6	135	7	5.2

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)

[b] Combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)

Note: In Study DORI-09, the clinical outcome at TOC for 1 patient was changed to from "clinical failure" to "clinical cure" by the BEC. Therefore, this patient was considered a "relapse" at LFU in Study-DORI-09.

7.4.2.5. Efficacy in Subgroups

Clinical cure rates for the pooled NP studies by the various subgroups are presented in Table 45.

Pooled clinical cure rates in clinically evaluable patients at the TOC visit in the various subgroups were comparable between the doripenem and comparator arms (Table 45). However, differences were seen overall (i.e.,in both treatment arms) in clinical cure rates in some subgroups. As expected, patients with VAP had lower clinical cure rates than patients without VAP (66.0% versus 85.4%). In contrast to some previously reported studies,[1] the doripenem studies showed lower clinical cure rates in patients with early-onset VAP (59.2%) compared to patients with late-onset VAP (72.8%) As expected, clinical cure rates were notably higher in patients with APACHE II scores ≤15. The efficacy of doripenem was evaluated in a relatively large number of patients in high-risk subgroups in both doripenem- and comparator-treated patients in the CE analysis set (e.g., 99 and 85 patients ≥65 years; 155 and 148 with VAP; and 34 and 35 with APACHE II scores >20, respectively). Within these subgroups, the efficacy of doripenem was high. It is recognized, however, that these data should be interpreted carefully due to the relatively small sample sizes for these subgroups. In Study DORI-09, optional adjunctive therapy for potential MRSA was administered relatively infrequently (~15% in the CE at TOC analysis set); but as required by the protocol based on label provisions, the majority of patients (~80%) received adjunctive therapy (mostly with amikacin) for potential *P. aeruginosa*.

Table 45: Clinical Cure Rate by Subgroup in the Pooled Data
(Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC Analysis Set)

	---- Doripenem[a] ---			-- Comparators[b] --				
	N	n	%	N	n	%	Diff[c](%)	95% CI[d]
Sex								
Female	60	49	81.7	76	56	73.7	8.0	(-7.4; 23.4)
Male	200	146	73.0	165	118	71.5	1.5	(-8.3; 11.3)
Age (Years)								
<65	161	122	75.8	156	112	71.8	4.0	(-6.3; 14.3)
≥65	99	73	73.7	85	62	72.9	0.8	(-13.1; 14.7)
<75	218	165	75.7	199	144	72.4	3.3	(-5.6; 12.2)
≥75	42	30	71.4	42	30	71.4	0.0	(-21.7; 21.7)
Race[e]								
White	209	157	75.1	200	147	73.5	1.6	(-7.3; 10.6)
Black or African American	18	13	72.2	10	6	60.0	12.2	
Hispanic or Latino	28	21	75.0	27	20	74.1	0.9	
Other	5	4	80.0	4	1	25.0	55.0	
Region[f]								
North America	72	54	75.0	67	43	64.2	10.8	(-5.8; 27.5)
USA	66	48	72.7	63	39	61.9	10.8	(-6.8; 28.5)
South America	41	28	68.3	37	25	67.6	0.7	(-22.6; 24.0)
Europe	117	95	81.2	109	88	80.7	0.5	(-10.7; 11.6)
Other	30	18	60.0	28	18	64.3	-4.3	
Ventilation Mode								
Non-VAP	105	89	84.8	93	80	86.0	-1.3	(-12.1; 9.6)
VAP	155	106	68.4	148	94	63.5	4.9	(-6.5; 16.2)
Early-onset VAP (<5 Days)	77	48	62.3	75	42	56.0	6.3	(-10.6; 23.3)
Late-onset VAP (≥5 Days)	78	58	74.4	73	52	71.2	3.1	(-12.4; 18.7)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)
[b] Combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)
[c] Difference=doripenem combined group minus combined comparator group
[d] The 2-sided 95% CI was based on the normal approximation to the difference of 2 binomial proportions with continuity correction, which was provided only if the pathogens isolated in 30 or more patients in both treatment groups.
[e] Race was classified as other if patient did not fit stated race categories or more than 1 race was checked on case report form.
[f] North America includes Canada and USA; South America includes Argentina, Brazil, and Chile; Europe includes Austria, Belarus, Belgium, Estonia, France, Georgia, Germany, Netherlands, Russia, Spain, and Ukraine; Other includes Australia and S. Africa, Serbia and Montenegro
Key: APACHE II=Acute Physiology and Chronic Health Evaluation II; CI=confidence interval; Diff=difference; n=number of patients who had a favorable clinical response in the subgroup; N=all the patients in the subgroup; VAP=ventilator-associated pneumonia

(continued)

Table 45: Clinical Cure Rate by Subgroup in the Pooled Data
(Studies JNJ38174942-DORI-09 and DORI-10: CE at TOC Analysis Set) (continued)

	---- Doripenem[a] ---			--- Comparators[b] --				
	N	n	%	N	n	%	Diff[c](%)	95% CI[d]
APACHE II Score								
≤15	158	129	81.6	152	118	77.6	4.0	(-5.6; 13.6)
>15	102	66	64.7	89	56	62.9	1.8	(-12.9; 16.5)
>20	34	22	64.7	35	22	62.9	1.8	(-23.7; 27.4)
Bacteremia[g]								
No	239	180	75.3	213	157	73.7	1.6	(-6.9; 10.1)
Yes	21	15	71.4	28	17	60.7	10.7	
Received Reduced Dose of Study Drug Due to Renal Impairment								
No	225	175	77.8	209	152	72.7	5.1	(-3.5; 13.6)
Yes	35	20	57.1	32	22	68.8	-11.6	(-37.5; 14.3)
Had Anti-MRSA Coverage								
No	206	156	75.7	186	141	75.8	-0.1	(-9.1; 8.9)
Yes	54	39	72.2	55	33	60.0	12.2	(-7.2; 31.7)

[a] Doripenem combined group (doripenem 500 mg 1-h inf q8h in DORI-09 and doripenem 500 mg 4-h inf q8h in DORI-10)
[b] Combined comparator group (piperacillin/ tazobactam 4.5 g 30-minute i.v. infusion q6h in DORI-09 and imipenem 500 mg 30-minute i.v. infusion q6h or 1,000 mg 1-h i.v. infusion q8h in DORI-10)
[c] Difference=doripenem combined group minus combined comparator group
[d] The 2-sided 95% CI was based on the normal approximation to the difference of 2 binomial proportions with continuity correction, which was provided only if the pathogens isolated in 30 or more patients in both treatment groups.
[g] Bacteremia was defined as 1 positive blood culture if associated with a pathogenic organism, or 2 positive blood cultures if associated with organisms generally not considered pathogenic.
Key: MRSA=methicillin-susceptible *S. Aureus*; n=number of patients who had a favorable clinical response in the subgroup; N=all the patients in the subgroup

7.5. Dosing Recommendations and the Impact of Infusion Time

The results of Studies DORI-09 and DORI-10 support the efficacy of doripenem 500 mg q8h in the treatment of NP, including VAP.

As only 1 dosage (500 mg) of doripenem was studied, a dose response assessment was not possible. However, 2 different infusion times were used: a 1-hour infusion in DORI-09 and an extended 4-hour infusion in DORI-10.

Prior to DORI-10, no previous study investigated the efficacy of 4-hour infusions of doripenem in humans. However, the greater pharmacodynamic activity of the 4-hour compared to the 1-hour infusion has been confirmed experimentally. The 500 mg 4-hour infusion was shown to be superior to the 1-hour infusion in an in vitro hollow fiber model.[71] An evaluation that mimicked the human PK profile of 500 mg doripenem 1-hour and 4-hour infusion in the mouse neutropenic thigh model showed that the 4-hour infusion provided better coverage of *P. aeruginosa* with higher MICs.[72]

Patients with VAP (DORI-10) were believed to be the most appropriate patient population to study the 500 mg q8h 4-hour infusion, as infections with non-fermentative multidrug-resistant gram-negative bacteria are known to occur in this population and pose a therapeutic dilemma. However, in DORI-10, there were a limited number of organisms with doripenem MICs ≥4 μg/L. This lower than anticipated incidence could be related to the study inclusion and exclusion criteria that limited prior and concomitant antibiotic use; prior antibiotic therapy is known to be an important risk factor for resistant infections. It should be noted that a direct comparison between the 1-hour and 4-hour infusions was not conducted in the clinical trials, and no conclusion can be drawn regarding the added benefit of longer infusion times. In particular, comparisons between DORI-09 and DORI-10 should be made cautiously because of numerous differences in the study populations. Although it is difficult, due to the limitations of registration trial design, to capture efficacy data for many organisms with high MICs, surveillance data show that resistant pathogens can occur more commonly, especially in certain regions or centers.[73] Because such infections will be encountered with doripenem use and cannot be reliably identified before therapy is initiated, maximizing the pharmacodynamic potential of doripenem is important when such infections are considered. The use of prolonged infusions is already an established practice, albeit on a limited

basis.[74-77] For patients at low risk for infection with organisms with high MICs, the 500 mg q8h 1-hour infusion should provide appropriate coverage. However, when organisms with higher MICs are suspected, the 4-hour extended infusion may provide a potential advantage. It is common practice for clinicians to choose higher doses when suspecting more resistant infections and the 4-hour infusion of doripenem is pharmacodynamically equivalent (in terms of %T>MIC) to increasing the dose with the same infusion time.

The clinical data show little difference by age or sex. Moreover, doripenem retained good efficacy in severe disease (e.g., as indicated by high APACHE II scores) and in patients with late onset VAP [Table 45]). Thus, no adjustment to the recommended dosage is required for these subgroups, although 4-hour infusions are recommended for VAP patients, particularly late onset VAP. Although, clinical outcomes were poorer in patients with renal dysfunction (Table 45), the efficacy of doripenem in patients who were renally impaired was similar to comparators, suggesting that the decreased efficacy was related to comorbidities. The comparable clinical data between the doripenem and comparator groups support the renal dose adjustment recommendations.

8. OVERVIEW OF SAFETY IN NOSOCOMIAL PNEUMONIA

All patients who received any dose of i.v. study drug therapy were included in the safety analysis set (also referred to as the ITT analysis set).

The overall safety of doripenem has been evaluated in 2,054 patients participating in 15 completed clinical studies: 8 Phase 1 clinical studies in healthy patients (n=172); 1 Phase 2 study in hospitalized patients with cUTI (n=121) and 6 Phase 3 studies in hospitalized patients with cUTI, cIAI or NP (n=1761). This briefing book focuses on the safety of 969 patients enrolled and treated in the two Phase 3 NP studies, DORI-09 and DORI-10, of which, 485 were treated with doripenem (Table 46). However, when relevant, safety information from the Phase 2 and 3 studies in all three indications is provided.

8.1. Critical Aspects of the Safety Population and the Extent of Exposure

In this safety discussion, study drug therapy refers to both i.v. doripenem or the i.v. comparator(s) agent and optional oral switch therapy, unless otherwise stated.

The duration of exposure to either i.v. or oral study drug therapy in the doripenem and comparator arms was generally similar within the individual NP studies. Most patients in the NP studies received ≤10 days of i.v. study drug. therapy (Table 46).

Table 46: Extent of Exposure
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

	DORI-09		DORI-10	
	Doripenem (N=223)	Piperacillin/ tazobatcam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Total duration (days)				
i.v. or iv plus oral therapy				
N	223	221	262	263
Category, n (%)				
<4	13 (6)	15 (7)	22 (8)	19 (7)
4 – 7	16 (7)	22 (10)	45 (17)	28 (11)
8 – 10	74 (33)	65 (29)	131 (50)	143 (54)
11 – 14	78 (35)	72 (33)	48 (18)	59 (22)
15 – 16	39 (17)	44 (20)	16 (6)	14 (5)
> 16	3 (1)	3 (1)	0	0
Mean (SD)	10.7 (3.78)	10.7 (3.86)	8.6 (3.28)	9.0 (3.09)
Median (Range)	11.0 (1;25)	11.0 (1;18)	8.0 (1;16)	9.0 (1;15)
i.v. therapy				
N	223	221	262	263
Category, n (%)				
<4	13 (6)	15 (7)	22 (8)	19 (7)
4 – 7	60 (27)	77 (35)	45 (17)	28 (11)
8 – 10	78 (35)	67 (30)	131 (50)	143 (54)
11 – 14	42 (19)	27 (12)	48 (18)	59 (22)
15 – 16	30 (13)	35 (16)	16 (6)	14 (5)
Mean (SD)	9.0 (3.63)	8.7 (3.85)	8.6 (3.28)	9.0 (3.09)
Median (Range)	8.0 (1;16)	8.0 (1;16)	8.0 (1;16)	9.0 (1;15)

(continued)

Table 46: Extent of Exposure
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set) (continued)

	----------DORI-09 ----------		---------- DORI-10 ----------	
	Doripenem (N=223)	Piperacillin/ tazobatcam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Total duration (days)				
Oral therapy [a]				
N	88	94	---	---
Category, n (%)				
<4	25 (28)	23 (24)	---	---
4 – 7	52 (59)	52 (55)	---	---
8 – 10	10 (11)	18 (19)	---	---
11 – 14	1 (1)	1 (1)	---	---
Mean (SD)	5.1 (2.14)	5.5 (2.21)	---	---
Median (Range)	5.0 (1;11)	5.0 (1;11)	---	---

[a] DORI-10 did not have the provision for oral switch. Therefore, N, n (%), and descriptive statistics did not include patients from this study.

Note: The formula used to calculate the duration of therapy counted partial days of therapy as full days, thereby slightly increasing the duration of therapy in some patients and resulting in most of these patients who were categorized as having received >14 days of therapy being reported as treated for a period of 15 days.

8.2. Adverse Events

8.2.1. Overview

An overall summary of adverse events in the NP studies is presented in Table 47. Rates of events summarized in this table varied between the 2 studies. However, given that rates of events were generally comparable between the doripenem and comparator treatment group within the same study, differences between the studies likely reflect differences in the study populations.

Table 47: Overall Summary of Adverse Events
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

	----------DORI-09 ---------		-------- DORI-10 ---------		
	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Any AE	171 (76.7)	172 (77.8)	249 (95.0)	238 (90.5)	420 (86.6)
Any study drug-related AE [a]	36 (16.1)	39 (17.6)	45 (17.2)	46 (17.5)	81 (16.7)
Any serious AE	67 (30.0)	58 (26.2)	70 (26.7)	72 (27.4)	137 (28.2)
Any study drug-related serious AE [a]	0	0	5 (1.9)	4 (1.5)	5 (1.0)
Deaths	43 (19.3)	39 (17.6)	35 (13.4)	32 (12.2)	78 (16.1)
Discontinuation from study drug due to AE	9 (4.0)	14 (6.3)	17 (6.5)	15 (5.7)	26 (5.4)
Discontinuation from study drug due to a study drug-related AE [a]	3 (1.3)	3 (1.4)	8 (3.1)	7 (2.7)	11 (2.3)

[a] Includes possibly and probably related adverse events and adverse events with a missing relationship. Adverse events were treatment-emergent, defined as defined as those adverse events with onset dates on or after the date of the start of the infusion of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy.
Key: AE=adverse event

8.2.2. Most Common Adverse Events

The types and rates of adverse events occurring in >1% of patients with doripenem therapy in the Phase 2 and 3 studies across the various indications (cUTI, cIAI, and NP) were consistent with the known safety profiles of carbapenems and similar to the comparator groups (Attachment 9.1). In general, the incidences of most adverse events in the doripenem group overall fell between those of the comparator groups. The only adverse event that occurred at a rate >1% higher in the doripenem group overall, versus all of the comparator groups combined, was asymptomatic bacteruria. This event was reported almost exclusively in the cUTI studies and reflects the similar microbiological cure rate but lower clinical failure rate seen in patients with cUTI who were treated with doripenem versus the comparator agent. Therefore this event is not believed to be clinically important in terms of safety. Of particular interest, the adverse events of anemia and renal failure/renal impairment that were noted to have clinically important differences in frequency between the doripenem and comparator agents in the cUTI and cIAI studies occurred at the following rates in the NP studies: anemia: 6.0% doripenem, 10.9% and 4.6% comparators; renal failure/renal impairment 3.5% doripenem, 3.6% and 3.4% comparators. Anemia and renal failure are discussed in more detail below.

Adverse events occurring in >1% of patients in any treatment group in the NP studies are summarized for Study DORI-09 and Study DORI-10 separately, and both studies combined, in Attachment 9.2. The only AE that occurred overall with doripenem at a rate >2% higher than in both comparator groups was pneumonia, which occurred in 5.4% of patients in the doripenem group, 2.7% in the piperacillin/tazobactam group, and 3.0% in the imipenem group. In DORI-09, pneumonia was reported as an adverse event for 17 (7.6%) patients treated with doripenem. In DORI-10, 9 (3.4%) patients treated with doripenem had an adverse event of pneumonia.

Across all treatment groups, the most commonly reported TEAEs were within the system organ classes of infections and infestations and gastrointestinal disorders; the overall rates of events in these system organ classes with doripenem were within the range of the comparator groups. The most commonly reported AEs overall with doripenem were diarrhea (12.0%), UTI (9.1%), and decubitus ulcer (8.7%). Each of these events 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. Although differences in the rates of TEAEs were seen between the doripenem treatment groups in both studies, rates of events were generally comparable between the doripenem and comparator treatment groups within the same study. Therefore, differences in rates of TEAEs between the doripenem groups in each study reflect differences in the study population under evaluation rather than differences in the safety of the 2 doripenem infusion regimens.

8.2.2.1. Anemia

The adverse event of anemia was noted to have a clinically important difference in frequency between the doripenem and comparator agents in the controlled Phase 3 cUTI (1.6% doripenem; 1.1% comparator) and cIAI (9.6% doripenem; 5.5% comparator) studies. However, in the NP studies this event was reported for 6.0% vs. 7.4% of the doripenem and comparator-treated patients, respectively. (DORI-09: 6.7% doripenem; 10.9% piperacillin/tazobactam, DORI-10: 5.3% doripenem; 4.6% imipenem).

8.2.2.2. Renal Failure

The adverse event of renal failure (including the terms renal failure, acute renal failure and renal impairment) was noted to have a clinically important difference in frequency between the doripenem and comparator agents in the controlled Phase 3 cUTI (0.8% doripenem; 0% comparator) and cIAI (1.3% doripenem; 0.2% comparator) studies. However, in the NP studies these events were reported for 3.5% vs. 3.7% of the doripenem and comparator-treated patients, respectively. (DORI-09: 4.0% doripenem; 4.1% piperacillin/tazobactam, DORI-10: 3.1% doripenem; 3.4% imipenem).

When data from all patients in the Phase 2 and 3 studies with an adverse event of renal failure, acute renal failure, or renal impairment were evaluated, a total of 33 doripenem-treated patients with NP, cIAI and cUTI (33/1817; 1.8%), 9 imipenem-treated patients with NP (9/263; 3.4%), 9 piperacillin/tazobactam-treated subjects with NP (9/221; 4.0%), 1 meropenem-treated subject with cIAI (1/469; 0.5%) and no levofloxacin-treated patients with cUTI subjects were reported as having these events (heretoforth described as renal failure).

Attachment 9.4 summarizes the clinical findings of the 33 doripenem-treated patients with a renal-related treatment-emergent adverse event. For all cases, there were either significant confounding medical or surgical conditions that provided alternative causes for renal failure and/or, there was a clear lack of temporal relationship between the administration of doripenem and the development of renal failure. Of the 33 doripenem-treated patients who had an adverse event of renal failure, 31 (94%) had significant comorbidities that predispose to renal disease and 26 (79%) were administered potentially nephrotoxic drugs prior to the occurrence of the event. Seventeen (51%) of the 33 patients who had an adverse event of renal failure/renal impairment had onset of the event after discontinuation of i.v. doripenem. Given that the half-life of doripenem is approximately 1 hour, that there is no known drug accumulation with multiple doripenem dosing, and that the serum creatinine was normal at the end of i.v. therapy in the majority of patients with AEs occurring post treatment, the renal failure occurring in the post treatment period (where the serum creatinine value was normal at the end of i.v. study drug therapy) was unlikely due to doripenem toxicity. Furthermore, many of these cases had other conditions or medications that provided alternative etiologies for renal disease. If there were a true deleterious drug effect of doripenem on kidney function, it

could reasonably be assumed that many more cases would occur while on therapy rather than post treatment.

8.2.3. Serious Adverse Events

The most common (occurring in ≥10 subjects in the doripenem arm of each study) serious adverse events for patients in either treatment arm in the 2 NP studies are summarized in Table 48 below. A Tabulation of all serious adverse events for both NP studies is provided in (Attachment 9.3).

In general, higher rates of serious adverse events were reported for both doripenem- and comparator-treated patients in the NP studies than in either the cUTI and cIAI indications, reflecting the greater severity of illness and number of co-morbid conditions in this population. Serious adverse events were frequently related to progression or complications of the infection under study (e.g., pneumonia and respiratory failure).

Table 48: Most Common Serious Adverse Events
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

	---------- DORI-09 ----------		---------- DORI-10 ----------		
Dictionary-derived Term	Doripenem (N=223) n(%)	Piperacillin/ tazobactam (N=221) n(%)	Doripenem (N=262) n(%)	Imipenem (N=263) n(%)	Total Doripenem[a] (N=485) n(%)
Pneumonia	12 (5.4)	3 (1.4)	2 (0.8)	5 (1.9)	14 (2.9)
Respiratory failure	5 (2.2)	3 (1.4)	6 (2.3)	6 (2.3)	11 (2.3)
Septic shock	9 (4.0)	5 (2.3)	2 (0.8)	4 (1.5)	11 (2.3)
Sepsis	3 (1.3)	2 (0.9)	6 (2.3)	6 (2.3)	9 (1.9)
Intracranial pressure increased	1 (0.4)	1 (0.5)	4 (1.5)	0	5 (1.0)
Multi-organ failure	1 (0.4)	2 (0.9)	4 (1.5)	6 (2.3)	5 (1.0)
Cardio-respiratory arrest	0	2 (0.9)	4 (1.5)	5 (1.9)	4 (0.8)
Cardiogenic shock	3 (1.3)	1 (0.5)	1 (0.4)	0	4 (0.8)
Pulmonary embolism	1 (0.4)	0	3 (1.1)	0	4 (0.8)
Renal failure acute	1 (0.4)	1 (0.5)	3 (1.1)	3 (1.1)	4 (0.8)

[a] Doripenem combined group (doripenem 500 mg 1-hour infusion q8h in DORI-09 and doripenem 500 mg 4-hour infusion q8h in DORI-10)

Note1: The table includes serious adverse events that were reported in ≥10 subjects in the doripenem arm.

Note2: Percentages calculated with the number of patients in each group as denominator.

Note3 : At each level of summarization, a patient is counted once if the patient reported one or more events. Treatment-emergent adverse events are defined as adverse events with onset dates on or after the date of the start of the infusion of first dose of study therapy and within 30 days after administration of the last dose of study therapy. AE terms are coded.

8.2.3.1. Pneumonia

Pneumonia was reported as a serious adverse event for 12 doripenem- and 3 piperacillin-tazobactam treated patients in DORI-09. Six of the 12 pneumonia serious adverse events in the doripenem group occurred before the end of study drug therapy, 1 occurred after the end of study therapy but before the TOC visit,

and 5 occurred after the TOC visit. Four of the 6 patients who developed pneumonia after the end of study drug. therapy were clinically cured at the time study drug therapy was stopped. Of the 12 subjects in the doripenem group with an serious adverse event of pneumonia, 10 died. Nine of the doripenem-treated patients died with pneumonia as a cause of death; 7 died of pneumonia as the single cause of death (1 patient had fungal pneumonia at baseline) and 2 died of pneumonia and respiratory failue or acute respiratory failure (1 patient had both *K. pneumoniae* and *S. aureus* [oxacillin susceptibility unknown] at baseline and did not receive concomitant vancomycin or linezolid therapy). One additional subject recovered from a non-fatal serious adverse event of pneumonia but subsequently died from "sudden cardiac death". All 3 pneumonia serious adverse events in the piperacillin-tazobactam group started at or after the TOC visit. One piperacillin-tazobactam-treated patient died and the investigator attributed the cause of this patient's death to the pneumonia. In addition to the cases described above, 2 additional pneumonia-type serious adverse events were reported: 1 patient in the doripenem treatment group had a fatal serious adverse event of "pneumonia fungal" (aspergillus species isolated at baseline) that started before the end of study drug therapy and 1 patient in the piperacillin/tazobactam group with *S. aureus* [oxacillin susceptibility unknown] isolated at baseline had a fatal serious adverse event of "pneumonia staphylococcal" that started before the end of therapy. In addition to receiving piperacillin/tazobactam, the patient with "pneumonia staphylococcal" received concomitant vancomycin the day before and linezolid the day of and for 9 days after the start of this serious adverse event.

In DORI-10, 2 and 5 doripenem- and imipenem-treated patients, respectively had an serious adverse event of pneumonia. In the doripenem group 1 pneumonia serious adverse event occurred before the end of i.v. therapy and the other after the end of i.v. therapy. The first patient died of dual causes: pneumonia and myocardial infarction and the second patient recovered from his pneumonia but later died of cerebral haematoma. All 5 pneumonia serious adverse events in the imipenem grouped started after the TOC visit. Two patients died; one from pneumonia and pneumothorax and the other from pneumonia and multiorgan failure. In addition to the cases described above, 3 additional pneumonia-type serious adverse events were reported in 2 patients in the imipenem group: 1 patient had a fatal serious adverse event of "bronchopneumonia" which started before the end of i.v. therapy, a second patient had a non-fatal serious adverse event of "pneumonia klebsiella" which

started after the end of i.v. therapy and a non-fatal serious adverse event of "pneumonia staphylococcal", (AE verbatim term "MRSA pneumonia") that started after the end of i.v therapy and was treated with vancomycin and linezolid.

8.2.3.2. Renal Failure

Patients with an adverse event of renal failure/acute renal failure/renal impairment are discussed in detail in Section 8.2.2.2 and summarized in Attachment 9.4. The 6 doripenem-treated patients with a serious adverse event of renal failure in the NP studies were: DORI-09: 93001504, 93202502, 94101007; DORI-10: 12302566, 13401519, 14402546.

8.2.3.3. Ventricular Arrythmia

Ventricular arrhythmias were captured under the following preferred terms: arrhythmia, Torsades de Pointes, ventricular fibrillation, and sudden death. There were 3 serious events of ventricular arrhythmias in 3 doripenem-treated patients: 2 in DORI-09 (1 arrhythmia and 1 Torsades to Pointes) and 1 in DORI-10 (ventricular fibrillation). In addition, there were 4 serious adverse events of ventricular arrhythmias (2 sudden death, 1 ventricular fibrillation, and 1 arrhythmia) in 4 separate patients in the piperacillin/tazobactam group and 1 in the imipenem group (ventricular fibrillation). All serious adverse events of ventricular arrhythmia in the doripenem treatment group were assessed by the investigator as not related to treatment with study drug.

One of the doripenem-treated patients in DORI-09 was a 75 year-old man with a past medical history significant for hypertension, heart failure and chronic atrial fibrillation who was initially hospitalized for an incarcerated inguinal hernia and secondary fecal peritonitis and underwent small bowel resection. His post-operative course was complicated by the need for a second abdominal surgery, acute renal failure, congestive heart failure and pneumonia. He was enrolled into the study and was found dead prior to receiving the third dose of study drug. The investigator considered the event of "sudden death" possibly precipitated by an undocumented arrhythmia and unlikely to be related to study drug therapy. This case of sudden death was coded to arrhythmia.

The second doripenem-treated patient in DORI-09 was a 67-year-old man who was being treated with amiodarone and haloperidol and who had underwent coronary artery bypass graft the day before enrollment into the study. He was noted to have a borderline elevated QTc at baseline and subsequently developed

hypocalcemia. After enrolling into the study, this patient had a documented episode of torsades de pointes ventricular arrhythmia followed by ventricular fibrillation. A cardiology consultation assessed the torsades de pointes to be related to haloperidol that had been administered during the previous 12 days (Study Day –5 to 7) at a dose of 2 mg i.v. from 1 to 4 times daily for multi-factorial delirium. After the haloperidol was discontinued, and while the patient remained on doripenem, there was no further recurrence of this arrhythmia. This patient's QT and QTc decreased by 18 hours after the last dose of haloperidol and returned to baseline values 3 days after the event. The investigator assessed the event as not related to treatment with study drug and agreed with the cardiologist that it was due to haloperidol.

The doripenem-treated patient in DORI-10 with ventricular arrhythmia was a 74-year-old man with a history significant for pulmonary hypertension, acute myocardial infarction, aortic and mitral valve regurgitation, arterial hypertension, coronary artery bypass graft, cardiomegaly, cardio-respiratory arrest, defibrillation, percutaneous transluminal coronary angioplasty with cardiac stent, myocardial infarction, and ventricular fibrillation. He was initially hospitalized for re-evaluation of cardiac medication after an unsuccessful cardiac stenting. He developed ventricular arrhythmia (tachycardia and extra systoles) after a myocardial infarction that rapidly led to cardiac ischemia and shock and subsequently developed pneumonia, fever, sepsis, and kidney failure. After receiving 3 doses of study drug he experienced worsening kidney failure, hemodynamic instability, another episode of ventricular fibrillation, and septic shock with multiple organ failure. Within an hour of initiating dialysis, he developed ventricular tachycardia and ventricular fibrillation and died. No autopsy was performed. The investigator considered the events to be unrelated to treatment with study drug therapy.

In addition, a comprehensive randomized double-blind, placebo and positive controlled crossover study to evaluate if doripenem was associated with QTc prolongation was performed and no events were reported that were suggestive of proarrythmia potential as specified in the ICH E14 guidance.[78] The results of the "negative" thorough QT/QTc study further support the cardiac safety of doripenem.

8.2.4. All-cause Mortality

All-cause mortality from Days 1-14, 1-28 and Day 1 through study drug administration and for 30 days afterwards is provided in Table 49 and 50 for DORI-09 and DORI-10 below.

Low mortality rates were seen in both studies and were similar or lower than those seen in other NP studies indicating therapy in these trials was appropriately effective.[1] In both doripenem studies, mortality rates during each time interval varied slightly between studies and between treatment groups within each study. However, as the overall mortality rates at the end of each study were comparable between treatment arms, differences in the number of deaths at particular time points are unlikely to be clinically meaningful. The higher overall mortality rates seen in DORI-09 reflect higher and more consistent death rates in this study during each time interval (Day 1-14, Day 15-28, and Day 28 to 30 days after administration of the last dose of study drug) than in DORI-10 where mortality rates decreased after the first 14 days of therapy. The higher and more consistent mortality rate over time seen in DORI-09 may be a reflection of the greater proportion of patients in this study with a history of chronic co-morbid conditions suggested by their higher median age (DORI-09: 61.5 years, 45.3% ≥65 years; DORI-10: 52.0 years, 29.5 % ≥65 years) and renal insufficiency (DORI-09: 64.9%; DORI-10 26.7%) at baseline which pose a continual increased risk for death. In contrast, in DORI-10, a greater proportion of patients were relatively healthy prior to hospitalization but required intensive medical management for an acute event such as head trauma. Such patients, who had fewer chronic illnesses that pose an ongoing risk for death, would be expected to have a greater chance of surviving following stabilization from their acute injury.

Table 49: All-Cause Mortality Rate
(Study: JNJ38174942-DORI-09: Safety Analysis Set)

	----- Doripenem -----			----- Comparator -----				
Time Interval	N	n	%	N	n	%	Diff[a] (%)	95% CI[b]
Day 1-14	223	21	9.4	221	14	6.3	3.1	(-2.4; 8.5)
Day 1-28	223	34	15.2	221	31	14.0	1.2	(-5.8; 8.2)
During study drug therapy + 30 days	223	43	19.3	221	38	17.2	2.1	(-5.5; 9.7)

[a] doripenem minus comparator
[b] The 2-sided 95% CI is based on the normal approximation to the difference of two binomial proportions with continuity correction.
Key: N=number of patients in the analysis set; n=number of patients who died.

Table 50: All-Cause Mortality Rate
(Study: JNJ38174942-DORI-10: Safety Analysis Set)

	--- Doripenem ---			--Comparator --				
Time Interval	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Day 1-14	262	19	7.3	263	22	8.4	-1.1	(-6.1; 3.9)
Day 1-28	262	30	11.5	263	26	9.9	1.6	(-4.1; 7.2)
During study drug therapy + 30 days	262	34	13.0	263	32	12.2	0.8	(-5.2; 6.9)

[a] doripenem minus comparator
[b] The 2-sided 95% CI is based on the normal approximation to the difference of two binomial proportions with continuity correction.
Key: N=number of patients in the analysis set; n=number of patients who died.

8.2.5. Deaths

All adverse events occurring in the safety population of the NP Studies (DORI-09 and DORI-10), which were attributed to death, independent of investigator assessment of relationship to study drug, are summarized in Table 51. The overall mortality rates in each NP study were comparable between treatment groups: DORI-09: 43 (19.3%) doripenem; 39 (17.6%) piperacillin/tazobactam, DORI-10: 35 (13.4%) doripenem; 32 (12.2%) imipenem. As patients had many serious underlying medical or surgical conditions and autopsies were not performed on many patients, the attributable cause of death was frequently confounded. No adverse events leading to death were considered by the investigator to be related to study drug therapy.

The most common cause of death overall in DORI-09 was septic shock; reported as the cause of death for 6 patients in the doripenem treatment group and 5 patients in the piperacillin/tazobactam group. In DORI-09, the most commonly reported cause of death in the doripenem treatment group was pneumonia: 9 patients in the doripenem group and 1 patient in the piperacillin/tazobactam group. In addition, "pneumonia fungal" was the attributed cause of death for 1 patient in the doripenem group and "pneumonia staphylococcal" was the cause for 1 patient in the piperacillin/tazobactam group. Patients who died of

pneumonia are discussed in Section 8.2.3.1. Given the similar overall mortality rates in the 2 treatment groups and the similar number of treatment failures (i.e., worsening or recurrent pneumonia) in the doripenem and piperacillin/tazobactam treatment groups, it is unlikely that there was truly an imbalance in deaths specifically due to pneumonia. It is possible, given the complexity of the patients' underlying cardiorespiratory conditions, that terms given as attributable causes of death in the piperacillin/tazobactam group, such as acute respiratory distress syndrome, chronic obstructive pulmonary disease, cardio-respiratory arrest and respiratory arrest may actually represent worsening pneumonia and the term "pneumonia" might have been applied if assessed by different investigators. Furthermore, the number of deaths due to pneumonia were similar in the doripenem versus imipenem groups in DORI-10 and thus, a consistent trend across studies was not observed. The only other events leading to death in 2 or more patients in 1 treatment group than the other were acute respiratory distress syndrome (0 doripenem; 2 piperacillin/tazobactam), cardio-respiratory arrest (0 doripenem; 2 piperacillin/tazobactam), brain edema (1 doripenem; 3 piperacillin/tazobactam), and sudden death (0 doripenem; 2 piperacillin/tazobactam). Of note, 1 patient who was randomly assigned to the piperacillin/tazobactam group died before receiving any study drug and is, therefore, not included in the safety analysis set and not included in Table 51.

The most common cause of death in DORI-10 was respiratory failure; reported as a cause of death in 5 patients in the doripenem group and 3 patients in the imipenem group. All attributed causes of death in DORI-10 were fairly well balanced between the 2 treatment groups. Events that occurred in 2 or more patients in 1 treatment group than the other were septic shock (1 doripenem; 3 imipenem), sepsis (3 doripenem; 1 imipenem), respiratory failure (5 doripenem; 3 imipenem), cardio-respiratory arrest (4 doripenem; 2 imipenem), cardiac failure (0 doripenem; 2 imipenem), intracranial pressure increased (2 doripenem; 0 imipenem), subarachnoid hemorrhage (1 doripenem; 3 imipenem), and multi-organ failure (4 doripenem; 6 imipenem). Unlike the trend toward higher pneumonia rates in the doripenem treatment group seen in DORI-09, pneumonia was the reported cause of death for only 1 patient in the doripenem treatment group in DORI-10 and 2 patients in the imipenem treatment group. One additional patient in the imipenem group died of "bronchopneumonia". Patients who died of pneumonia are discussed in Section 8.2.3.1. Of note, 2 patients who were randomly assigned to the imipenem group are not included in Table 51: 1 patient died before receiving

any study drug and is, therefore, not included in the safety analysis set, and the other patient died from an event which started more than 30 days after administration of the last dose of study drug and therefore this event is not included in tabular summaries.

Table 51: Adverse Events Leading to Death
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

	DORI-09		DORI-10		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Total no. patients who died due to Adverse events	**43 (19.3)**	**39 (17.6)**	**35 (13.4)**	**32 (12.2)**	**78 (16.1)**
Infections and infestations	**19 (8.5)**	**9 (4.1)**	**5 (1.9)**	**8 (3.0)**	**24 (4.9)**
Pneumonia	9 (4.0)	1 (0.5)	1 (0.4)	2 (0.8)	10 (2.1)
Septic shock	6 (2.7)	5 (2.3)	1 (0.4)	3 (1.1)	7 (1.4)
Sepsis	2 (0.9)	1 (0.5)	3 (1.1)	1 (0.4)	5 (1.0)
Endocarditis	1 (0.4)	0	0	0	1 (0.2)
Pneumonia fungal	1 (0.4)	0	0	0	1 (0.2)
Bronchopneumonia	0	0	0	1 (0.4)	0
Fungemia	0	0	0	1 (0.4)	0
Meningitis	0	1 (0.5)	0	0	0
Pneumonia staphylococcal	0	1 (0.5)	0	0	0
Respiratory, thoracic and mediastinal disorders	**12 (5.4)**	**8 (3.6)**	**8 (3.1)**	**9 (3.4)**	**20 (4.1)**
Respiratory failure	4 (1.8)	3 (1.4)	5 (1.9)	3 (1.1)	9 (1.9)
Aspiration	1 (0.4)	0	1 (0.4)	0	2 (0.4)
Pneumonia aspiration	2 (0.9)	1 (0.5)	0	0	2 (0.4)
Pulmonary embolism	1 (0.4)	0	1 (0.4)	0	2 (0.4)
Acute respiratory distress syndrome	0	2 (0.9)	1 (0.4)	2 (0.8)	1 (0.2)
Acute respiratory failure	1 (0.4)	0	0	1 (0.4)	1 (0.2)
Emphysema	0	0	1 (0.4)	0	1 (0.2)
Pneumonitis	1 (0.4)	0	0	0	1 (0.2)
Pulmonary artery thrombosis	1 (0.4)	0	0	0	1 (0.2)
Pulmonary edema	1 (0.4)	0	0	0	1 (0.2)
Chronic obstructive pulmonary disease	0	1 (0.5)	0	1 (0.4)	0
Obstructive airways disorder	0	0	0	1 (0.4)	0
Pneumothorax	0	0	0	1 (0.4)	0
Respiratory arrest	0	1 (0.5)	0	0	0
Respiratory distress	0	1 (0.5)	0	0	0
Cardiac disorders	**6 (2.7)**	**6 (2.7)**	**11 (4.2)**	**8 (3.0)**	**17 (3.5)**
Cardio-respiratory arrest	0	2 (0.9)	4 (1.5)	2 (0.8)	4 (0.8)
Cardiogenic shock	3 (1.3)	1 (0.5)	1 (0.4)	0	4 (0.8)
Cardiac arrest	0	0	2 (0.8)	3 (1.1)	2 (0.4)
Acute myocardial infarction	1 (0.4)	0	0	1 (0.4)	1 (0.2)
Aortic valve incompetence	0	0	1 (0.4)	0	1 (0.2)
Arrhythmia	1 (0.4)	1 (0.5)	0	0	1 (0.2)
Bradycardia	0	0	1 (0.4)	0	1 (0.2)
Cardiac failure	1 (0.4)	0	0	2 (0.8)	1 (0.2)
Cardiopulmonary failure	0	0	1 (0.4)	0	1 (0.2)

Note: At each level of summarization, a patient was counted once if the patient reported 1 or more events. Adverse events were treatment-emergent, defined as those adverse events with onset dates on or after the date of the start of the infusion of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

(continued)

Table 51: Adverse Events Leading to Death
(Studies JNJ38174942-DORI-09 and 10: Safety Analysis Set) (continued)

	DORI-09		DORI-10		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Cardiac disorders (continued)					
Myocardial infarction	0	1 (0.5)	1 (0.4)	0	1 (0.2)
Myocardial ischemia	1 (0.4)	0	0	0	1 (0.2)
Ventricular fibrillation	0	1 (0.5)	0	0	0
Nervous system disorders	**5 (2.2)**	**9 (4.1)**	**8 (3.1)**	**6 (2.3)**	**13 (2.7)**
Brain edema	1 (0.4)	3 (1.4)	2 (0.8)	1 (0.4)	3 (0.6)
Intracranial pressure increased	1 (0.4)	1 (0.5)	2 (0.8)	0	3 (0.6)
Cerebral disorder	0	0	1 (0.4)	0	1 (0.2)
Cerebral hematoma	0	0	1 (0.4)	0	1 (0.2)
Cerebral hemorrhage	0	0	1 (0.4)	0	1 (0.2)
Cerebrovascular accident	1 (0.4)	2 (0.9)	0	0	1 (0.2)
Coma	1 (0.4)	0	0	0	1 (0.2)
Ischemic stroke	1 (0.4)	1 (0.5)	0	0	1 (0.2)
Subarachnoid hemorrhage	0	0	1 (0.4)	3 (1.1)	1 (0.2)
Anoxic encephalopathy	0	0	0	1 (0.4)	0
Cerebral infarction	0	0	0	1 (0.4)	0
Cerebrovascular spasm	0	1 (0.5)	0	0	0
Dementia Alzheimer's type	0	1 (0.5)	0	0	0
General disorders and administration site conditions	**2 (0.9)**	**4 (1.8)**	**5 (1.9)**	**7 (2.7)**	**7 (1.4)**
Multi-organ failure	1 (0.4)	2 (0.9)	4 (1.5)	6 (2.3)	5 (1.0)
General physical health deterioration	0	0	1 (0.4)	0	1 (0.2)
Sudden cardiac death	1 (0.4)	0	0	0	1 (0.2)
Brain death	0	0	0	1 (0.4)	0
Sudden death	0	2 (0.9)	0	0	0
Gastrointestinal disorders	**2 (0.9)**	**1 (0.5)**	**0**	**0**	**2 (0.4)**
Gastrointestinal hemorrhage	1 (0.4)	0	0	0	1 (0.2)
Thrombosis mesenteric vessel	1 (0.4)	0	0	0	1 (0.2)
Large intestine perforation	0	1 (0.5)	0	0	0
Injury, poisoning and procedural complications	**0**	**0**	**1 (0.4)**	**1 (0.4)**	**1 (0.2)**
Traumatic brain injury	0	0	1 (0.4)	0	1 (0.2)
Decerebration	0	0	0	1 (0.4)	0
Metabolism and nutrition disorders	**1 (0.4)**	**1 (0.5)**	**0**	**0**	**1 (0.2)**
Failure to thrive	1 (0.4)	0	0	0	1 (0.2)
Dehydration	0	1 (0.5)	0	0	0
Vascular disorders	**0**	**1 (0.5)**	**1 (0.4)**	**0**	**1 (0.2)**
Aneurysm ruptured	0	0	1 (0.4)	0	1 (0.2)
Neurogenic shock	0	1 (0.5)	0	0	0

Note: At each level of summarization, a patient was counted once if the patient reported 1 or more events. Adverse events were treatment-emergent, defined as those adverse events with onset dates on or after the date of the start of the infusion of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

8.2.6. Study Drug Discontinuations

The number of patients with adverse events leading to discontinuation from study drug was comparable between treatment groups in each study: in DORI-09, 9 and 14 patients in the doripenem and piperacillin/tazobactam groups, respectively; in DORI-10, 17 and 15 patients in the doripenem and imipenem groups, respectively (Table 52). The only adverse events leading to study drug discontinuation in 2 or more doripenem-treated patients in either study were pneumonia, occurring in 2 patients in DORI-09 and 1 patient in DORI-10, hepatic enzyme increase, occurring in 3 patients in DORI-10 and none in DORI-09, and rash, occurring in 0 patients in DORI-09 and 2 patients in DORI-10. No case of pneumonia, all 3 cases of hepatic enzyme increase, and 1 case or rash leading to discontinuation of doripenem were considered to be related to study drug by the investigator.

Table 52: Adverse events Leading to Discontinuation From Study Drug
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

	DORI-09		DORI-10		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Total no. patients who discontinued due to AEs	**9 (4.0)**	**14 (6.3)**	**17 (6.5)**	**15 (5.7)**	**26 (5.4)**
Infections and infestations	**3 (1.3)**	**4 (1.8)**	**5 (1.9)**	**6 (2.3)**	**8 (1.6)**
Pneumonia	2 (0.9)	0	1 (0.4)	0	3 (0.6)
Abdominal abscess	0	0	1 (0.4)	0	1 (0.2)
Meningitis	0	2 (0.9)	1 (0.4)	2 (0.8)	1 (0.2)
Pulmonary tuberculosis	1 (0.4)	0	0	0	1 (0.2)
Sepsis	0	0	1 (0.4)	2 (0.8)	1 (0.2)
Staphylococcal infection	0	0	1 (0.4)	0	1 (0.2)
Bacterial sepsis	0	1 (0.5)	0	0	0
Central nervous system infection	0	0	0	1 (0.4)	0
Pneumonia staphylococcal	0	1 (0.5)	0	0	0
Septic shock	0	0	0	1 (0.4)	0
Investigations	**0**	**0**	**4 (1.5)**	**1 (0.4)**	**4 (0.8)**
Hepatic enzyme increased	0	0	3 (1.1)	1 (0.4)	3 (0.6)
Blood cholesterol increased	0	0	1 (0.4)	0	1 (0.2)
Liver function test abnormal	0	0	1 (0.4)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**4 (1.8)**	**1 (0.5)**	**0**	**0**	**4 (0.8)**
Acute pulmonary edema	1 (0.4)	0	0	0	1 (0.2)
Aspiration	1 (0.4)	0	0	0	1 (0.2)
Bronchospasm	1 (0.4)	0	0	0	1 (0.2)
Pulmonary embolism	1 (0.4)	0	0	0	1 (0.2)
Respiratory failure	0	1 (0.5)	0	0	0
Gastrointestinal disorders	**1 (0.4)**	**3 (1.4)**	**1 (0.4)**	**0**	**2 (0.4)**
Diarrhea	1 (0.4)	2 (0.9)	1 (0.4)	0	2 (0.4)
Abdominal pain	0	0	1 (0.4)	0	1 (0.2)
Pharyngoesophageal diverticulum	0	1 (0.5)	0	0	0

Note: At each level of summarization, a patient was counted once if the patient reported 1 or more events. Adverse events were treatment-emergent, defined as those adverse events with onset dates on or after the date of the start of the infusion of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

(continued)

Table 52: Adverse events Leading to Discontinuation From Study Drug
(NP Study Group – Studies JNJ38174942-DORI-09, 10: Safety Analysis Set) (continued)

	DORI-09		DORI-10		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=486) n (%)
Renal and urinary disorders	**1 (0.4)**	**0**	**1 (0.4)**	**0**	**2 (0.4)**
Renal failure acute	1 (0.4)	0	1 (0.4)	0	2 (0.4)
Skin and subcutaneous tissue disorders	**0**	**1 (0.5)**	**2 (0.8)**	**2 (0.8)**	**2 (0.4)**
Rash	0	0	2 (0.8)	1 (0.4)	2 (0.4)
Angioneurotic edema	0	1 (0.5)	0	0	0
Erythema multiforme	0	0	0	1 (0.4)	0
Vascular disorders	**0**	**1 (0.5)**	**2 (0.8)**	**0**	**2 (0.4)**
Aneurysm ruptured	0	0	1 (0.4)	0	1 (0.2)
Hypotension	0	0	1 (0.4)	0	1 (0.2)
Neurogenic shock	0	1 (0.5)	0	0	0
Cardiac disorders	**0**	**0**	**1 (0.4)**	**0**	**1 (0.2)**
Cardiac arrest	0	0	1 (0.4)	0	1 (0.2)
Hepatobiliary disorders	**0**	**0**	**1 (0.4)**	**0**	**1 (0.2)**
Cholestasis	0	0	1 (0.4)	0	1 (0.2)
Nervous system disorders	**0**	**2 (0.9)**	**1 (0.4)**	**4 (1.5)**	**1 (0.2)**
Cerebral hemorrhage	0	0	1 (0.4)	0	1 (0.2)
Brain edema	0	1 (0.5)	0	0	0
Convulsion	0	0	0	2 (0.8)	0
Epilepsy	0	0	0	1 (0.4)	0
Intracranial pressure increased	0	1 (0.5)	0	0	0
Tremor	0	0	0	1 (0.4)	0
Psychiatric disorders	**1 (0.4)**	**0**	**0**	**0**	**1 (0.2)**
Anxiety	1 (0.4)	0	0	0	1 (0.2)
Surgical and medical procedures	**0**	**0**	**1 (0.4)**	**0**	**1 (0.2)**
Dialysis	0	0	1 (0.4)	0	1 (0.2)
Blood and lymphatic system disorders	**0**	**1 (0.5)**	**0**	**0**	**0**
Lymphadenopathy	0	1 (0.5)	0	0	0
General disorders and administration site conditions	**0**	**1 (0.5)**	**0**	**2 (0.8)**	**0**
Multi-organ failure	0	0	0	1 (0.4)	0
Pyrexia	0	1 (0.5)	0	1 (0.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (0.5)**	**0**	**0**	**0**
Lung cancer metastatic	0	1 (0.5)	0	0	0

Note: At each level of summarization, a patient was counted once if the patient reported one or more events. Adverse events were treatment-emergent, defined as those adverse events with onset dates on or after the date of the start of the infusion of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

8.2.7. Risk for Seizures

The propensity of some β-lactam antibacterial agents, including imipenem, to induce seizures has been noted clinically, and studied in various in vitro and in vivo animal models.[79-82] The mechanism for carbapenem-associated

neurotoxicity is thought to be a result of their effects on central neuroinhibitory tone. The binding of gamma aminobutyric acid (GABA), the principal inhibitory central neurotransmitter, to receptor sites in the CNS is antagonized to varying degrees by various carbapenems, resulting, in some cases, in CNS excitation and convulsions.[83] However, not all carbapenems are alike with regard to the propensity to induce seizures and seizures are not believed to be a class effect.[80] Imipenem/cilastatin remains the principal example of a carbapenem associated with neurotoxicity, most often manifesting as seizures, but there is much less evidence that other carbapenems pose a similar risk.

Patients in the cUTI and cIAI studies had a relatively lower risk for seizures and no seizures were reported for patients in the doripenem-treatment groups. In contrast, a substantial proportion of patients in the NP studies were at increased risk for seizures due to underlying medical conditions including head trauma, intracranial bleeds and a prior history of seizures. Despite this elevated risk, the overall incidence of seizures in the NP studies was low for doripenem and, within each study, lower than that of the comparator agent. In DORI-09, seizures were reported for 3 doripenem-treated and 6 piperacillin/tazobactam-treated patients. None were considered by the investigator to be related to treatment with study drug and all could be explained by underlying medical conditions. In DORI-10, seizures were reported for 3 doripenem-treated and 10 imipenem-treated patients. All patients in the doripenem group and 8 of the 10 patients in the imipenem group who experienced seizures had a condition predisposing the patient for seizures, including subarachnoid hemorrhage, existing epilepsy, cerebrovascular accident, or head trauma. The remaining 2 patients in the imipenem group who experienced a seizure did not have an identified predisposing condition. One patient had a seizure while on study drug therapy. The second patient completed his imipenem study drug therapy without a seizure event. However this patient was started on non-study imipenem 3 weeks later and he had a seizure the same day.

Based on the detailed review of all cases, seizure was determined not to be an ADR for doripenem. In contrast, at least 2 patients receiving imipenem did not have an alternative explanation for inciting a seizure. Thus, although the number of seizures was small in all groups, the difference in seizure rates between doripenem and imipenem is in keeping with preclinical data indicating doripenem has a low propensity to induce seizures. This finding may be particularly important in patients with both known or previously unknown

predisposing risk factors for seizures. J&JPRD has agreed to monitor the incidence of seizures in doripenem-treated patients.

8.2.8. Adverse Drug Reactions

The definition and method for determination of ADRs is discussed in Section 7.2.7. Events identified as ADRs are nausea, *C. difficile* colitis, diarrhea, headache, phlebitis, rash, pruritus, hypesensitivity reactions, hepatic enzyme increased, oral candidiasis, and volvomycotic infections. Adverse drug reactions are presented in Table 53.

The most frequently observed ADRs (≥5% in any indication) in the doripenem-treated patients were headache, nausea, diarrhea, phlebitis and rash. Although the incidence of investigator-assessed study drug-related "hepatic enzyme increased" adverse events were uncommon in the doripenem treatment arm, this term was included as an ADR on the basis of a detailed examination of clinical laboratory abnormalities and the known association of this adverse event with other β-lactams.

Discontinuations from doripenem due to ADRs were uncommon (<1% for each ADR).

Table 53: Adverse Drug Reactions by Indication in the Controlled Phase 3 Clinical Studies
(Study JNJ38174942-DORI-05, DORI-07, DORI-08, DORI-09, DORI-10)

	NP Studies DORI-09 & DORI-10			cUTI Study DORI-05		cIAI Studies DORI-07 & DORI-08	
	Doripenem 500 mg	Pip/Tazo 4.5 g	Imipenem 500 mg h	Doripenem 500 mg	Levofloxacin 250 mg	Doripenem 500 mg	Meropenem 1 g bolus inj
ADR Derived Term	(N=485)	(N=221)	(N=263)	(N=376)	(N=372)	(N=477)	(N=469)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. patients with any ADR	**137 (28.2)**	**46 (20.8)**	**94 (35.7)**	**116 (30.9)**	**119 (32.0)**	**158 (33.1)**	**142 (30.3)**
C. difficile **colitis**	5 (1.0)	2 (0.9)	6 (2.3)	1 (0.3)	0	2 (0.4)	0
Diarrhea	58 (12.0)	24 (10.9)	45 (17.1)	22 (5.9)	38 (10.2)	51 (10.7)	52 (11.1)
Headache	14 (2.9)	5 (2.3)	8 (3.0)	59 (15.7)	54 (14.5)	21 (4.4)	24 (5.1)
Hepatic enzyme increased [a]	9 (3.2)	2 (1.6)	5 (3.2)	2 (0.6)	1 (0.3)	2 (0.5)	3 (0.8)
Hypersensitivity	0	1 (0.5)	0	*5 (1.3)*	3 (0.8)	*1 (0.2)*	*1 (0.2)*
Nausea	33 (6.8)	7 (3.2)	28 (10.6)	16 (4.3)	22 (5.9)	57 (11.9)	44 (9.4)
Oral candidiasis	13 (2.7)	1 (0.5)	6 (2.3)	4 (1.1)	0	5 (1.0)	8 (1.7)
Phlebitis	10 (2.1)	5 (2.3)	2 (0.8)	15 (4.0)	15 (4.0)	36 (7.5)	26 (5.5)
Pruritus	7 (1.4)	1 (0.5)	5 (1.9)	3 (0.8)	4 (1.1)	13 (2.7)	9 (1.9)
Rash	31 (6.4)	7 (3.2)	16 (6.1)	2 (0.5)	3 (0.8)	21 (4.4)	11 (2.3)
Vulvomycotic infection	0	0	1 (0.4)	6 (1.6)	4 (1.1)	5 (1.0)	2 (0.4)

[a] Percentages calculated using the number of patients with laboratory values ≤ULN at baseline and non-missing post-baseline laboratory values. Patients with AST or ALT increased were defined as patients with AST or ALT laboratory values ≤ULN at baseline and >5x ULN at end of the i.v. therapy period. End of i.v. therapy period was defined as the measurement within the 24-hour window before and after the last dose of i.v. study drug.

Note: Percentages calculated with the number of patients in each group as denominator. Patients from DORI-03 who received doripenem 250 mg are not included. Rashes were AEs with MedDRA preferred terms of 'Dermatitis', 'Dermatitis bullous', 'Erythema multiforme', 'Rash', 'Rash erythematous', 'Rash generalized', 'Rash macular', 'Rash maculo-papular', 'Rash papular', 'Rash pruritic', and 'Drug eruption'. Anaphylactic reactions were AEs with MedDRA high level group term of 'Anaphylactic responses'. Hypersensitivity was AEs with MedDRA preferred term of 'Hypersensitivity', 'Drug hypersensitivity', 'Type I hypersensitivity', 'Type II hypersensitivity', 'Type III immune complex-mediated reaction', 'Type IV hypersensitivity reaction', 'Angioneurotic edema', 'Urticaria', and 'Urticaria localized'. *Clostridium difficile* colitis was AEs with MedDRA preferred terms of 'Clostridium colitis', '*Clostridium difficile* colitis', '*Clostridium difficile* sepsis', and 'Gastroenteritis clostridial'. Diarrhea was AEs with MedDRA preferred term of 'Diarrhea'. Headache was AEs with MedDRA preferred term of 'Headache'. Nausea was AEs with MedDRA preferred term of 'Nausea'. Oral candidiasis was AEs with MedDRA preferred term of 'Oral candidiasis'. Phlebitis was AEs with MedDRA preferred terms of 'Phlebitis' and 'Infusion site phlebitis'. Pruritus was AEs with MedDRA preferred terms of 'Pruritus', 'Pruritus allergic', and 'Pruritus generalized'. Vulvomycotic infection was AEs with MedDRA preferred terms of 'Vulvovaginal mycotic infection' and 'Vaginal candidiasis'. Hepatic enzyme increased was AEs with MedDRA preferred terms of 'Hepatic enzyme increased', 'Alanine aminotransferase increased', 'Aspartate aminotransferase increased', and 'Transaminases increased'. Treatment-Emergent AEs were defined as AEs with onset dates on or after the date of the start of the infusion of first dose of study medication, and within 30 days after administration of the last dose of study medication. AE terms were coded using MedDRA version 9.0.

8.2.9. Clinical Laboratory Values

Serum chemistry and hematology evaluations were assessed as described in Section 7.2.7. Few notable differences in the rates or degrees of abnormalities of hematology or serum chemistry laboratory abnormalities were seen between doripenem-treated patients and the respective comparator-treated patients in each of the NP studies. Shifts in laboratory values from normal at baseline (i.e., Grade 0) to Grade 4 were rare for all values.

No notable differences in hematology parameters between the doripenem and comparator groups were observed. Differences in the mean changes in hemoglobin, platelets, and neutrophils were seen between studies however, observed changes were consistent between the doripenem group and the respective comparator group within each study.

In DORI-09, mean baseline hemoglobin values were comparable between the doripenem and piperacillin/tazobactam groups (108.6 g/L and 111.2 g/L, respectively) and mean changes in hemoglobin from baseline to the LFU visit were 14.7 g/L for the doripenem group and 10.6 g/L for the piperacillin/tazobactam group. In DORI-10, mean baseline hemoglobin values were lower than in DORI-09 but comparable between the two treatment groups (97.0 g/L and 97.3 g/L, respectively). Mean changes in hemoglobin from baseline to the LFU visit were 23.1 g/L for the doripenem group and 18.5 g/L for the imipenem group in DORI-10. Greater mean increases in hemoglobin values in DORI-10 were likely related to the lower mean baseline values in this study as well as the possibility of more frequent RBC transfusions in the DORI-10 intensive-care-unit population. The increase in hemoglobin values observed in these studies represents normalization of low baseline values (Attachment 10).

8.2.9.1. Summary of Creatinine Laboratory Values

To evaluate a potential difference in renal toxicity between treatment groups in the Phase 2 and 3 clinical studies, the proportion of patients who had a >20% increase from their baseline serum creatinine at any were evaluated. No difference was observed between the treatment groups in terms of the proportion of patients who met this criterion (Table 54). For the combined doripenem group, 22.8% (415/1817) patients (including 26.0% [58/223] in DORI-09) and 29.8% [78/262] in DORI-10) had a 20% increase in serum creatinine from baseline during the study compared to 14.5% (54/372) for the levofloxacin

group, 20.9% (98/469) for the meropenem group, 22.8% (60/263) for the imipenem group, and 29.0% (64/221) for the piperacillin/tazobactam group. During i.v. therapy, 9.8% (178/1817) patients in doripenem group (including 15.7% [35/223] in DORI-09) and 17.6% [46/262] in DORI-10), 8.1% (30/372) in the levofloxacin group, 9.2% (43/469) in the meropenem group, 12.2% (32/263) for imipenem group, and 21.3% (47/221) in the piperacillin/tazobactam group had a 20% increase in serum creatinine from baseline.

Table 54: Proportion of Patients With a 20% Increase in Serum Creatinine From Baseline in the Phase2/3 Studies
(Studies JNJ38174942-DORI-03, DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, and DORI-10)

Treatment Group	N	During i.v. Therapy	After i.v. Therapy	Any Time During the Study
Doripenem	1817	178 (9.8%)	259(13.4%)	415 (22.8%)
Levofloxacin	372	30 (8.1%)	36 (9.7%)	54 (14.5%)
Meropenem	469	43 (9.2%)	71 (15.1%)	98 (20.9%)
Imipenem	263	32 (12.2%)	40 (15.2%)	60 (22.8%)
Piperacillin/Tazobactam	221	47 (21.3%)	33 (14.9%)	64 (29.0%)

Serum creatinine values for the 33 affected doripenem-treated patients with an adverse event of renal failure (Attachment 9.4) were further evaluated in order to have an objective measure of the reported adverse events of renal failure/impairment. The serum creatinine value (where available) at baseline, EOT (i.v.) visit, day of AE onset and at early follow-up are presented in Table 55.

As noted in the Table 55, patients who had renal failure reported as an adverse event had onset of the event in the post-treatment period. In 11 of these 17 patients, their serum creatinine value at the EOT(i.v.) visit was no higher than at baseline, indicating that these patients did not have objective evidence for renal damage while receiving doripenem therapy. Of the 6 remaining patients who had a renal failure reported as an adverse event in the post-treatment period, 2 had increases at EOT(i.v.) visit that were ≤44 μmol/L (Patients 04602510, 40503504); a threshold discussed above that is commonly used to define acute renal failure. (Patient 3830410 has no baseline serum creatinine measurement). The remaining 3 patients (Patients 63000035, 10006028, 12302566) had other significant medical conditions preceding the event that the investigator assessed

as contributing to the renal failure: Patient 63000035 had sepsis and dehydration; Patient 10006028 had cardiac decompensation; and Patient 12302566 had sepsis. For the 16 patients who had renal failure reported as an adverse event during i.v. therapy, 4 had serum creatinine levels values at the EOT(i.v.) visit that was the same or lower than the value at baseline and 4 had increases at the EOT(i.v.) visit that were ≤44 μmol/L (negative rechallenge). Therefore, for these 8 patients, it is unlikely that the administration of doripenem contributed to the reported renal failure. Of the 8 patients (30306011, 35700366, 12806502, 31204035, 94101007, 13401519, 14402546, 75005521) who had a serum creatinine level >44 μmol/L higher at the EOT(i.v.) visit than at baseline, 4 patients had other significant medical conditions preceding the events that the investigator assessed as contributing to renal failure. Patient 30306011 had post-obstructive nephropathy secondary to a prostatic adenoma. The event resolved after placement of urinary catheter. Patient 35700366 had bladder carcinoma. A right nephrostomy was performed on Day 22 and by Day 27, this patient's serum creatinine values had decreased to near baseline values. Patient 14402546 had a nephrology consultation that stated the most likely reason for the renal failure was rhabdomyolysis (serum CK values range from 1669 to 24400 at Day 8; normal range, 24-195). Patient 75005521 developed sepsis and cardiogenic shock; the investigator assessed the subsequent renal failure most likely secondary to hypoperfusion. The remaining 4 cases (31204035, 12806502, 94101007, 13401519) had confounding events and received concomitant nephrotoxic drugs. Vancomycin was previously administered in 4 of those 8 patients (12806502, 31204035, 94101007, 13401519).

Table 55: Creatinine Values for Doripenem-Treated Patients With Renal-Related Adverse Event in the Phase 3 Studies
(Studies JNJ38174942-DORI-05, DORI-06, DORI-07, DORI–08, DORI-09, DORI-10

Patient Number	End of i.v. Therapy	TEAE/SAE Day of Onset	Creatinine at baseline (μmol/L)	Creatinine at onset of AE (μmol/L)	Creatinine at EOT (i.v.) (μmol/L)	Creatinine at EFU (μmol/L)
			DORI 05			
01303031#	Day 9	Day 3	115	239	80	62 (Day 21)
30306011*#	Day 6	Day 4	88	371	433	97 (Day 19)
30704002	Day 5	Day 11	194	460	124	115 (Day 34)
			DORI 06			
35100066*	Day 5	Day 12	97	N/A	97	71 (Day 16)
35700366*#	Day 11	Day 11	71	592	592	716 (Day 18)
63000035*	Day 2	Day 3	203	318	318	97 (Day 14)
63300108#	Day 15	Day 4	186	301	97	141 (Day 23)
63300210#	Day 14	Day 3	124	371	124	115 (Day 22)
64300217*	Day 2	Day 1 (TEAE) Day 13 (SAE)	194 Same	194 N/A	124 Same	124 (Day 2) Same
			DORI 07			
04102020*	Day 4	Day 23	97	N/A	88	133 (Day 11)
04602510	Day 6	Day 14	106	N/A	141	141 (Day 23)
10006028*	Day 6	Day 18 (SAE Day 32 (TEAE)	80	N/A	221	309 (Day 19)
			DORI 08			
02902030	Day 6	Day 30	80	N/A	62	71 (Day 13)
12606026*	Day 6	Day 32	71	N/A	53	53 (Day 6)
12806502#	Day 11	Day 10	133	N/A	194	124 (Day 21)
38304104*	Day 6	Day 16	N/A	N/A	62	133 (Day 16)
			DORI-09			
19706030#	Day 8	Day 6	177	195	186	133 (Day 42)
30604514	Day 8	Day 20	141	N/A (195 Day 18)	115	141 (Day 38)
31204035#	Day 15	Day 9	71	N/A (98 Day 8)	212	N/A
40503023	Day 11	Day 33	62	N/A	35	35 (Day 44)
40503504	Day 15	Day 17	124	N/A	133	N/A
93001504*#	Day 8	Day 7	230	N/A (256 Day 8)	256	N/A
93202502*#	Day 9	Day 2 (SAE Day 22)	194	N/A (203 Day 3)	221	212 (Day 43)
94101007*#	Day 9	Day 9	115	248	248	239 (Day 40)
94402010#	Day 15	Day 11	80	62	80	N/A
			DORI 10			
00705020#	Day 14	Day 11	124	239	168	N/A
12302566*	Day 4	Day 18	141	N/A	195	398 (Day 33)
12801525	Day 1	Day 3	106	N/A	106	N/A
13401519*#	Day 3	Day 2	106	N/A (512 Day 3)	513	N/A
14402510	Day 9	Day 32	88	N/A	88	N/A
14402546*#	Day 8	Day 8	80	362	362	N/A
14502007	Day 12	Day 41	80	N/A	80	N/A
75005521#	Day 2	Day 2	168	256	256	N/A

Key: * = Patient with SAE; # = SAE/TEAE occurred during i.v. study therapy; SAE=serious adverse event; TEAE=treatment-emergent adverse event

8.2.9.2. Hepatobiliary Parameters

Mean values for hepatobiliary parameters (ALT, AST, GGT, ALP and bilirubin) were generally higher at baseline for patients in all treatment groups in the NP studies compared to the cUTI and cIAI indications. In general, mean values and shift in toxicity grade of ALT, AST, GGT and ALP increased from baseline to the end of i.v. therapy, then decreased by follow-up in all treatment groups. Shifts in ALT and AST to abnormal toxicity grade ranges in DORI-09 and DORI-10 are summarized in Attachment 11.1 and Attachment 11.2, respectively. Most patients in both treatment arms in each study had values that were less than 3x ULN. Elevations to >3xULN in ALT and AST values at the end of i.v. therapy (end point [i.v.]) were uncommon (≤6%). Although clinically important enzyme elevations were rare in doripenem-treated patients, mild reversible hepatic enzyme elevations have been associated with β-lactam use. Therefore, increased hepatic enzyme was included as an ADR.

8.2.9.3. Hy's Risk Classification

Nine patients met the criteria for HHR classification (ALT >3 times ULN and concomitant elevations in total bilirubin >1.5 times ULN, with an ALP value ≤1.5xULN.[63,84]) after the administration of the first dose of study drug: 4 patients treated with doripenem, 2 treated with piperacillin/tazobactam, and 3 treated with imipenem. Evaluation of all patients revealed that all had underlying medical conditions that explained the liver function values or confounded the assessment of drug-related injury.

The first doripenem-treated patient met HHR on the eighth day of treatment and had multiple contributing factors including deteriorating cardiac function, treatment with amiodarone and passive liver congestion, which was confounded by a progressively rising ALP. The second doripenem-treated patient met HHR criteria on the third day of treatment when he was septic, hypotensive and had respiratory failure and renal failure and compartment syndrome. The third patient treated with doripenem who met HHR criteria was enrolled into the study with an elevated bilirubin level and an ALP that was just <1.5 ULN, and risk factors for gallstones and biliary sludge. The interpretation of this case was confounded by the prior and concomitant administration of medications with potential for prolonged hepatic enzyme changes, blood transfusions, and possibly progressive biliary duct obstruction. The fourth patient met HHR on the second day of doripenem administration following sepsis and cardiogenic shock which probably contributed to passive liver congestion and necrosis.

8.3. Postmarketing Experience

Between September 2005 when doripenem was launched in Japan and August 2007, an estimated 235,000 patients were exposed to doripenem in Japan. The following adverse drug reactions have been identified from postmarketing spontaneous reports from Japan: anaphylaxis, pseudomembranous colitis, and neutropenia. Note that *Clostridium difficile* colitis is listed as an adverse drug reaction, based on clinical study data. Because the reactions anaphylaxis and neutropenia were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

An estimated 3,926 patients were exposed to doripenem in the U.S. from 01 October 2008 through 30 April 2008. No new adverse drug reactions have been identified from the post-marketing experience in the U.S.

9. BENEFITS AND RISKS CONCLUSIONS

9.1. Dosing Recommendations

The only dosage of doripenem evaluated in the Phase 3 NP (and cUTI and cIAI) clinical studies was 500 mg q8h; however, 2 different infusion durations were studied. DORI-09 utilized a 1-hour infusion, whereas DORI-10 utilized a 4-hour infusion. Both infusion regimens were found to be effective and well tolerated. The efficacy and safety of the 1-hour infusion regimen was established in patients with NP (DORI-09) and, therefore, this dosage regimen is appropriate for most cases within this patient population. This is also the dosage regimen recommended for the approved indications of cUTI and cIAI. The safety and efficacy of the 4-hour infusion regimen for treatment of VAP patients was established in DORI-10. Although, the 4-hour infusion was anticipated to provide added benefit to patients infected with less susceptible pathogens this was not clearly established in DORI-10 because of the paucity of such pathogens isolated. However, PK data collected in DORI-10 confirmed that doripenem plasma concentrations achieved with the 4-hour infusions were consistent with those predicted and that PD targets likely to be effective against pathogens with MICs up to 4 μg/mL were attained. PK data collected during the NP submission are discussed in Section 6. Although there are no clinical data directly showing the advantages of the 4-hour over the 1-hour regimen, the 4-hour infusion is recommended for NP infection suspected to be caused by less susceptible infections or have late-onset (intubated ≥5 days) VAP on the basis of PK/PD analyses.

As doripenem is excreted by the kidneys, dosage adjustments are recommended for patients with moderate or severe renal failure (see the approved label in Attachment 1).

9.2. Summary of Benefits and Risks

The results of the Phase 3 investigations confirmed the favorable benefit to risk profile for doripenem for patients with NP, including VAP. The comparators used in the pivotal clinical studies are agents of choice and are reliable therapies for these indications. Thus, demonstration of noninferiority to these agents provides a stringent evaluation of doripenem therapy. In addition, the high clinical and microbiological success rates predict that doripenem would be a clinically useful addition to the antibacterial armamentarium in the treatment of NP, including VAP caused by susceptible bacteria. Both trials independently met not only the prespecified noninferiority margin but also the conservative margin estimates from the noninferiority margin justification, which were determined after the studies were completed. The results from these clinical studies are supported by numerous in vitro studies highlighting the potent broad-spectrum activity of doripenem. These include, in particular, greater activity and lower rates of resistant mutant selection in *P. aeruginosa*, an important target pathogen, versus other carbapenems.[35-37]

In addition to the demonstration of noninferiority in these studies, a number of findings support the potential benefit of doripenem. In vitro resistance among baseline gram-negative isolates was greater for the comparators, particularly piperacillin/tazobactam, than for doripenem, emphasizing, in particular, the global spread of ESBL-producing Enterobacteriaceae and multidrug-resistant *P. aeruginosa*. The carbapenems are widely considered the drugs of choice for ESBL-producing organisms[85,86] and are thus likely to become more prominent treatment options for infections caused by Enterobacteriaceae. In both NP studies, doripenem showed some evidence of improved efficacy for gram-negative infections, although differences were not considered to be statistically significant. The lower rates in *P. aeruginosa* of high MICs (i.e., ≥8 ug/mL) at baseline, and emerging during therapy with doripenem, compared with imipenem, are consistent with in vitro studies showing a lower propensity of doripenem to select for resistant mutants. The potential disadvantages of piperacillin/tazobactam compared with doripenem were also highlighted in the NP study DORI-09; these included lower in vitro activity

against key gram-negative pathogens, such as *Klebsiella spp., P. aeruginosa* and *A. baumanni,* and, as a result, the need for combination with an aminoglycoside.

A total of 969 NP patients, 485 of whom received the 500 mg dose of doripenem, were evaluated for safety in the pivotal Phase 3 studies (a detailed discussion of safety is included in Section 8). This cohort provides a substantial database from which to draw conclusions regarding the safety of doripenem. Safety evaluations demonstrated that doripenem was well tolerated with a similar safety profile compared to the comparator agents (i.e., piperacillin/tazobactam, and imipenem), which have known good safety profiles. Furthermore, there is experience in an additional 1,332 patients enrolled in the previous Phase 2 and 3 cUTI and cIAI trials.

No new ADRs were identified in the NP studies that were not previously seen in the cIAI and cUTI studies. ADRs identified in the Phase 2 and 3 studies were generally similar to those associated with agents in the carbapenem class. These were generally mild to moderate in severity, and reversible. The mortality rate was low in cUTI and cIAI, and at the lower end of the range reported in the literature in NP.[1] No deaths were reported by the investigators as related to study drug. Study drug-related discontinuations or serious adverse events were rare.

Seizures and other CNS events have been reported for patients treated with approved carbapenems, especially imipenem, and the U.S. product inserts for carbapenems contain a precautionary statement regarding seizures. Preclinical data did not identify a risk for seizures associated with doripenem and no seizures were recorded on doripenem therapy in the cIAI and cUTI studies. In the NP studies, which included patients at high risk for seizures (such as head trauma and subarachnoid hemorrhage), a lower proportion of patients had seizures in the doripenem treatment arm than in either of the comparator arms and no causal relationship to doripenem could be established.

Doripenem offers a number of potential advantages as a treatment option for NP, including VAP. Doripenem is generally 2- to 4-fold more potent against *P. aeruginosa* than other carbapenems in vitro and may be effective against some strains resistant to imipenem, although clinical data to date are limited. Doripenem is stable in solution, allowing it to be administered safely as an extended infusion, which, based on PK/PD principles, offers a potential therapeutic benefit. This theoretical advantage could not be confirmed in the clinical studies because strains with decreased susceptibility to doripenem were

infrequent. Emergence of resistance is always a concern with antimicrobial agents, and lower rates of emergent doripenem resistant mutants in *P. aeruginosa*, compared to other carbapenems, were seen both in vitro and in the clinical studies. Finally, doripenem exhibited a lower potential for neurotoxicity in preclinical studies (especially compared with imipenem). This potential advantage was supported by findings in the clinical studies, although small numbers preclude firm conclusions.

In conclusion, doripenem is a potent broad-spectrum antibacterial agent shown to be statistically non-inferior to comparators in the treatment of NP (including VAP), with a safety profile generally similar to these comparators. The potential benefits for patient care are discussed above. The overall risks are similar to those of highly regarded and widely used standard therapies.

10. CONCLUSIONS

Doripenem shares the bactericidal mode of action of other β-lactam antibiotics by targeting PBPs to inhibit the biosynthesis of the bacterial cell wall. In vitro and in vivo studies support the effectiveness of doripenem against the pathogens that cause infections, including those that cause pneumonia. The frequency of in vitro doripenem resistance selection in *P. aeruginosa* is lower than that of other anti-pseudomonal antibiotics and resistance profiles are similar to those seen with other anti-pseudomonal β-lactam antibiotics.

Doripenem was evaluated for the treatment of NP and VAP. Two studies, DORI-09 and DORI-10, were conducted in this patient population and each met their primary objective, the establishment of noninferiority between doripenem and the respective comparator treatment in the clinical cure rate at the TOC visit conducted 6 to 20 days after the completion of i.v. study drug therapy. In addition, doripenem was shown to be effective against the major causative pathogens of NP, including *S. aureus* (methicillin-susceptible strains), *S. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *H. influenzae*, and Enterobacteriaceae (*K. pneumoniae, E. cloacae*, *E. coli*) at the TOC visit. Rates of microbiological cure (eradication or presumed eradication) in gram-negative infections were generally higher for doripenem than for comparator. Doripenem was also shown to be effective against resistant gram-negative pathogens, per the assessment of clinical cure rates. Emergent infections were infrequent and, the emergence of decreased susceptibility (defined as a ≥4-fold increase in MIC) among baseline pathogens was uncommon with doripenem. The adverse event profile observed with doripenem in patients with NP was consistent with that of previously approved indications, and other carbapenems, and it was similar to the respective comparator arm in each study. A favorable benefit to risk ratio is concluded.

The currently limited therapeutic choices in NP support doripenem as a useful new option. In NP, combination therapy is frequently recommended (especially for *P. aeruginosa* infections) because of the broad range of potential causative pathogens and high rates of resistance to existing therapies. Adjunctive antipseudomonal therapy was given in combination with doripenem in only approximately 20% of patients with VAP (in DORI-10). However, the benefit of combination therapy in this study was not assessable because patients were not randomized to receive combination therapy or monotherapy. In addition, the decision to start combination therapy empirically was likely a marker for greater

severity of illness, and thus, clinical responses were generally lower when combination therapy was used. Overall, for gram-negative infections (including most *P. aeruginosa* infections), doripenem monotherapy can be considered sufficient. However, doripenem should be combined with an appropriate agent when MRSA is suspected.

The proposed indication for doripenem is:

> the treatment of patients with nosocomial pneumonia, including ventilator-associated pneumonia, caused by *Staphylococcus aureus* (methicillin-susceptible strains only), *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Enterobacter cloacae*, *Escherichia coli, Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa.*

The proposed dosage of doripenem for this indication is:

> 500 mg every 8 hours by i.v. infusion administered over 1 hour for patients ≥18 years of age. For most infections 1-hour infusions are recommended. For patients with nosocomial pneumonia including ventilator-associated pneumonia who are at risk for infections with less susceptible pathogens, 4-hour infusions are recommended.

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SUPPORTING DATA

The Supporting Data section is organized using a flexible numbering system that provides logical groups of data while minimizing the number of decimal levels. Numbering can start at any level (e.g., 1 or 1.1 or 1.1.1) to provide the most efficient organization for a particular set of data. Levels that are omitted do not indicate missing data.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DORIBAX™ safely and effectively. See full prescribing information for DORIBAX™.

DORIBAX™ (doripenem for injection) for Intravenous Infusion
Initial U.S. Approval: 2007

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX™ and other antibacterial drugs, DORIBAX™ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

----------INDICATIONS AND USAGE----------

DORIBAX™ is a penem antibacterial indicated in the treatment of the following infections caused by designated susceptible bacteria:

- Complicated intra-abdominal infections (1.1)
- Complicated urinary tract infections, including pyelonephritis (1.2)

----------DOSAGE AND ADMINISTRATION----------

- 500 mg every 8 hours by intravenous infusion administered over one hour for patients ≥18 years of age. (2.1)
- Dosage in patients with impaired renal function (2.2):

CrCl (mL/min)	Recommended Dose of DORIBAX™
> 50	No dosage adjustment necessary
≥ 30 to ≤ 50	250 mg IV (over 1 hour) every 8 hours
> 10 to < 30	250 mg IV (over 1 hour) every 12 hours

----------DOSAGE FORMS AND STRENGTHS----------

500 mg single-use vial (3)

----------CONTRAINDICATIONS----------

Patients with known serious hypersensitivity to doripenem or to other drugs in the same class or patients who have demonstrated anaphylactic reactions to beta-lactams (4)

----------WARNINGS AND PRECAUTIONS----------

- Serious hypersensitivity (anaphylactic) reactions have been reported with carbapenems and other beta-lactams (5.1)
- Loss of seizure control due to lower serum valproic acid levels may result from interaction with sodium valproate (5.2)
- *Clostridium difficile*-associated diarrhea (ranging from mild diarrhea to fatal colitis): Evaluate if diarrhea occurs (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 5%) are headache, nausea, diarrhea, rash and phlebitis.

To report SUSPECTED ADVERSE REACTIONS, contact Ortho-McNeil Pharmaceutical, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Interacting Drug	Interaction
Valproic acid	Carbapenems may reduce serum valproic acid levels (7.1)
Probenecid	Reduces renal clearance of doripenem, resulting in increased doripenem concentrations (7.2, 12.3)
Drugs metabolized by cytochrome P450 enzymes	Doripenem neither inhibits nor induces major cytochrome P450 enzymes (12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Dosage adjustment is required in patients with moderately or severely impaired renal function (2.2, 12.3)
- DORIBAX™ has not been studied in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX™ and other antibacterial drugs, DORIBAX™ should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Complicated Intra-Abdominal Infections

DORIBAX™ (doripenem for injection) is indicated as a single agent for the treatment of complicated intra-abdominal infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Bacteroides caccae, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Streptococcus intermedius, Streptococcus constellatus* and *Peptostreptococcus micros*.

1.2 Complicated Urinary Tract Infections, Including Pyelonephritis

DORIBAX™ (doripenem for injection) is indicated as a single agent for the treatment of complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli* including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii.*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of DORIBAX™ is 500 mg administered every 8 hours by intravenous infusion over one hour in patients ≥18 years of age. The recommended dosage and administration by infection is described in Table 1:

Table 1: Dosage of DORIBAX™ by Infection

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Complicated intra-abdominal infection	500 mg	q8h	1	5-14 days*
Complicated UTI, including pyelonephritis	500 mg	q8h	1	10 days*§

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

§ Duration can be extended up to 14 days for patients with concurrent bacteremia.

2.2 Patients with Renal Impairment

Table 2: Dosage of DORIBAX™ in Patients with Renal Impairment

Estimated CrCl (mL/min)	Recommended Dosage Regimen of DORIBAX™
> 50	No dosage adjustment necessary
≥ 30 to ≤ 50	250 mg intravenously (over 1 hour) every 8 hours
> 10 to < 30	250 mg intravenously (over 1 hour) every 12 hours

The following formula may be used to estimate CrCl. The serum creatinine used in the formula should represent a steady state of renal function.

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: Creatinine clearance (mL/min) = 0.85 x value calculated for males

DORIBAX™ is hemodialyzable; however, there is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

2.3 Preparation of Solutions

DORIBAX™ does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparation of the infusion solution.

Preparation of 500 mg dose:

- Constitute the vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is 50 mg/mL. **CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.**
- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear. The final infusion solution concentration is 4.5 mg/mL.

Preparation of 250 mg dose for patients with moderate or severe renal impairment:

- Constitute the vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is 50 mg/mL. **CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.**
- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear. Remove 55 mL of this solution from the bag and discard. Infuse the remaining solution, which contains 250 mg (4.5 mg/mL).

To prepare DORIBAX infusions in Baxter Minibag Plus™ infusion bags consult the infusion bag manufacturer's instructions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit. DORIBAX infusions range from clear, colorless solutions to solutions that are clear and slightly yellow. Variations in color within this range do not affect the potency of the product.

2.4 Compatibility

The compatibility of DORIBAX™ with other drugs has not been established. DORIBAX™ should not be mixed with or physically added to solutions containing other drugs.

2.5 Storage of Constituted Solutions

Upon constitution with sterile water for injection or 0.9% sodium chloride (normal saline) injection, DORIBAX suspension in the vial may be held for 1-hour prior to transfer and dilution in the infusion bag.

Following dilution of the suspension with normal saline or 5% dextrose, DORIBAX infusions stored at controlled room temperature or under refrigeration should be completed according to the times in Table 3.

Table 3: Storage and Stability Times of Infusion Solutions Prepared in Normal Saline or 5% Dextrose

Infusion prepared in	Stability Time at Room Temp. (includes room temperature storage and infusion time)	Stability time at 2-8°C (Refrigeration) (includes refrigerator storage and infusion time)
Normal saline	8 hours	24 hours
5% Dextrose	4 hours	24 hours

Constituted DORIBAX suspension or DORIBAX infusion should not be frozen. This storage information applies also to DORIBAX™ diluted in Baxter Minibag Plus™.

3 DOSAGE FORMS AND STRENGTHS

Single use clear glass vials containing 500 mg (on an anhydrous basis) of sterile doripenem powder.

4 CONTRAINDICATIONS

DORIBAX™ is contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with DORIBAX™ is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other carbapenems, cephalosporins, penicillins or other allergens. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross-hyperreactivity among beta-lactam antibiotics has been clearly documented.

If an allergic reaction to DORIBAX™ occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

5.2 Interaction with Sodium Valproate

Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be

considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur. [see *Drug Interactions (7.1*)]

5.3 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. [see *Adverse Reactions (6.1)*]

5.4 Development of Drug-Resistant Bacteria

Prescribing DORIBAX™ in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.5 Pneumonitis with Inhalational Use

When DORIBAX™ has been used investigationally via inhalation, pneumonitis has occurred. DORIBAX™ should not be administered by this route.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Anaphylaxis and serious hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- Interaction with sodium valproate [see *Warnings and Precautions (5.2)* and *Drug Interactions (7.1)*]
- *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.3)*]

- Development of drug-resistant bacteria [see *Warnings and Precautions (5.4)*]
- Pneumonitis with inhalational use [see *Warnings and Precautions (5.5)*]

6.1 Adverse Reactions from Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of another drug and may not reflect rates observed in practice.

During clinical investigations, 853 adult patients were treated with DORIBAX™ IV (500 mg administered over 1 hour q8h) in the three comparative phase 3 clinical studies; in some patients, parenteral therapy was followed by a switch to an oral antimicrobial. [see *Clinical Studies (14)*] The median age of patients treated with DORIBAX™ was 54 years (range 18-90) in the comparative cUTI study and 46 years (range 18-94) in the pooled comparative cIAI studies. There was a female predominance (62%) in the comparative cUTI study and a male predominance (63%) in the pooled cIAI studies. The patients treated with DORIBAX™ were predominantly Caucasian (77%) in the three pooled phase 3 studies.

The most common adverse reactions (≥ 5%) observed in the DORIBAX™ phase 3 clinical trials were headache, nausea, diarrhea, rash and phlebitis. During clinical trials, adverse drug reactions that led to DORIBAX™ discontinuation were nausea (0.2%), vulvomycotic infection (0.1%) and rash (0.1%).

Adverse reactions due to DORIBAX™ 500 mg q8h that occurred at a rate ≥ 1 % in either indication are listed in Table 4. Hypersensitivity reactions related to intravenous study drug and *C. difficile* colitis occurred at a rate of less than 1% in the three controlled phase 3 clinical trials.

Table 4: Adverse Reactions† with Incidence Rates (%) of ≥1% and Adverse Events†† Having Clinically Important Differences in Frequency by Indication in the Three Controlled, Comparative DORIBAX™ Phase 3 Clinical Trials

	Complicated Urinary Tract Infections (one trial)		Complicated Intra-Abdominal Infections (two trials)	
System organ class	DORIBAX™ 500 mg q8h (n =376)	Levofloxacin 250 mg IV q24h (n = 372)	DORIBAX™ 500 mg q8h (n = 477)	Meropenem 1 g q8h (n = 469)
Nervous system disorders				
Headache	16	15	4	5
Vascular disorders				
Phlebitis	4	4	8	6
Gastro-intestinal disorders				
Nausea	4	6	12	9
Diarrhea	6	10	11	11
Blood and Lymphatic System Disorders				
Anemia††	2	1	10	5
Renal and Urinary Disorders				
Renal impairment/Renal failure††	<1	0	1	<1
Skin and subcutaneous disorders				
Pruritus	<1	1	3	2
Rash*	1	1	5	2
Investigations				
Hepatic enzyme elevation**	2	3	1	3
Infection and Infestations				
Oral candidiasis	1	0	1	2
Vulvomycotic infection	2	1	1	<1

*includes reactions reported as allergic and bullous dermatitis, erythema, macular/papular eruptions, urticaria and erythema multiforme

**includes reactions reported as alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased

† An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of DORIBAX™ that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

†† An adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of doripenem outside of the U.S. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency or establish a causal relationship to drug exposure.

Anaphylaxis

The following treatment-emergent adverse events (known to occur with beta-lactams including carbapenems) have been reported voluntarily during post-approval use of DORIBAX™ outside of the U.S. They are included due to their seriousness, although it is not possible to estimate their frequency and causality has not been established:

Stevens Johnson Syndrome
Toxic epidermal necrolysis
Interstitial pneumonia
Seizure

7 DRUG INTERACTIONS

7.1 Valproic Acid

A clinically significant reduction in serum valproic acid concentrations has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from *in vitro* and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or a seizure occurs. [see *Warnings and Precautions (5.2)*]

7.2 Probenecid

Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. [see *Clinical Pharmacology (12.3)*] Coadministration of probenecid with DORIBAX™ is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category B: Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1 g/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least 2.4 and 0.8 times the exposure to humans dosed at 500 mg q8h, respectively). There are no adequate

and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DORIBAX™ is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of DORIBAX™, 28% were 65 and over, while 12% were 75 and over. Clinical cure rates in complicated intra-abdominal and complicated urinary tract infections were slightly lower in patients ≥ 65 years of age and also in the subgroup of patients ≥ 75 years of age versus patients < 65. These results were similar between doripenem and comparator treatment groups.

No overall differences in safety were observed between older and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Elderly subjects had greater doripenem exposure relative to non-elderly subjects; however, this increase in exposure was mainly attributed to age-related changes in renal function. [see *Clinical Pharmacology (12.3)*]

This drug is known to be excreted substantially by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function or pre-renal azotemia. Because elderly patients are more likely to have decreased renal function or pre-renal azotemia, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Patients with Renal Impairment

Dosage adjustment is required in patients with moderately or severely impaired renal function. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*] In such patients, renal function should be monitored.

10 OVERDOSAGE

In the event of overdose, DORIBAX™ should be discontinued and general supportive treatment given.

Doripenem can be removed by hemodialysis. In subjects with end-stage renal disease administered DORIBAX™ 500 mg, the mean total recovery of doripenem and doripenem-M1 in

the dialysate following a 4-hour hemodialysis session was 259 mg (52% of the dose). However, no information is available on the use of hemodialysis to treat overdosage. [see *Clinical Pharmacology (12.3)*]

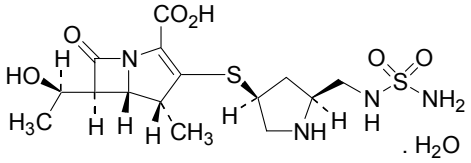
11 DESCRIPTION

DORIBAX™, doripenem monohydrate for injection vials contain 500 mg of doripenem on an anhydrous basis, a white to slightly-yellowish off-white sterile crystalline powder. All references to doripenem activity are expressed in terms of the active doripenem moiety. The powder is constituted for intravenous infusion. The pH of the infusion solution is between 4.5 and 5.5.

DORIBAX™ is not formulated with any inactive ingredients.

DORIBAX™ (doripenem monohydrate) is a synthetic broad-spectrum carbapenem antibiotic structurally related to beta-lactam antibiotics. The chemical name for doripenem monohydrate is (4*R*,5*S*,6*S*)-3-[((3*S*,5*S*)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl)thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Its molecular weight is 438.52, and its chemical structure is:



12 CLINICAL PHARMACOLOGY

Doripenem is a carbapenem with *in vitro* antibacterial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria.

12.1 Mechanism of Action

Doripenem is an antibacterial drug. [see *Clinical Pharmacology (12.4)*]

12.2 Pharmacodynamics

Similar to other beta-lactam antimicrobial agents, the time that unbound plasma concentration of doripenem exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in animal models of infection. However, the pharmacokinetic/pharmacodynamic relationship for doripenem has not been evaluated in patients.

In a randomized, positive- and placebo-controlled crossover QT study, 60 healthy subjects were administered DORIBAX™ 500 mg IV every 8 hours x 4 doses and DORIBAX™ 1g IV every 8 hours x 4 doses, placebo, and a single oral dose of positive control. At both the 500 mg and 1g

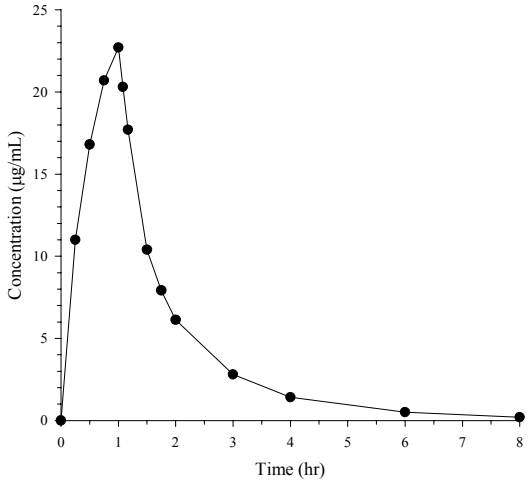
DORIBAX™ doses, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

12.3 Pharmacokinetics

- **Plasma Concentrations**

Mean plasma concentrations of doripenem following a single 1-hour intravenous infusion of a 500 mg dose of DORIBAX™ to 24 healthy subjects are shown below in Figure 1. The mean (SD) plasma C_{max} and $AUC_{0-\infty}$ values were 23.0 (6.6) µg/mL and 36.3 (8.8) µg•hr/mL, respectively.

Figure 1. Average Doripenem Plasma Concentrations Versus Time Following a Single 1-Hour Intravenous Infusion of DORIBAX™ 500 mg in Healthy Subjects (N=24)



The pharmacokinetics of doripenem (C_{max} and AUC) are linear over a dose range of 500 mg to 1g when intravenously infused over 1 hour. There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1g administered every 8 hours for 7 to 10 days in subjects with normal renal function.

- **Distribution**

The average binding of doripenem to plasma proteins is approximately 8.1% and is independent of plasma drug concentrations. The median (range) volume of distribution at steady state in healthy subjects is 16.8 L (8.09-55.5 L), similar to extracellular fluid volume (18.2 L).

Doripenem penetrates into several body fluids and tissues, including those at the site of infection for the approved indications. Doripenem concentrations in peritoneal and retroperitoneal fluid either match or exceed those required to inhibit most susceptible bacteria; however, the clinical

relevance of this finding has not been established. Concentrations achieved in selected tissues and fluids following administration of DORIBAX™ are shown in Table 5:

Table 5: Doripenem Concentrations in Selected Tissues and Fluids

Tissue or Fluid	Dose (mg)	Infusion Duration (h)	Number of Samples or Subjects[a]	Sampling Period[b]	Concentration Range (µg/mL or µg/g)	Tissue- or Fluid-To-Plasma Concentration Ratio (%) Mean (Range)
Retroperitoneal fluid	250	0.5	9[c]	30-90 min[d]	3.15-52.4	Range: 4.1(0.5-9.7) at 0.25 h to 990 (173-2609) at 2.5 h
	500	0.5	4[c]	90 min[d]	9.53-13.9	Range: 3.3 (0.0-8.1) at 0.25 h to 516 (311-842) at 6.5 h
Peritoneal exudate	250	0.5	5[c]	30-150 min[d]	2.36-5.17	Range: 19.7 (0.00-47.3) at 0.5 h to 160 (32.2-322) at 4.5 h
Gallbladder	250	0.5	10	20-215 min	BQL-1.87[e]	8.02 (0.00-44.4)
Bile	250	0.5	10	20-215 min	BQL-15.4[f]	117 (0.00-611)
Urine	500	1	110	0-4 hr	601 (BQL[f]-3360)[g]	---
	500	1	110	4-8 hr	49.7 (BQL[f]-635)[g]	---

[a] Unless stated otherwise, only one sample was collected per subject; [b] Time from start of infusion; [c] Serial samples were collected; maximum concentrations reported; [d] t_{max} range ; [e] BQL (Below Quantifiable Limits) in 6 subjects; [f] BQL in 1 subject; [g] Median (range)

- **Metabolism**

Metabolism of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M1) occurs primarily via dehydropeptidase-I. The mean (SD) plasma doripenem-M1-to-doripenem AUC ratio following single 500 mg and 1 g doses in healthy subjects is 18% (7.2%).

In pooled human liver microsomes, no *in vitro* metabolism of doripenem could be detected, indicating that doripenem is not a substrate for hepatic CYP450 enzymes.

- **Excretion**

Doripenem is primarily eliminated unchanged by the kidneys. The mean plasma terminal elimination half-life of doripenem in healthy non-elderly adults is approximately 1 hour and mean (SD) plasma clearance is 15.9 (5.3) L/hour. Mean (SD) renal clearance is 10.8 (3.5) L/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem with concomitant probenecid administration, suggests that doripenem undergoes both glomerular filtration and active tubular secretion. In healthy adults given a single 500 mg dose of DORIBAX™, a mean of 70% and 15% of the dose was recovered in urine as unchanged drug and the ring-opened metabolite, respectively, within 48 hours. Following the administration of a

single 500 mg dose of radiolabeled doripenem to healthy adults, less than 1% of the total radioactivity was recovered in feces after one week.

- **Special Populations**

Patients with Renal Impairment

Following a single 500 mg dose of DORIBAX™, the mean AUC of doripenem in subjects with mild (CrCl 50-79 mL/min), moderate (CrCl 31-50 mL/min), and severe renal impairment (CrCl ≤30 mL/min) was 1.6-, 2.8-, and 5.1-times that of age-matched healthy subjects with normal renal function (CrCl ≥80 mL/min), respectively. Dosage adjustment is necessary in patients with moderate and severe renal impairment. [see *Dosage and Administration (2.2)*]

A single 500 mg dose of DORIBAX™ was administered to subjects with end stage renal disease (ESRD) either one hour prior to or one hour after hemodialysis (HD). The mean doripenem AUC following the post-HD infusion was 7.8-times that of healthy subjects with normal renal function. The mean total recovery of doripenem and doripenem-M1 in the dialysate following a 4-hour HD session was 231 mg and 28 mg, respectively, or a total of 259 mg (52% of the dose). There is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

Patients with Hepatic Impairment

The pharmacokinetics of doripenem in patients with hepatic impairment have not been established. As doripenem does not appear to undergo hepatic metabolism, the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment.

Geriatric Patients

The impact of age on the pharmacokinetics of doripenem was evaluated in healthy male (n=6) and female (n=6) subjects ≥ 66 years of age. Mean doripenem $AUC_{0-\infty}$ was 49% higher in elderly adults relative to non-elderly adults. This difference in exposure was mainly attributed to age-related changes in creatinine clearance. No dosage adjustment is recommended for elderly patients with normal (for their age) renal function.

Gender

The effect of gender on the pharmacokinetics of doripenem was evaluated in healthy male (n=12) and female (n=12) subjects. Doripenem C_{max} and AUC were similar between males and females. No dose adjustment is recommended based on gender.

Race

The effect of race on doripenem pharmacokinetics was examined using a population pharmacokinetic analysis of data from phase 1 and 2 studies. Compared to Caucasians, mean doripenem clearance was 14% greater in Hispanic/Latino subjects whereas no difference in clearance was observed for African Americans. Doripenem clearance in Japanese studies is similar to what has been observed in Western populations. No dosage adjustment is recommended based on race.

- **Drug Interactions**

Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations. Probenecid increased doripenem AUC by 75% and prolonged the plasma elimination half-life by 53%. [see also *Drug Interactions (7.2)*]

In vitro studies in human liver microsomes and hepatocytes indicate that doripenem does not inhibit the major cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11). Therefore, DORIBAX™ is not expected to inhibit the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

DORIBAX™ is also not expected to have CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4/5, or UGT1A1 enzyme-inducing properties based on *in vitro* studies in cultured human hepatocytes.

12.4 Microbiology

- **Mechanism of Action**

Doripenem belongs to the carbapenem class of antimicrobials. Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death. In *E. coli* and *P. aeruginosa,* doripenem binds to PBP 2, which is involved in the maintenance of cell shape, as well as to PBPs 3 and 4.

- **Mechanism(s) of Resistance**

Bacterial resistance mechanisms that affect doripenem include drug inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired PBPs, decreased outer membrane permeability and active efflux. Doripenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria, with the exception of carbapenem hydrolyzing beta-lactamases. Although cross-resistance may occur, some isolates resistant to other carbapenems may be susceptible to doripenem.

- **Interaction with Other Antimicrobials**

In vitro synergy tests with doripenem show doripenem has little potential to antagonize or be antagonized by other antibiotics (e.g., levofloxacin, amikacin, trimethoprim-sulfamethoxazole, daptomycin, linezolid, and vancomycin).

Doripenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections. [see *Indications and Usage (1)*]

Facultative Gram-negative microorganisms
Acinetobacter baumannii
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Facultative Gram-positive microorganisms
Streptococcus constellatus
Streptococcus intermedius

Anaerobic microorganisms
Bacteroides caccae
Bacteroides fragilis
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Peptostreptococcus micros

At least 90 percent of the following microorganisms exhibit an *in vitro* minimal inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for doripenem of organisms of the same type shown in Table 6. The safety and efficacy of doripenem in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Facultative Gram-positive microorganisms
Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus agalactiae
Streptococcus pyogenes

Facultative Gram-negative microorganisms
Citrobacter freundii
Enterobacter cloacae
Enterobacter aerogenes
Klebsiella oxytoca
Morganella morganii
Serratia marcescens

- **Susceptibility Test Methods**

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of doripenem powder. The MIC values should be interpreted according to the criteria provided in Table 6.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 μg of doripenem to test the susceptibility of microorganisms to doripenem. Results should be interpreted according to the criteria in Table 6.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doripenem as MICs should be determined by standardized test methods [4]. The MIC values obtained should be interpreted according to the criteria in Table 6.

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Table 6. Susceptibility Test Result Interpretive Criteria for Doripenem

	Minimum Inhibitory Concentrations (μg/mL)	Disk Diffusion (zone diameters in mm)
Pathogen	Susceptible[a]	Susceptible
Enterobacteriaceae	≤0.5	≥23
Pseudomonas aeruginosa	≤2	≥24
Acinetobacter baumannii	≤1	≥17
Streptococcus anginosus group (*S. constellatus* and *S. intermedius)*	≤0.12	≥24
Anaerobes	≤1	n/a[b]

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC or disk diffusion results suggestive of "Nonsusceptible" should be subjected to additional testing.
[b] n/a = not applicable

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard doripenem powder should provide the MIC values provided in Table 7. For the diffusion techniques using a 10 μg doripenem disk, the criteria noted in Table 7 should be achieved.

Table 7. Acceptable Quality Control Ranges for Susceptibility Testing

QC Organism	Minimum Inhibitory Concentrations (μg/mL)	Disk Diffusion (zone diameters in mm)
Escherichia coli ATCC 25922	0.015-0.06	28-35
Pseudomonas aeruginosa ATCC 27853	0.12-0.5	29-35
Streptococcus pneumoniae ATCC 49619[a]	0.03-0.12	30-38
Bacteroides fragilis ATCC 25285	0.12-0.5	n/a
Bacteroides thetaiotaomicron ATCC 29741	0.12-1	n/a

[a] This organism may be used for validation of susceptibility test results when testing organisms of the *Streptococcus anginosus* group

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Because of the short duration of treatment and intermittent clinical use, long-term carcinogenicity studies have not been conducted with doripenem.

Doripenem did not show evidence of mutagenic activity in standard tests that included bacterial reverse mutation assay, chromosomal aberration assay with Chinese hamster lung fibroblast cells, and mouse bone marrow micronucleus assay.

Intravenous injection of doripenem had no adverse effects on general fertility of treated male and female rats or on postnatal development and reproductive performance of the offspring at doses as high as 1g/kg/day (based on AUC, greater than 1.5 times the exposure to humans at the dose of 500 mg q8h).

14 CLINICAL STUDIES

14.1 Complicated Intra-Abdominal Infections

A total of 946 adults with complicated intra-abdominal infections were randomized and received study medications in two identical multinational, multi-center, double-blind studies comparing DORIBAX™ (500 mg administered over 1 hour q8h) to meropenem (1 g administered over 3-5 minutes q8h). Both regimens allowed the option to switch to oral amoxicillin/clavulanate (875 mg/125 mg twice daily) after a minimum of 3 days of intravenous therapy for a total of 5-14 days of intravenous and oral treatment. Patients with complicated appendicitis, or other complicated intra-abdominal infections, including bowel perforation, cholecystitis, intra-abdominal or solid organ abscess and generalized peritonitis were enrolled.

DORIBAX™ was non-inferior to meropenem with regard to clinical cure rates in microbiologically evaluable (ME) patients, i.e., in patients with susceptible pathogens isolated at baseline and no major protocol deviations at test of cure (TOC) visit, 25-45 days after completing therapy. DORIBAX™ was also non-inferior to meropenem in microbiological modified intent-to-treat (mMITT) patients, i.e., patients with baseline pathogens isolated regardless of susceptibility. Clinical cure rates at TOC are displayed by patient populations in Table 8. Microbiological cure rates at TOC by pathogen in ME patients are presented in Table 9.

Table 8. Clinical Cure Rates in Two Phase 3 Studies of Adults with Complicated Intra-Abdominal Infections

Analysis Populations	DORIBAX™ [a] n/N (%)[c]	Meropenem[b] n/N (%)[c]	Treatment Difference (2-sided 95% CI[f])
Study 1:			
ME[d]	130/157 (82.8)	128/149 (85.9)	-3.1 (-11.3; 5.2)
mMITT[e]	143/194 (73.7)	149/191 (78.0)	-4.3 (-12.8; 4.3)
Study 2:			
ME[d]	128/158 (81.0)	119/145 (82.1)	-1.1 (-9.8; 7.8)
mMITT[e]	143/199 (71.9)	138/186 (74.2)	-2.3 (-11.2; 6.6)

[a] 500 mg administered over 1 hour q8h
[b] 1 g administered over 3 - 5 minutes q8h
[c] n = number of patients in the designated population who were cured; N = number of patients in the designated population
[d] ME = microbiologically evaluable patients
[e] mMITT = microbiological modified intent-to-treat patients
[f] CI = confidence interval

Table 9. Microbiological Cure Rates by Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Intra-abdominal Infections

Pathogen	DORIBAX™			Meropenem		
	N[a]	n[b]	%	N[a]	n[b]	%
Gram-positive, aerobic						
Streptococcus constellatus	10	9	90.0	7	5	71.4
Streptococcus intermedius	36	30	83.3	29	21	72.4
Gram-positive, anaerobic						
Peptostreptococcus micros	13	11	84.6	14	11	78.6
Gram-negative, aerobic						
Enterobacteriaceae	315	271	86.0	274	234	85.4
Escherichia coli	216	189	87.5	199	168	84.4
Klebsiella pneumoniae	32	25	78.1	20	19	95.0
Non-fermenters	51	44	86.3	39	28	71.8
Pseudomonas aeruginosa	40	34	85.0	32	24	75.0
Gram-negative, anaerobic						
Bacteroides fragilis group	173	152	87.9	181	152	84.0
Bacteroides caccae	25	23	92.0	19	18	94.7
Bacteroides fragilis	67	56	83.6	68	54	79.4
Bacteroides thetaiotaomicron	34	30	88.2	36	32	88.9
Bacteroides uniformis	22	19	86.4	18	15	83.3
Non-fragilis Bacteroides	14	13	92.9	13	9	69.2
Bacteroides vulgatus	11	11	100.0	8	6	75.0

[a] N = number of unique baseline isolates
[b] n = number of pathogens assessed as cured

14.2 Complicated Urinary Tract Infections, Including Pyelonephritis

A total of 1171 adults with complicated urinary tract infections, including pyelonephritis (49 percent of microbiologically evaluable patients) were randomized and received study medications in two multi-center, multinational studies. Complicated pyelonephritis, i.e., pyelonephritis associated with predisposing anatomical or functional abnormality, comprised

17% of patients with pyelonephritis. One study was double-blind and compared DORIBAX™ (500 mg administered over 1 hour q8h) to IV levofloxacin (250 mg q24h). The second study was a non-comparative study but of otherwise similar design. Both studies permitted the option of switching to oral levofloxacin (250 mg every q24h) after a minimum of 3 days of IV therapy for a total of 10 days of treatment. Patients with confirmed concurrent bacteremia were allowed to receive 500 mg of IV levofloxacin (either IV or oral as appropriate) for a total of 10 to 14 days of treatment.

DORIBAX™ was non-inferior to levofloxacin with regard to the microbiological eradication rates in microbiologically evaluable (ME) patients, i.e., patients with baseline uropathogens isolated, no major protocol deviations and urine cultures at test of cure (TOC) visit 5-11 days after completing therapy. DORIBAX™ was also non-inferior to levofloxacin in microbiological modified intent-to-treat (mMITT) patients, i.e., patients with pretreatment urine cultures. Overall microbiological eradication rates at TOC and the 95% CIs for the comparative study are displayed in Table 10. Microbiological eradication rates at TOC by pathogen in ME patients are presented in Table 11.

Table 10. Microbiological Eradication Rates from the Phase 3 Comparative Study of Adults with Complicated Urinary Tract Infections, Including Pyelonephritis

Analysis populations	DORIBAX™ [a] n/N (%)[c]	Levofloxacin[b] n/N (%)[c]	Treatment Difference (2-sided 95% CI[f])
ME [d]	230/280 (82.1)	221/265 (83.4)	-1.3 (-8.0, 5.5)
mMITT [e]	259/327 (79.2)	251/321 (78.2)	1.0 (-5.6, 7.6)

[a] 500 mg administered over 1 hour q8h
[b] 250 mg administered intravenously q24h
[c] n = number of patients in the designated population who were cured; N = number of patients in the designated population
[d] ME = microbiologically evaluable patients
[e] mMITT = microbiological modified intent-to-treat patients
[f] CI= confidence interval

Table 11. Microbiological Eradication Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Urinary Tract Infections, Including Pyelonephritis

Pathogen	DORIBAX™ [a]			Levofloxacin		
	N[b]	n[c]	%	N[b]	n[c]	%
Gram-negative, aerobic						
Escherichia coli	357	313	87.7	211	184	87.2
Klebsiella pneumoniae	33	26	78.8	8	5	62.5
Proteus mirabilis	30	22	73.3	15	13	86.7
Non-fermenters	38	27	71.1	8	5	62.5
Acinetobacter baumannii	10	8	80.0	1	0	0.0
Pseudomonas aeruginosa	27	19	70.4	7	5	71.4

[a] data from comparative and non-comparative studies
[b] N = number of unique baseline isolates
[c] n = number of pathogens with a favorable outcome (eradication)

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 7th ed. CLSI Document M7-A7. CLSI, 940 West Valley Rd., Suite 1400, Wayne, PA 19087, 2006.

2. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 9th ed. CLSI Document M2-A9. CLSI, Wayne, PA 19087, 2006.

3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 17th Informational Supplement. CLSI document M100-S17. CLSI, Wayne, PA 19087, 2007.

4. CLSI. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – 7th ed. CLSI document M11-A7. CLSI, Wayne, PA 19087, 2007.

16 HOW SUPPLIED/STORAGE AND HANDLING

- DORIBAX™ is supplied as single use type 1 clear glass vials containing 500 mg (on an anhydrous basis) of sterile doripenem powder. Vials are packaged individually (NDC: 0062-4010-01) in cartons containing 10 vials (NDC: 0062-4010-02).

- Storage of DORIBAX vials: DORIBAX™ should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59° to 86°F) [refer to USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report

any previous hypersensitivity reactions to DORIBAX™, other carbapenems, beta-lactams or other allergens.

- Patients should be counseled that anti-bacterial drugs including DORIBAX™ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DORIBAX™ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DORIBAX™ or other antibacterial drugs in the future.
- Keep out of the reach of children.

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Osaka 541-0045, Japan

Distributed by: Ortho-McNeil Pharmaceutical, Inc.
Raritan, NJ 08869

DORI-09 PROTOCOL INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

1. Males or females aged 18 years or older.

2. Subjects hospitalized for greater than or equal to 48 hours or those with prior hospital admission of at least 48 hours who were discharged within the last 7 days. Residents of chronic care facilities admitted with pneumonia were also eligible.

3. CPIS of 5 or more (for intubated subjects only).

4. Presence of a new or progressive infiltrate on chest radiograph.

5. At least one of the following:

    a. Fever, defined as an oral temperature greater than 38˚C (100.4˚F), a tympanic temperature greater than 38.5˚C (101.2˚F) or a rectal/core temperature greater than 39˚C (102.2˚F) OR hypothermia, defined as a rectal/core body temperature of less than 35˚C (95.2˚F);

    b. Elevated total peripheral WBC count (greater than or equal to 10,000/mm^3) or greater than 15% bands regardless of total peripheral WBC count; or leukopenia with total peripheral WBC less than 4,500/mm^3 (caused by the infection).

6. The subject also had respiratory failure requiring mechanical ventilation

    OR at least 2 of the following 5 signs and symptoms:

    a. Cough;

    b. New onset of purulent sputum production or other respiratory secretions (e.g., tracheal secretions), or a change in the character of sputum;

    c. Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony);

    d. Dyspnea, tachypnea, or respiratory rate ≥ 30 per minute, particularly if any or all of these were progressive in nature;

e. Hypoxemia with an arterial oxygen pressure (PaO_2) less than 60 mmHg while the subject was breathing room air, as determined by arterial blood gas (or equivalent oxygen saturation by pulse oximetry).

7. Infection was caused (based on earlier cultures) or was presumed to be caused by microorganisms susceptible to both piperacillin/tazobactam and meropenem (surrogate for doripenem). Subjects could have been enrolled pending culture results. The addition of vancomycin therapy was allowed for suspected or confirmed MRSA infection.

8. Females of childbearing potential must have had a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) prior to enrollment in the study (a urine pregnancy test may have been used at the time of screening, but the result must have been confirmed by the serum test) and, subsequently, for at least 1 month after study treatment, must have agreed to use adequate birth control measures. Hormonal contraceptives were not permitted as the sole method of birth control.

9. Subject initially required i.v. antibacterial therapy.

10. Subject was able to provide informed consent. If the subject was unable, the subject's legally acceptable representative was permitted to provide written consent as approved by institution-specific guidelines.

Exclusion Criteria

1. Known at study entry to have NP caused by pathogen(s) resistant to meropenem or piperacillin/tazobactam (other than MRSA that could have been treated with vancomycin).

2. APACHE II score less than 8 and greater than 25.

3. Mechanical ventilation for greater than or equal to 5 days.

4. Considered unlikely to survive the 5- to 7-week study period.

5. Presence of known bronchial obstruction or a history of postobstructive pneumonia. (Subjects with chronic obstructive pulmonary disease were allowed).

6. Presence of cavitary lung disease based on chest x-ray findings, primary lung cancer or another malignancy metastatic to the lungs, Adult Respiratory Distress Syndrome (ARDS) (e.g., diffuse radiographic infiltrates and ratio of PaO_2 to fraction of inspired oxygen [FiO_2] of less than 200, whatever the peak end expiratory pressure), cystic fibrosis, or known or suspected *Pneumocystis carinii* pneumonia, *Legionella* or active tuberculosis.

7. Any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure or septic shock.

8. Use of systemic antibiotic therapy for 24 or more hours within 72 hours prior to start of study drug therapy (unless the subject was a clinical failure for NP, or developed symptoms of NP and a new infiltrate while taking the prior antibiotic regimen).

9. The need for concomitant systemic antimicrobial agents (other than vancomycin or amikacin) in addition to study drug therapy.

10. Requirement for peritoneal dialysis, hemodialysis or hemofiltration.

11. Any of the following clinical laboratory abnormalities: alanine aminotransferase (ALT)/glutamic pyruvic transaminase (GPT), or aspartate aminotransferase (AST)/glutamic oxaloacetic transaminase (GOT) > 4 x the upper limit of normal (ULN); bilirubin > 2 x ULN; alkaline phosphatase > 4 x ULN. Subjects with values > 4 x ULN and < 5 x ULN were eligible if this value was historically stable.

12. Any of the following clinical laboratory abnormalities: hematocrit (Hct) < 20%; neutropenia with absolute neutrophil count < 500/mm^3; or platelet count < 40,000/mm^3.

13. Immunocompromising illness including known infection with human immunodeficiency virus (HIV), Acquired Immunodeficiency Syndrome (AIDS), hematological malignancy, and bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, and the administration of corticosteroids equivalent to or greater than 10 mg of prednisone per day administered for more than 14 days.

14. Women who were pregnant, nursing, or if of childbearing potential not using a medically accepted, effective method of birth control (e.g., condom, oral contraceptive, indwelling intrauterine device, or sexual abstinence).

15. History of moderate or severe hypersensitivity reactions to carbapenems, penicillins, other beta-lactam antibiotics, or β-lactamase inhibitors. Subjects with a history of mild skin rash documented not to have been related to β-lactam use were permitted to enroll.

16. Participation in any investigational drug or device study within 30 days prior to study entry.

17. Any condition or circumstance that, in the opinion of the investigator, would have compromised the safety of the subject or the quality of study data.

18. Subjects who had previously received more than 1 dose of piperacillin/tazobactam or a carbapenem for the current infection; or subjects who had previously received doripenem.

DORI-10 PROTOCOL INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

1. Males or females aged 18 years or older;
2. Had received mechanical ventilation for more than 24 hours or had been weaned from mechanical ventilation within 72 hours;
3. CPIS of 5 or more;
4. Presence of a new or progressive infiltrate on chest x-ray;
5. At least 1 of the following:
    a Fever, defined as an oral temperature greater than 38˚ C (100.4˚ F) or a rectal/core temperature greater than 39˚ C (102.2˚ F) or hypothermia, defined as a rectal/core body temperature less than 35˚ C (95.2˚ F);
    b Elevated total peripheral white blood cell (WBC) count (greater than or equal to 10,000/mm^3) or greater than 15% immature forms (bands) regardless of total peripheral WBC count; or leukopenia with total peripheral WBC less than 4,500/mm^3 (caused by the infection);
6. Infection was known or presumed at time of enrollment to be caused by microorganisms susceptible to both study drug therapies. The addition of adjunctive vancomycin (or alternative) therapy was allowed for suspected MRSA (e.g. gram-positive cocci seen on Gram stain in centers where 20% or more of *S. aureus* isolates were methicillin resistant) or in subjects from whom MRSA was previously isolated. Subjects could have been enrolled pending culture results;
7. Females of childbearing potential had to have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-HCG]) prior to enrollment in the study and, subsequently, for at least 1 month after study drug therapy had agreed to use adequate birth control measures. Hormonal contraceptives were not permitted as the sole method of birth control;
8. Subject required i.v. antibacterial therapy;
9. Subject was able to provide informed consent. If the subject was unable, the subject's legally acceptable representative was permitted to provide written consent as approved by institution-specific guidelines;

10. Respiratory specimen: All subjects who met the clinical and radiographic criteria for VAP had to provide an acceptable specimen of LRT secretions taken prior to inclusion in the study and randomization. Specimens obtained within 24 hours prior to start of study drug therapy were acceptable if no antibiotic therapy had been given since the time that specimen was obtained. However, subjects could have been enrolled in the study before the results of the LRT culture were known. The respiratory specimen was obtained by endotracheal aspiration or other method, e.g. by BAL or protected-specimen brush (bronchoscopically or non bronchoscopically). For extubated subjects, expectorated sputum was acceptable provided microscopic examination of a gram-stained smear showed more than 25 polymorphonuclear cells and less than 10 epithelial cells per high power field (100 times magnification).

Exclusion Criteria

1. Believed at study entry to have VAP caused solely by pathogen(s) resistant to either imipenem or meropenem (other than MRSA which could have been treated with vancomycin therapy);

2. APACHE II score less than 8 or more than 29;

3. Considered unlikely to survive to the LFU visit (28 to 35 days after the last dose of study drug therapy);

4. Subjects with an order of "no cardiopulmonary resuscitation" in case of cardiac arrest;

5. Presence of an infection or a complication that required non-study systemic antibacterial therapy (other than per protocol adjunctive therapy for *Pseudomonas* or MRSA coverage) or prolonged (i.e., more than 14 days) antimicrobial treatment;

6. Presence of cavitary lung disease based on radiographic findings, primary lung cancer or another malignancy metastatic to the lungs, cystic fibrosis, known or suspected *Pneumocystis carinii* pneumonia; empyema, structural lung disease (e.g. bronchiectasis) or Adult Respiratory Distress Syndrome (ARDS) (e.g., diffuse radiographic infiltrates and arterial oxygen pressure [PaO_2] to fraction of inspired oxygen [FiO_2] ratio less than 200). Subjects with chronic obstructive pulmonary disease (COPD) could have been enrolled;

7. Any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure or septic shock;

8. Use of systemic antibiotic therapy (with activity against the likely causative respiratory pathogens) for 24 or more hours within 48 hours prior to randomization (unless the subject had evidence of failure of the prior therapy for VAP, or had a new infiltrate that developed while the subject was taking the prior antibiotic regimen);

9. The need for Xigris® (drotrecogin alpha);

10. Requirement for peritoneal dialysis, hemodialysis or hemofiltration;

11. Any of the following clinical laboratory abnormalities: alanine aminotransferase (ALT) or aspartate aminotransferase AST >4 x upper limit of normal (ULN); bilirubin >2 x ULN; or alkaline phosphatase >4 x ULN. Subjects with values up to 5 x ULN were eligible if this value was historically stable;

12. Any of the following clinical laboratory abnormalities: hematocrit (Hct) < 20%, neutropenia with absolute neutrophil count < 500 cells/mm^3, or platelet count < 40,000/mm^3;

13. Immunocompromising illness including known infection with human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hematological malignancy, and organ transplantation (including bone marrow), or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, and the administration of corticosteroids equivalent to 10 mg or more of prednisone per day administered for more than 14 days;

14. Women who were pregnant, nursing, or if of childbearing potential, not using a medically accepted, effective method of birth control (e.g., condom, oral contraceptive, indwelling intrauterine device, or sexual abstinence);

15. History of moderate or severe hypersensitivity reactions to carbapenems, penicillins, other beta-lactam antibiotics, or β-lactamase inhibitors. Subjects with a history of mild skin rash documented not to have been related to β-lactam use were allowed to enroll;

16. Subjects who had previously received more than 1 dose of a carbapenem for the current infection; or subjects who had previously received doripenem;
17. Participation in any investigational drug or device study within 30 days prior to study entry;
18. Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of study data.

Attachment 3: List of Blinded Evaluation Committee Members

BLINDED EVALUATION COMMITTEE CONTACT LIST
(info from member's CVs)

Name	Function	Affiliation
Marin H. Kollef, M.D.	Chairman	1) Washington University School of Medicine Professor of Medicine Department of Internal Medicine; Division of Pulmonary and Critical Care Medicine; and Division of General Medical Sciences and Biostatistics 2) Director, Medical Intensive Care Unit, Barnes-Jewish Hospital 3) Director, Respiratory Care Services, Barnes-Jewish Hospital
Antonio Anzueto, M.D.	Committee Member	1) University of Texas Health Science Center at San Antonio 2) The South Texas Veterans Health Care System, Audie L. Murphy Memorial Veterans Hospital Division
Kenneth V. Leeper, Jr., MD	Committee Member	Emory University School of Medicine / Crawford Long Hospital Pulmonary/Critical Care Medicine
Lee Morrow, M.D.	Committee Member	Creighton University Medical Center Division of Pulmonary and Critical Care Medicine
Mike Neiderman, M.D.	Committee Member (No longer participating)	Winthrop-University Hospital Pulmonary & Critical Care Medicine
Patrick Petitpretz, M.D.	Committee Member	Centre Hospitalier deVersailles – André Mignot
Marcos I. Restrepo, M.D. MSc	Committee Member	1) Investigator, VERDICT, an HSR&D Center, South Texas Veterans Health Care System, Audie L Murphy Division 2) Assistant Professor, University of Texas Health Science Center at San Antonio, Department of Medicine, Division of Pulmonary/Critical Care Medic
William Rodriguez, M.D.	Committee Member	Chief, Pulmonary & Critical Care Medicine San Juan VAMC/UPR School of Medicine
Andrew Shorr, M.D.	Committee Member	1) Assoc. Director, Pulmonary & Critical Care Medicine, Washington Hospital Center (WHC) 2) Chief, Pulmonary Clinic, WHC
Richard Wunderink	Committee Member	Professor, Northwestern University Feinberg School of Medicine Pulmonary and Critical Care Medicine

Attachment 4.1.1: Study Completion/Withdrawal Information (Study JNJ38174942-DORI-09: Intent-to-Treat Analysis Set [Discontinued Within the First 2 Days of Study.])

Table TSUB03_9_1: Study Completion/Withdrawal Information

(STUDY JNJ38174942-DORI-09: Intent-to-Treat Analysis Set [Discontinued within the first 2 days of study.])

Completion Status Reason for Withdrawal	DORIPENEM (N=223) n (%)	PIPERACILLIN/ TAZOBACTAM (N=221) n (%)	Total (N=444) n (%)
Subject did not complete study per protocol	7 (3.1)	10 (4.5)	17 (3.8)
Missing	0	0	0
Adverse event	0	1 (0.5)	1 (0.2)
Treatment failure	1 (0.4)	0	1 (0.2)
Need for additional antibacterial therapy for an infection other than index infection	0	0	0
At request of subject, investigator, or sponsor	2 (0.9)	1 (0.5)	3 (0.7)
Death	4 (1.8)	6 (2.7)	10 (2.3)
Non-compliance	0	0	0
Lost to follow up	0	1 (0.5)	1 (0.2)
Randomized but study drug not given	0	0	0
Other	0	1 (0.5)	1 (0.2)

Treatment failures are considered study completers if they returned for the LFU visit. However, some sites ca
tegorized these as early
discontinuations as well.
tsub03_9_1_rdsub04.rtf generated by rdsub04.sas.

Attachment 4.1.2: Study Completion/Withdrawal Information (Study JNJ38174942-DORI-09: Intent-to-Treat Analysis Set [Discontinued on Days 3 or 4.])

Table TSUB03_9_2: Study Completion/Withdrawal Information
(STUDY JNJ38174942-DORI-09: Intent-to-Treat Analysis Set [Discontinued on Days 3 or 4.])

Completion Status Reason for Withdrawal	DORIPENEM (N=223) n (%)	PIPERACILLIN/ TAZOBACTAM (N=221) n (%)	Total (N=444) n (%)
Subject did not complete study per protocol	6 (2.7)	2 (0.9)	8 (1.8)
Missing	0	0	0
Adverse event	1 (0.4)	0	1 (0.2)
Treatment failure	1 (0.4)	0	1 (0.2)
Need for additional antibacterial therapy for an infection other than index infection	0	1 (0.5)	1 (0.2)
At request of subject, investigator, or sponsor	0	0	0
Death	3 (1.3)	1 (0.5)	4 (0.9)
Non-compliance	0	0	0
Lost to follow up	0	0	0
Randomized but study drug not given	0	0	0
Other	1 (0.4)	0	1 (0.2)

Treatment failures are considered study completers if they returned for the LFU visit. However, some sites categorized these as early
discontinuations as well.
tsub03_9_2_rdsub04.rtf generated by rdsub04.sas.

Attachment 4.2.1: Study Completion/Withdrawal Information (Study JNJ38174942-DORI-10: Intent-to-Treat Analysis Set [Discontinued Within the First 2 Days of Study.])

Table SC108A: Study Completion/Withdrawal Information for Subjects Discontinued on Days 1 or 2
(Study: JNJ38174942-ADCOM: Intent-to-Treat Analysis Set)

Study: Dori-10

Completion Status Reason for Withdrawal	DORIPENEM (N=262) n (%)	COMPARATOR (N=263) n (%)	Total (N=525) n (%)
Subject did not complete study per protocol	7 (2.7)	4 (1.5)	11 (2.1)
Missing	0	0	0
Adverse event	0	2 (0.8)	2 (0.4)
Treatment failure	0	0	0
Need for additional antibacterial therapy for an infection other than index infection	0	0	0
At request of subject, investigator, or sponsor	0	0	0
Death	7 (2.7)	2 (0.8)	9 (1.7)
Non-compliance	0	0	0
Lost to follow up	0	0	0
Randomized but study drug not given	0	0	0
Other	0	0	0

See footnotes on the first page of the table.
tsc108a_rsc108.rtf generated by rsc108.sas.

Attachment 4.2.2: Study Completion/Withdrawal Information (Study JNJ38174942-DORI-10: Intent-to-Treat Analysis Set [Discontinued on Days 3 or 4.])

Table SC108B: Study Completion/Withdrawal Information for Subjects Discontinued on Days 3 or 4
(Study: JNJ38174942-ADCOM: Intent-to-Treat Analysis Set)

Study: Dori-10

Completion Status Reason for Withdrawal	DORIPENEM (N=262) n (%)	COMPARATOR (N=263) n (%)	Total (N=525) n (%)
Subject did not complete study per protocol	7 (2.7)	3 (1.1)	10 (1.9)
Missing	0	0	0
Adverse event	0	0	0
Treatment failure	0	0	0
Need for additional antibacterial therapy for an infection other than index infection	1 (0.4)	0	1 (0.2)
At request of subject, investigator, or sponsor	1 (0.4)	0	1 (0.2)
Death	4 (1.5)	2 (0.8)	6 (1.1)
Non-compliance	0	0	0
Lost to follow up	0	0	0
Randomized but study drug not given	0	0	0
Other	1 (0.4)	1 (0.4)	2 (0.4)

See footnotes on the first page of the table.
tsc108b_rsc108.rtf generated by rsc108.sas.

APPENDIX DORI-10.2: CLINICAL PULMONARY INFECTION SCORE

CPIS Points	**0**	**1**	**2**
Tracheal secretions*	Few	Moderate	Large
Chest x-ray infiltrates†	None	Patchy or diffuse	Localized
Core/rectal temperature (ºC)	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ 36.0
Leukocytes (per mm^3) †	≥ 4,000 and ≤ 11,000	< 4.000 or > 11,000	
$Pa0_2/FiO_2$ (mmHg) ‡	> 240 or ARDS		≤ 240 and no evidence of ARDS

* If purulent: +1

† For post-baseline CPI scores where the radiograph or leukocytosis has improved: -1

‡ Use first blood gas measured in morning. Patients with ARDS and PF ratio < 200 are not eligible for enrollment.

Source: Luna et al. Crit Care Med 2003; 31:676-682.

Peninsula Pharmaceuticals, Inc, Modified Division of Microbiology and Infectious Diseases Adult Toxicity Table (PPImDMID)

The DMID Adult Toxicity Table was modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values are not collected systemically in this study. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed.

For toxicity grades based a multiple of the ULN, the normal range from the laboratory in which the sample was processed will be applied.

HEMATOLOGY*					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (gm/dL)	>10.5	9.5-10.5	8.0-9.4	6.5-7.9	<6.5
Absolute Neutrophil Count/mm^3	>1500	1000-1500	750-999	500-749	<500
Platelets/mm^3	≥100,000	75,000-99,999	50,000-74,999	20,000-49,999	<20,000
WBCs/mm^3	1000-11,000	11,000-13,000	13,000-15,000	15,000-30,000	>30,000 or <1,000
% Polymorphonuclear Leucocytes + Band Cells	≤80%	>80%-90%	>90–95%	>95%	----------

* Standard rounding rule (rounding up if ≥0.5, rounding down if <0.5) will be used for results between grades. For example: a calcium value of 7.76 mg/dL will be rounded up to 7.8 to be a Grade 1 event.

Attachment 6: Modified Toxicity Scale

CHEMISTRY*					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia (mEq/L)	>135	130-135	123-129	116-122	<116
Hyperatremia (mEq/L)	<146	146-150	151-157	158-165	>165
Hypokalemia (mEq/L)	>3.4	3.0-3.4	2.5-2.9	2.0-2.4	<2.0
Hyperkalemia (mEq/L)	<5.6	5.6-6.0	6.1-6.5	6.6-7.0	>7.0
Hypoglycemia (mg/dL)	≥65	55-64	40-54	30-39	<30
Hyperglycemia (mg/dL) (nonfasting and regardless of prior history of diabetes)**	<116	116-160	161-250	251-500	>500
Hypocalcemia (mg/dL) (corrected for albumin***)	>8.4	8.4-7.8	7.7-7.0	6.9-6.1	<6.1
Hypercalcemia (mg/dL) (corrected for albumin***)	≤10.5	10.6-11.5	11.6-12.5	12.6-13.5	>13.5
Hypomagnesemia (mEq/L)	>1.4	1.4- 1.2	1.1-0.9	0.8-0.6	<0.6
Hypophosphatemia (mg/dL)	≥2.5	2.0-2.4	1.5-1.9	1.0-1.4	<1.0
Hyperbilirubinemia (total bilirubin)	<1.1xULN	1.1-1.5xULN	>1.5-2.5xULN	>2.5-5xULN	>5xULN
BUN	<1.25xULN	1.25-2.5xULN	>2.5-5xULN	>5.0-10xULN	>10xULN
Hyperuricemia (uric acid) (mg/dL)	<7.5	7.5–10.0	10.1–12.0	12.1–15.0	>15.0
Creatinine	<1.1xULN	1.1-1.5xULN	>1.5-3.0xULN	>3.0-6xULN	>6xULN

* Standard rounding rule (rounding up if ≥0.5, rounding down if <0.5) will be used for results between grades. For example: a calcium value of 7.76 mg/dL will be rounded up to 7.8 to be a Grade 1 event.

** The DMID toxicity table reports hyperglycemia detected in nonfasting specimens obtained from patients with no prior diabetes.

*** 1 mg/dL of calcium will be added to the serum calcium level for every 1 g/dL of albumin when the serum albumin is below 4 g/dL. For example if a serum calcium level is 7.8 mg/dL and serum albumin is 3 gm/dL, then the serum calcium is corrected by adding 1 mg/dL to 8.8 mg/dL.

Attachment 6: Modified Toxicity Scale

ENZYMES					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	<1.25xULN	1.25-2.5xULN	>2.5-5xULN	>5.0-10xULN	>10xULN
ALT (SGPT)	<1.25xULN	1.25-2.5xULN	>2.5-5xULN	>5.0-10xULN	>10xULN
GGT	<1.25xULN	1.25-2.5xULN	>2.5-5xULN	>5.0-10xULN	>10xULN
Alkaline Phosphatase	<1.25xULN	1.25-2.5xULN	>2.5-5xULN	>5.0-10xULN	>10xULN

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10

Analysis Set: Clinical MITT

	Dori 500 mg 1-h inf (N=217)	Pip/Taz (N=212)	Dori 500 mg 4-h inf (N=249)	Imi (N=252)	Dori 500 mg (N=466)
Sex, n (%)					
N	217	212	249	252	466
MALE	154 (71.0)	144 (67.9)	195 (78.3)	192 (76.2)	349 (74.9)
FEMALE	63 (29.0)	68 (32.1)	54 (21.7)	60 (23.8)	117 (25.1)
Age					
N	217	212	249	252	466
Category, n (%)					
< 18	0	0	0	0	0
18 - 44	60 (27.6)	51 (24.1)	96 (38.6)	90 (35.7)	156 (33.5)
45 - 64	62 (28.6)	63 (29.7)	77 (30.9)	91 (36.1)	139 (29.8)
65 - 74	46 (21.2)	38 (17.9)	39 (15.7)	40 (15.9)	85 (18.2)
>= 75	49 (22.6)	60 (28.3)	37 (14.9)	31 (12.3)	86 (18.5)
Mean (SD)	57.4 (19.67)	59.5 (19.63)	51.4 (19.81)	51.7 (18.67)	54.2 (19.95)
Median	58.0	63.0	51.0	53.0	56.0
Range	(19;94)	(18;97)	(18;93)	(18;86)	(18;94)

APACHE II = Acute Physiology and Chronic Health Evaluation II; HAP = hospital-acquired pneumonia; N = number of subjects in the analysis set;
NP = nosocomial pneumonia; SCE = Summary of Clinical Efficacy; SD = standard deviation; VAP = ventilator-associated pneumonia.
1. Doripenem refers to the combined doripenem group, where the regimens of doripenem were 500 mg, 1-hour infusion, q8h in Dori-09, and 500 mg, 4-hour infusion, q8h in Dori-10;
2. Comparators refers to the combined comparator group, where the regimen of piperacillin/ tazobactam was 4.5 g, 30-minute infusion, q6h in Dori-09, and the regimen of imipenem was 2-3g daily divided in 3 to 4 doses in Dori-10;
3. Baseline value was defined as the last available value before the start of infusion of the first dose of study drug therapy;
4. Race was classified as other if subject was not any of the stated race categories or more than 1 race was checked on CRF;
5. North America comprised Canada and USA; South America consisted of Argentina, Brazil, and Chile; Europe contained Austria, Belarus, Belgium, Estonia, France, Georgia, Germany, Netherlands, Russia, Spain, and Ukraine; Other included Australia, S. Africa, Serbia and Montenegro;
6. Ventilation Status could be Yes or No for the subjects in Dori-09, but should be always Yes for the subjects in Dori-10;
7. Duration of mechanical ventilation was applicable to ventilated subjects only; Early-onset VAP and Late-onset VAP were defined as the duration of mechanical ventilation <5 days and ³5 days, respectively;
8. Clinical pulmonary infection score was applicable to ventilated subjects only;
9. Bacteremia was defined as 1 positive blood culture if associated with a pathogenic organism, or 2 positive blood cultures if associated with organisms generally non-considered pathogenic;
10. Creatinine clearance was calculated using the subject's actual body weight, the serum creatinine level measured at the local laboratory and the Cockroft-Gault formula.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	---- Comparator --- (N=464)
Sex, n (%)	
N	464
MALE	336 (72.4)
FEMALE	128 (27.6)
Age	
N	464
Category, n (%)	
< 18	0
18 - 44	141 (30.4)
45 - 64	154 (33.2)
65 - 74	78 (16.8)
>= 75	91 (19.6)
Mean (SD)	55.3 (19.48)
Median	57.0
Range	(18;97)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	Dori 500 mg 1-h inf (N=217)	Pip/Taz (N=212)	Dori 500 mg 4-h inf (N=249)	Imi (N=252)	Dori 500 mg (N=466)
Age Group 1 (years), n (%)					
N	217	212	249	252	466
<65	122 (56.2)	114 (53.8)	173 (69.5)	181 (71.8)	295 (63.3)
>=65	95 (43.8)	98 (46.2)	76 (30.5)	71 (28.2)	171 (36.7)
Age Group 2 (years), n (%)					
N	217	212	249	252	466
<75	168 (77.4)	152 (71.7)	212 (85.1)	221 (87.7)	380 (81.5)
>=75	49 (22.6)	60 (28.3)	37 (14.9)	31 (12.3)	86 (18.5)
Race, n (%)					
N	217	212	249	252	466
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.5)	0	1 (0.4)	0	2 (0.4)
ASIAN	2 (0.9)	0	0	4 (1.6)	2 (0.4)
BLACK OR AFRICAN AMERICAN	14 (6.5)	11 (5.2)	22 (8.8)	28 (11.1)	36 (7.7)
WHITE	161 (74.2)	165 (77.8)	217 (87.1)	209 (82.9)	378 (81.1)
NATIVE HAWAIIAN, OTHER PACIFIC ISLANDER	0	0	0	0	0
HISPANIC OR LATINO	35 (16.1)	35 (16.5)	9 (3.6)	10 (4.0)	44 (9.4)
OTHER	4 (1.8)	1 (0.5)	0	1 (0.4)	4 (0.9)
Region 1, n (%)					
N	217	212	249	252	466
NORTH AMERICA	43 (19.8)	44 (20.8)	116 (46.6)	117 (46.4)	159 (34.1)
SOUTH AMERICA	71 (32.7)	70 (33.0)	0	0	71 (15.2)
EUROPE	93 (42.9)	93 (43.9)	87 (34.9)	91 (36.1)	180 (38.6)
OTHER	10 (4.6)	5 (2.4)	46 (18.5)	44 (17.5)	56 (12.0)
Region 2, n (%)					
N	217	212	249	252	466
USA	36 (16.6)	35 (16.5)	116 (46.6)	115 (45.6)	152 (32.6)
NON-USA	181 (83.4)	177 (83.5)	133 (53.4)	137 (54.4)	314 (67.4)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	---- Comparator --- (N=464)
Age Group 1 (years), n (%)	
N	464
<65	295 (63.6)
>=65	169 (36.4)
Age Group 2 (years), n (%)	
N	464
<75	373 (80.4)
>=75	91 (19.6)
Race, n (%)	
N	464
AMERICAN INDIAN OR ALASKA NATIVE	0
ASIAN	4 (0.9)
BLACK OR AFRICAN AMERICAN	39 (8.4)
WHITE	374 (80.6)
NATIVE HAWAIIAN, OTHER PACIFIC ISLANDER	0
HISPANIC OR LATINO	45 (9.7)
OTHER	2 (0.4)
Region 1, n (%)	
N	464
NORTH AMERICA	161 (34.7)
SOUTH AMERICA	70 (15.1)
EUROPE	184 (39.7)
OTHER	49 (10.6)
Region 2, n (%)	
N	464
USA	150 (32.3)
NON-USA	314 (67.7)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	Dori 500 mg 1-h inf (N=217)	Pip/Taz (N=212)	Dori 500 mg 4-h inf (N=249)	Imi (N=252)	Dori 500 mg (N=466)
Height (cm)					
N	212	209	247	249	459
Mean (SD)	169.9 (7.95)	170.2 (9.28)	174.0 (10.66)	173.2 (11.51)	172.1 (9.70)
Median	170.0	170.0	175.0	175.0	172.7
Range	(152;191)	(148;191)	(102;196)	(70;201)	(102;196)
Weight (kg)					
N	217	212	249	252	466
Mean (SD)	75.7 (16.91)	74.6 (17.30)	83.2 (18.67)	82.7 (19.73)	79.7 (18.24)
Median	72.0	70.0	80.0	80.0	77.0
Range	(36;163)	(38;179)	(43;145)	(45;190)	(36;163)
Disease Type, n (%)					
N	217	212	249	252	466
NON-VAP	154 (71.0)	151 (71.2)	0	0	154 (33.0)
VAP	63 (29.0)	61 (28.8)	249 (100)	252 (100)	312 (67.0)
Duration of mechanical ventilation, n (%)					
N	63	61	249	252	312
EARLY ONSET VAP	63 (100)	61 (100)	98 (39.4)	97 (38.5)	161 (51.6)
LATE ONSET VAP	0	0	151 (60.6)	155 (61.5)	151 (48.4)
APACHE II Score 1, n (%)					
N	217	212	249	252	466
< 10	45 (20.7)	44 (20.8)	13 (5.2)	22 (8.7)	58 (12.4)
10-15	114 (52.5)	111 (52.4)	104 (41.8)	98 (38.9)	218 (46.8)
16-20	47 (21.7)	39 (18.4)	79 (31.7)	80 (31.7)	126 (27.0)
21-25	11 (5.1)	18 (8.5)	47 (18.9)	46 (18.3)	58 (12.4)
> 25	0	0	6 (2.4)	6 (2.4)	6 (1.3)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	---- Comparator --- (N=464)
Height (cm)	
N	458
Mean (SD)	171.8 (10.64)
Median	172.7
Range	(70;201)
Weight (kg)	
N	464
Mean (SD)	79.0 (19.08)
Median	76.0
Range	(38;190)
Disease Type, n (%)	
N	464
NON-VAP	151 (32.5)
VAP	313 (67.5)
Duration of mechanical ventilation, n (%)	
N	313
EARLY ONSET VAP	158 (50.5)
LATE ONSET VAP	155 (49.5)
APACHE II Score 1, n (%)	
N	464
< 10	66 (14.2)
10-15	209 (45.0)
16-20	119 (25.6)
21-25	64 (13.8)
> 25	6 (1.3)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	Dori 500 mg 1-h inf (N=217)	Pip/Taz (N=212)	Dori 500 mg 4-h inf (N=249)	Imi (N=252)	Dori 500 mg (N=466)
APACHE II Score 2, n (%)					
N	217	212	249	252	466
<=15	160 (73.7)	155 (73.1)	117 (47.0)	120 (47.6)	277 (59.4)
>15	57 (26.3)	57 (26.9)	132 (53.0)	132 (52.4)	189 (40.6)
Clinical Pulmonary Infection Score, n (%)					
N	62	61	248	252	310
< 5	0	0	1 (0.4)	0	1 (0.3)
5	14 (22.6)	14 (23.0)	38 (15.3)	51 (20.2)	52 (16.8)
6	17 (27.4)	11 (18.0)	47 (19.0)	52 (20.6)	64 (20.6)
7	5 (8.1)	15 (24.6)	62 (25.0)	64 (25.4)	67 (21.6)
> 7	26 (41.9)	21 (34.4)	100 (40.3)	85 (33.7)	126 (40.6)
Baseline Creatinine Clearance Group, n (%)					
N	217	212	249	252	466
MISSING	4 (1.8)	5 (2.4)	0	1 (0.4)	4 (0.9)
NORMAL (>=80)	118 (54.4)	121 (57.1)	200 (80.3)	189 (75.0)	318 (68.2)
MILD RENAL FAILURE (>50-<80)	52 (24.0)	51 (24.1)	19 (7.6)	36 (14.3)	71 (15.2)
MODERATE RENAL FAILURE (>30-<=50)	30 (13.8)	24 (11.3)	25 (10.0)	18 (7.1)	55 (11.8)
SEVERE RENAL FAILURE (<=30)	13 (6.0)	11 (5.2)	5 (2.0)	8 (3.2)	18 (3.9)
Bacteremia, n (%)					
N	217	212	249	252	466
NO	201 (92.6)	180 (84.9)	222 (89.2)	233 (92.5)	423 (90.8)
YES	16 (7.4)	32 (15.1)	27 (10.8)	19 (7.5)	43 (9.2)
Bacteremia with Same Pathogen Isolated from Both LRT and Blood, n (%)					
N	16	32	27	19	43
NO	12 (75.0)	17 (53.1)	16 (59.3)	9 (47.4)	28 (65.1)
YES	4 (25.0)	15 (46.9)	11 (40.7)	10 (52.6)	15 (34.9)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	---- Comparator --- (N=464)
APACHE II Score 2, n (%)	
N	464
<=15	275 (59.3)
>15	189 (40.7)
Clinical Pulmonary Infection Score, n (%)	
N	313
< 5	0
5	65 (20.8)
6	63 (20.1)
7	79 (25.2)
> 7	106 (33.9)
Baseline Creatinine Clearance Group, n (%)	
N	464
MISSING	6 (1.3)
NORMAL (>=80)	310 (66.8)
MILD RENAL FAILURE (>50-<80)	87 (18.8)
MODERATE RENAL FAILURE (>30-<=50)	42 (9.1)
SEVERE RENAL FAILURE (<=30)	19 (4.1)
Bacteremia, n (%)	
N	464
NO	413 (89.0)
YES	51 (11.0)
Bacteremia with Same Pathogen Isolated from Both LRT and Blood, n (%)	
N	51
NO	26 (51.0)
YES	25 (49.0)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	Dori 500 mg 1-h inf (N=217)	Pip/Taz (N=212)	Dori 500 mg 4-h inf (N=249)	Imi (N=252)	Dori 500 mg (N=466)
Any Adjunctive Therapy, n (%)					
N	217	212	249	252	466
NO	36 (16.6)	23 (10.8)	156 (62.7)	140 (55.6)	192 (41.2)
YES	181 (83.4)	189 (89.2)	93 (37.3)	112 (44.4)	274 (58.8)
Anti-MRSA Coverage, n (%)					
N	217	212	249	252	466
NO	161 (74.2)	154 (72.6)	176 (70.7)	171 (67.9)	337 (72.3)
YES	56 (25.8)	58 (27.4)	73 (29.3)	81 (32.1)	129 (27.7)
Anti-Pseudomonas Coverage, n (%)					
N	217	212	249	252	466
NO	51 (23.5)	30 (14.2)	195 (78.3)	187 (74.2)	246 (52.8)
YES	166 (76.5)	182 (85.8)	54 (21.7)	65 (25.8)	220 (47.2)

See footnotes on the first page of the table.

Attachment 7: Demographic and Baseline Characteristics (Studies JNJ38174942-DORI-09 and -10: cMITT Analysis Set)

10MAY2007 10:20
System Used: Arrow5.1(U)/rtdm

Study: JNJ38174942-ISENP01

Output TSUB005.2: Demographics and Baseline Characteristics - JNJ38174942-DORI-09 and JNJ38174942-DORI-10 (continued)

Analysis Set: Clinical MITT

	---- Comparator --- (N=464)
Any Adjunctive Therapy, n (%)	
N	464
NO	163 (35.1)
YES	301 (64.9)
Anti-MRSA Coverage, n (%)	
N	464
NO	325 (70.0)
YES	139 (30.0)
Anti-Pseudomonas Coverage, n (%)	
N	464
NO	217 (46.8)
YES	247 (53.2)

See footnotes on the first page of the table.

Attachment 8: Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set)

Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set)

Isolate Classification										
Isolate High-level Group		---------- Doripenem ----------			-----Piperacillin/tazobactam------			---------- Imipenem ----------		
Baseline LRT Isolate	NI	S	R	Total	S	R	Total	S	R	Total
Gram positive, aerobic	451	283(90%)	26(8%)	315	180(79%)	49(21%)	229	233(87%)	28(10%)	268
Enterococcus spp.	24	15(94%)	0	16	0	0	0	0	0	0
Enterococcus spp.	24	15(94%)	0	16	0	0	0	0	0	0
Enterococcus faecalis	22	15(94%)	0	16	0	0	0	0	0	0
Enterococcus species (not speciated)	2	0	0	0	0	0	0	0	0	0
Miscellaneous gram positive aerobes	13	3(100%)	0	3	0	0	0	0	0	0
Bacillus cereus	1	0	0	0	0	0	0	0	0	0
Bacillus species (not speciated)	1	0	0	0	0	0	0	0	0	0
Corynebacterium pseudodiphtheriticum	1	1(100%)	0	1	0	0	0	0	0	0
Corynebacterium species (not speciated)	5	0	0	0	0	0	0	0	0	0
Corynebacterium striatum	1	1(100%)	0	1	0	0	0	0	0	0
Diphteroid species (not speciated)	1	1(100%)	0	1	0	0	0	0	0	0
Micrococcus species (not speciated)	1	0	0	0	0	0	0	0	0	0
Rothia species (not speciated)	2	0	0	0	0	0	0	0	0	0
Staphylococcus spp.	293	199(87%)	26(11%)	230	180(79%)	49(21%)	229	200(87%)	28(12%)	230
Coagulase negative staphylococci	27	2(33%)	4(67%)	6	0	0	0	3(50%)	3(50%)	6
Staphylococcus epidermidis	8	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Staphylococcus haemolyticus	3	0	3(100%)	3	0	3(100%)	3	0	3(100%)	3
Staphylococcus saprophyticus	2	0	0	0	0	0	0	0	0	0
Staphylococcus simulans	1	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Staphylococcus species (cns)	11	0	1(100%)	1	0	1(100%)	1	1(100%)	0	1
Staphylococcus species (not speciated)	2	0	0	0	0	0	0	0	0	0

Key: NI=the number of baseline isolates; Total=the total number of isolates tested for which an interpretation of susceptibility results was available.
Note 1: The denominator for the percentage was Total
Note 2: For doripenem, interpretive criteria were Susceptible (S), Intermediate (I) or Resistant (R) if the MIC level was ≤ 4µg/mL, =8 µg/mL or ≥16 µg/mL, respectively; for the comparators, the interpretive criteria were according to the Clinical and Laboratory Standards Institute (CLSI) recommendations.
Note 3: Isolates included both pathogenic and non-pathogenic organisms.

(continued)

Attachment 8: Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set)

Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set) (continued)

Isolate Classification Isolate High-level Group / Baseline LRT Isolate	NI	Doripenem S	Doripenem R	Doripenem Total	Piperacillin/tazobactam S	Piperacillin/tazobactam R	Piperacillin/tazobactam Total	Imipenem S	Imipenem R	Imipenem Total
Gram positive, aerobic (Cont'd)	451	283(90%)	26(8%)	315	180(79%)	49(21%)	229	233(87%)	28(10%)	268
Staphylococcus spp. (Cont'd)	293	199(87%)	26(11%)	230	180(79%)	49(21%)	229	200(87%)	28(12%)	230
Coagulase negative staphylococci (continued)	27	2(33%)	4(67%)	6	0	0	0	3(50%)	3(50%)	6
Staphylococcus aureus	266	197(88%)	22(10%)	224	178(80%)	45(20%)	223	197(88%)	25(11%)	224
Staphylococcus aureus	266	197(88%)	22(10%)	224	178(80%)	45(20%)	223	197(88%)	25(11%)	224
MRSA	63	36(57%)	22(35%)	63	18(29%)	45(71%)	63	36(57%)	25(40%)	63
MSSA	161	161(100%)	0	161	160(100%)	0	160	161(100%)	0	161
Streptococcus pneumoniae	50	38(100%)	0	38	0	0	0	33(87%)	0	38
Streptococcus pneumoniae	50	38(100%)	0	38	0	0	0	33(87%)	0	38
Streptococcus pneumoniae	50	38(100%)	0	38	0	0	0	33(87%)	0	38
Streptococcus spp. other than *Streptococcus pneumoniae*	71	28(100%)	0	28	0	0	0	0	0	0
Streptococcus spp.	71	28(100%)	0	28	0	0	0	0	0	0
Streptococcus agalactiae	10	8(100%)	0	8	0	0	0	0	0	0
Streptococcus alpha hemolytic	12	0	0	0	0	0	0	0	0	0
Streptococcus anginosus	3	2(100%)	0	2	0	0	0	0	0	0
Streptococcus beta hemolytic	1	0	0	0	0	0	0	0	0	0
Streptococcus constellatus	1	1(100%)	0	1	0	0	0	0	0	0
Streptococcus group C	5	1(100%)	0	1	0	0	0	0	0	0
Streptococcus group F	4	3(100%)	0	3	0	0	0	0	0	0
Streptococcus group G	3	1(100%)	0	1	0	0	0	0	0	0
Streptococcus intermedius	1	1(100%)	0	1	0	0	0	0	0	0
Streptococcus mitis	1	1(100%)	0	1	0	0	0	0	0	0
Streptococcus oralis	6	5(100%)	0	5	0	0	0	0	0	0
Streptococcus pyogenes	1	1(100%)	0	1	0	0	0	0	0	0
Streptococcus salivarius	1	1(100%)	0	1	0	0	0	0	0	0
Streptococcus species (not speciated)	4	0	0	0	0	0	0	0	0	0
Streptococcus viridans group (not speciated)	18	3(100%)	0	3	0	0	0	0	0	0

(continued)

Attachment 8: Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set)

Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set) (continued)

Isolate Classification Isolate High-level Group / Baseline LRT Isolate	NI	Doripenem S	Doripenem R	Doripenem Total	Piperacillin/tazobactam S	Piperacillin/tazobactam R	Piperacillin/tazobactam Total	Imipenem S	Imipenem R	Imipenem Total
Gram negative, aerobic	704	547(94%)	27(5%)	581	482(84%)	75(13%)	572	523(91%)	40(7%)	572
Acinetobacter spp.	61	36(77%)	11(23%)	47	27(57%)	18(38%)	47	37(79%)	10(21%)	47
Acinetobacter spp.	61	36(77%)	11(23%)	47	27(57%)	18(38%)	47	37(79%)	10(21%)	47
Acinetobacter baumannii	54	34(76%)	11(24%)	45	25(56%)	18(40%)	45	35(78%)	10(22%)	45
Acinetobacter calcoaceticus	4	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Acinetobacter lwoffii	1	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Acinetobacter species (not speciated)	2	0	0	0	0	0	0	0	0	0
Burkholderia spp.	4	0	0	1	0	1(100%)	1	0	0	0
Burkholderia spp.	4	0	0	1	0	1(100%)	1	0	0	0
Burkholderia cepacia	4	0	0	1	0	1(100%)	1	0	1(100%)	1
Enterobacteriaceae	357	308(100%)	0	308	264(86%)	31(10%)	307	307(100%)	0	307
Citrobacter spp.	17	14(100%)	0	14	0	0	0	0	0	0
Citrobacter braakii	2	2(100%)	0	2	2(100%)	0	2	2(100%)	0	2
Citrobacter freundii	6	6(100%)	0	6	6(100%)	0	6	6(100%)	0	6
Citrobacter koseri	9	6(100%)	0	6	6(100%)	0	6	6(100%)	0	6
Enterobacter spp.	83	75(100%)	0	75	65(88%)	6(8%)	74	74(100%)	0	74
Enterobacter aerogenes	22	21(100%)	0	21	18(86%)	1(5%)	21	21(100%)	0	21
Enterobacter amnigenus	2	2(100%)	0	2	2(100%)	0	2	2(100%)	0	2
Enterobacter asburiae	1	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Enterobacter cloacae	58	51(100%)	0	51	44(88%)	5(10%)	50	50(100%)	0	50
Escherichia spp.	73	61(100%)	0	61	58(95%)	2(3%)	61	0	0	0
Escherichia coli	73	61(100%)	0	61	58(95%)	2(3%)	61	61(100%)	0	61
Hafnia spp.	3	3(100%)	0	3	0	0	0	0	0	0
Hafnia alvei	3	3(100%)	0	3	3(100%)	0	3	3(100%)	0	3

(continued)

Attachment 8: Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set)

Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set) (continued)

Isolate Classification		---------- Doripenem ----------			-----Piperacillin/tazobactam------			---------- Imipenem ----------		
Isolate High-level Group Baseline LRT Isolate	NI	S	R	Total	S	R	Total	S	R	Total
Gram negative, aerobic (Cont'd)	704	547(94%)	27(5%)	581	482(84%)	75(13%)	572	523(91%)	40(7%)	572
Klebsiella spp.	118	105(100%)	0	105	78(74%)	22(21%)	105	0	0	0
Klebsiella oxytoca	20	16(100%)	0	16	15(94%)	1(6%)	16	16(100%)	0	16
Klebsiella ozaenae	1	0	0	0	0	0	0	0	0	0
Klebsiella pneumoniae	96	89(100%)	0	89	63(71%)	21(24%)	89	89(100%)	0	89
Klebsiella species (not speciated)	1	0	0	0	0	0	0	0	0	0
Morganella spp.	8	7(100%)	0	7	0	0	0	0	0	0
Morganella morganii	8	7(100%)	0	7	7(100%)	0	7	7(100%)	0	7
Proteus spp.	24	19(100%)	0	19	0	0	0	0	0	0
Proteus mirabilis	21	18(100%)	0	18	18(100%)	0	18	18(100%)	0	18
Proteus species (not speciated)	1	0	0	0	0	0	0	0	0	0
Proteus vulgaris	2	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Providencia spp.	2	2(100%)	0	2	0	0	0	0	0	0
Providencia rettgeri	1	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Providencia stuartii	1	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Serratia spp.	29	22(100%)	0	22	18(82%)	1(5%)	22	0	0	0
Serratia liquefaciens	1	0	0	0	0	0	0	0	0	0
Serratia marcescens	28	22(100%)	0	22	18(82%)	1(5%)	22	22(100%)	0	22
Haemophilus spp.	132	94(100%)	0	94	0	0	0	0	0	0
Haemophilus spp.	132	94(100%)	0	94	0	0	0	0	0	0
Haemophilus influenzae	124	90(100%)	0	90	90(100%)	0	90	90(100%)	0	90
Haemophilus parainfluenzae	6	4(100%)	0	4	4(100%)	0	4	4(100%)	0	4
Haemophilus species (not speciated)	2	0	0	0	0	0	0	0	0	0
Miscellaneous gram negative aerobes	1	1(100%)	0	1	0	0	0	0	0	0
Vibrio vulnificus	1	1(100%)	0	1	0	0	0	0	0	0

(continued)

Attachment 8: Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set)

Overall In Vitro Baseline LRT Isolate Susceptibility Characteristics to Study Drug for Pooled Doripenem Data, Piperacillin/tazobactam, and Imipenem (Studies JNJ38174942-DORI-09 and DORI-10: mMITT Analysis Set) (continued)

Isolate Classification										
Isolate High-level Group		---------- Doripenem ----------			-----Piperacillin/tazobactam------			---------- Imipenem ----------		
Baseline LRT Isolate	NI	S	R	Total	S	R	Total	S	R	Total
Gram negative, aerobic (Cont'd)	704	547(94%)	27(5%)	581	482(84%)	75(13%)	572	523(91%)	40(7%)	572
Non-Enterobacteriaceae	135	107(92%)	4(3%)	116	90(83%)	19(17%)	109	85(78%)	15(14%)	109
Moraxella spp.	9	6(100%)	0	6	0	0	0	0	0	0
Moraxella catarrhalis	9	6(100%)	0	6	0	0	0	0	0	0
Neisseria spp.	11	0	0	0	0	0	0	0	0	0
Neisseria species (not speciated)	11	0	0	0	0	0	0	0	0	0
Pseudomonas spp.	114	100(92%)	4(4%)	109	90(83%)	19(17%)	109	85(78%)	15(14%)	109
Pseudomonas aeruginosa	110	96(91%)	4(4%)	105	86(82%)	19(18%)	105	81(77%)	15(14%)	105
Pseudomonas fluorescens	1	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Pseudomonas species (not speciated)	2	2(100%)	0	2	2(100%)	0	2	2(100%)	0	2
Pseudomonas stutzeri	1	1(100%)	0	1	1(100%)	0	1	1(100%)	0	1
Shewanella spp.	1	1(100%)	0	1	0	0	0	0	0	0
Shewanella algae	1	1(100%)	0	1	0	0	0	0	0	0
Stenotrophomonas maltophilia	14	1(7%)	12(86%)	14	7(50%)	6(43%)	14	0	14(100%)	14
Stenotrophomonas maltophilia	14	1(7%)	12(86%)	14	7(50%)	6(43%)	14	0	14(100%)	14
Stenotrophomonas maltophilia	14	1(7%)	12(86%)	14	7(50%)	6(43%)	14	0	14(100%)	14

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	**456 (29.3)**	**125 (47.7)**	**581 (32.0)**	**101 (27.2)**	**167 (35.6)**	**59 (26.7)**	**117 (44.5)**
Diarrhoea	127 (8.2)	36 (13.7)	163 (9.0)	38 (10.2)	52 (11.1)	24 (10.9)	45 (17.1)
Nausea	113 (7.3)	29 (11.1)	142 (7.8)	22 (5.9)	44 (9.4)	7 (3.2)	28 (10.6)
Vomiting	98 (6.3)	21 (8.0)	119 (6.5)	16 (4.3)	39 (8.3)	3 (1.4)	20 (7.6)
Constipation	73 (4.7)	29 (11.1)	102 (5.6)	18 (4.8)	18 (3.8)	5 (2.3)	31 (11.8)
Abdominal pain	44 (2.8)	8 (3.1)	52 (2.9)	13 (3.5)	20 (4.3)	4 (1.8)	4 (1.5)
Abdominal pain upper	40 (2.6)	2 (0.8)	42 (2.3)	13 (3.5)	7 (1.5)	1 (0.5)	1 (0.4)
Dyspepsia	33 (2.1)	3 (1.1)	36 (2.0)	2 (0.5)	12 (2.6)	1 (0.5)	0
Flatulence	33 (2.1)	1 (0.4)	34 (1.9)	6 (1.6)	11 (2.3)	1 (0.5)	2 (0.8)
Abdominal distension	20 (1.3)	8 (3.1)	28 (1.5)	1 (0.3)	11 (2.3)	4 (1.8)	7 (2.7)
Dysphagia	6 (0.4)	6 (2.3)	12 (0.7)	0	3 (0.6)	2 (0.9)	4 (1.5)
Ascites	8 (0.5)	2 (0.8)	10 (0.6)	0	4 (0.9)	2 (0.9)	3 (1.1)
Gastritis	6 (0.4)	3 (1.1)	9 (0.5)	1 (0.3)	2 (0.4)	1 (0.5)	2 (0.8)
Ileus	6 (0.4)	3 (1.1)	9 (0.5)	0	3 (0.6)	0	5 (1.9)
Impaired gastric emptying	5 (0.3)	3 (1.1)	8 (0.4)	0	2 (0.4)	0	5 (1.9)
Peritonitis	4 (0.3)	4 (1.5)	8 (0.4)	0	4 (0.9)	1 (0.5)	2 (0.8)
Faecal incontinence	4 (0.3)	3 (1.1)	7 (0.4)	0	0	0	2 (0.8)
Gastrointestinal haemorrhage	4 (0.3)	1 (0.4)	5 (0.3)	0	0	3 (1.4)	1 (0.4)
Abdominal pain lower	4 (0.3)	0	4 (0.2)	1 (0.3)	6 (1.3)	0	0
Small intestinal obstruction	2 (0.1)	1 (0.4)	3 (0.2)	0	3 (0.6)	1 (0.5)	3 (1.1)
Gastric disorder	0	1 (0.4)	1 (0.1)	0	0	0	3 (1.1)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

(continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections and infestations	**376 (24.2)**	**123 (46.9)**	**499 (27.5)**	**36 (9.7)**	**103 (22.0)**	**56 (25.3)**	**116 (44.1)**
Urinary tract infection	69 (4.4)	33 (12.6)	102 (5.6)	6 (1.6)	11 (2.3)	7 (3.2)	39 (14.8)
Asymptomatic bacteriuria	50 (3.2)	0	50 (2.8)	5 (1.3)	0	0	0
Pneumonia	41 (2.6)	9 (3.4)	50 (2.8)	1 (0.3)	7 (1.5)	6 (2.7)	8 (3.0)
Wound infection	20 (1.3)	8 (3.1)	28 (1.5)	0	9 (1.9)	0	9 (3.4)
Oral candidiasis	12 (0.8)	11 (4.2)	23 (1.3)	0	8 (1.7)	1 (0.5)	6 (2.3)
Fungal infection	10 (0.6)	9 (3.4)	19 (1.0)	1 (0.3)	4 (0.9)	3 (1.4)	3 (1.1)
Sepsis	11 (0.7)	8 (3.1)	19 (1.0)	0	7 (1.5)	5 (2.3)	7 (2.7)
Postoperative wound infection	15 (1.0)	1 (0.4)	16 (0.9)	1 (0.3)	12 (2.6)	1 (0.5)	0
Septic shock	14 (0.9)	2 (0.8)	16 (0.9)	0	5 (1.1)	7 (3.2)	7 (2.7)
Cellulitis	6 (0.4)	5 (1.9)	11 (0.6)	0	1 (0.2)	0	2 (0.8)
Urinary tract infection fungal	8 (0.5)	3 (1.1)	11 (0.6)	0	11 (2.3)	1 (0.5)	3 (1.1)
Clostridium difficile colitis	5 (0.3)	4 (1.5)	9 (0.5)	0	0	2 (0.9)	5 (1.9)
Candidiasis	7 (0.5)	1 (0.4)	8 (0.4)	0	3 (0.6)	4 (1.8)	5 (1.9)
Bacteraemia	3 (0.2)	4 (1.5)	7 (0.4)	1 (0.3)	1 (0.2)	2 (0.9)	6 (2.3)
Abdominal abscess	4 (0.3)	2 (0.8)	6 (0.3)	0	11 (2.3)	2 (0.9)	1 (0.4)
Fungal skin infection	3 (0.2)	3 (1.1)	6 (0.3)	0	2 (0.4)	1 (0.5)	3 (1.1)
Lung abscess	3 (0.2)	3 (1.1)	6 (0.3)	0	0	2 (0.9)	0
Staphylococcal infection	3 (0.2)	3 (1.1)	6 (0.3)	0	0	1 (0.5)	0
Bronchitis	1 (0.1)	4 (1.5)	5 (0.3)	1 (0.3)	0	2 (0.9)	2 (0.8)
Sinusitis	2 (0.1)	3 (1.1)	5 (0.3)	0	0	1 (0.5)	3 (1.1)
Tracheobronchitis	3 (0.2)	2 (0.8)	5 (0.3)	0	0	1 (0.5)	3 (1.1)
Vaginal candidiasis	5 (0.3)	0	5 (0.3)	4 (1.1)	0	0	0

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

(continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections and infestations (continued)							
Catheter related infection	0	4 (1.5)	4 (0.2)	0	2 (0.4)	0	4 (1.5)
Central line infection	1 (0.1)	3 (1.1)	4 (0.2)	0	0	1 (0.5)	3 (1.1)
Empyema	1 (0.1)	3 (1.1)	4 (0.2)	0	1 (0.2)	0	4 (1.5)
Oral fungal infection	1 (0.1)	3 (1.1)	4 (0.2)	0	0	1 (0.5)	1 (0.4)
Pseudomonas infection	1 (0.1)	3 (1.1)	4 (0.2)	0	0	0	0
Meningitis	1 (0.1)	2 (0.8)	3 (0.2)	0	0	2 (0.9)	3 (1.1)
Staphylococcal bacteraemia	0	3 (1.1)	3 (0.2)	0	0	0	3 (1.1)
Eye infection	0	0	0	0	0	0	3 (1.1)
Nervous system disorders	**258 (16.6)**	**49 (18.7)**	**307 (16.9)**	**67 (18.0)**	**47 (10.0)**	**35 (15.8)**	**44 (16.7)**
Headache	177 (11.4)	6 (2.3)	183 (10.1)	54 (14.5)	24 (5.1)	5 (2.3)	8 (3.0)
Dizziness	43 (2.8)	3 (1.1)	46 (2.5)	10 (2.7)	15 (3.2)	1 (0.5)	2 (0.8)
Intracranial pressure increased	3 (0.2)	5 (1.9)	8 (0.4)	0	0	1 (0.5)	1 (0.4)
Convulsion	3 (0.2)	2 (0.8)	5 (0.3)	0	0	5 (2.3)	7 (2.7)
Brain oedema	2 (0.1)	2 (0.8)	4 (0.2)	0	0	3 (1.4)	2 (0.8)
Hemiparesis	1 (0.1)	2 (0.8)	3 (0.2)	0	0	1 (0.5)	4 (1.5)
Subarachnoid haemorrhage	0	1 (0.4)	1 (0.1)	0	0	0	3 (1.1)
General disorders and administration site conditions	**237 (15.2)**	**45 (17.2)**	**282 (15.5)**	**49 (13.2)**	**95 (20.3)**	**31 (14.0)**	**51 (19.4)**
Pyrexia	81 (5.2)	9 (3.4)	90 (5.0)	6 (1.6)	44 (9.4)	8 (3.6)	9 (3.4)
Oedema peripheral	50 (3.2)	8 (3.1)	58 (3.2)	3 (0.8)	15 (3.2)	10 (4.5)	13 (4.9)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0. (continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem			Levofloxacin	Meropenem	Piperacillin/ Tazobactam	Imipenem
	----------500 mg ----------			250 mg	1 g (bolus inj)	4.5 g	500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions (continued)							
Asthenia	18 (1.2)	0	18 (1.0)	3 (0.8)	5 (1.1)	0	4 (1.5)
Generalised oedema	15 (1.0)	3 (1.1)	18 (1.0)	0	3 (0.6)	3 (1.4)	5 (1.9)
Chills	13 (0.8)	1 (0.4)	14 (0.8)	6 (1.6)	6 (1.3)	0	3 (1.1)
Non-cardiac chest pain	12 (0.8)	2 (0.8)	14 (0.8)	3 (0.8)	6 (1.3)	2 (0.9)	6 (2.3)
Oedema	10 (0.6)	2 (0.8)	12 (0.7)	1 (0.3)	0	3 (1.4)	5 (1.9)
Pain	11 (0.7)	1 (0.4)	12 (0.7)	1 (0.3)	8 (1.7)	3 (1.4)	2 (0.8)
Injection site pain	7 (0.5)	0	7 (0.4)	6 (1.6)	5 (1.1)	0	0
Multi-organ failure	3 (0.2)	4 (1.5)	7 (0.4)	0	2 (0.4)	2 (0.9)	6 (2.3)
Injection site reaction	6 (0.4)	0	6 (0.3)	4 (1.1)	3 (0.6)	1 (0.5)	0
Infusion site pain	5 (0.3)	0	5 (0.3)	6 (1.6)	0	0	0
Respiratory, thoracic and mediastinal disorders	**194 (12.5)**	**75 (28.6)**	**269 (14.8)**	**20 (5.4)**	**71 (15.1)**	**49 (22.2)**	**80 (30.4)**
Pleural effusion	30 (1.9)	13 (5.0)	43 (2.4)	1 (0.3)	13 (2.8)	6 (2.7)	23 (8.7)
Dyspnoea	31 (2.0)	4 (1.5)	35 (1.9)	6 (1.6)	17 (3.6)	3 (1.4)	3 (1.1)
Cough	23 (1.5)	3 (1.1)	26 (1.4)	4 (1.1)	15 (3.2)	0	3 (1.1)
Atelectasis	18 (1.2)	6 (2.3)	24 (1.3)	1 (0.3)	14 (3.0)	2 (0.9)	5 (1.9)
Respiratory failure	13 (0.8)	8 (3.1)	21 (1.2)	1 (0.3)	6 (1.3)	7 (3.2)	9 (3.4)
Tachypnoea	10 (0.6)	6 (2.3)	16 (0.9)	0	3 (0.6)	0	2 (0.8)
Bronchospasm	10 (0.6)	4 (1.5)	14 (0.8)	1 (0.3)	3 (0.6)	3 (1.4)	3 (1.1)
Pharyngolaryngeal pain	11 (0.7)	3 (1.1)	14 (0.8)	0	5 (1.1)	1 (0.5)	3 (1.1)
Pulmonary oedema	11 (0.7)	1 (0.4)	12 (0.7)	0	2 (0.4)	1 (0.5)	4 (1.5)
Pneumothorax	6 (0.4)	5 (1.9)	11 (0.6)	0	3 (0.6)	5 (2.3)	4 (1.5)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

(continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders (continued)							
Hypoxia	6 (0.4)	4 (1.5)	10 (0.6)	2 (0.5)	1 (0.2)	0	5 (1.9)
Wheezing	5 (0.3)	4 (1.5)	9 (0.5)	0	3 (0.6)	1 (0.5)	4 (1.5)
Pulmonary embolism	5 (0.3)	3 (1.1)	8 (0.4)	2 (0.5)	2 (0.4)	0	3 (1.1)
Acute respiratory distress syndrome	5 (0.3)	2 (0.8)	7 (0.4)	0	0	3 (1.4)	12 (4.6)
Hiccups	4 (0.3)	3 (1.1)	7 (0.4)	0	0	1 (0.5)	1 (0.4)
Respiratory distress	3 (0.2)	4 (1.5)	7 (0.4)	0	0	4 (1.8)	5 (1.9)
Increased bronchial secretion	1 (0.1)	4 (1.5)	5 (0.3)	0	2 (0.4)	0	2 (0.8)
Aspiration	1 (0.1)	3 (1.1)	4 (0.2)	0	0	2 (0.9)	2 (0.8)
Epistaxis	4 (0.3)	0	4 (0.2)	2 (0.5)	2 (0.4)	3 (1.4)	0
Hydropneumothorax	1 (0.1)	3 (1.1)	4 (0.2)	0	0	0	0
Pulmonary fibrosis	0	0	0	0	0	4 (1.8)	0
Vascular disorders	**200 (12.9)**	**49 (18.7)**	**249 (13.7)**	**28 (7.5)**	**66 (14.1)**	**36 (16.3)**	**48 (18.3)**
Phlebitis	101 (6.5)	1 (0.4)	102 (5.6)	15 (4.0)	26 (5.5)	5 (2.3)	2 (0.8)
Hypertension	41 (2.6)	12 (4.6)	53 (2.9)	5 (1.3)	22 (4.7)	14 (6.3)	14 (5.3)
Hypotension	38 (2.4)	15 (5.7)	53 (2.9)	3 (0.8)	5 (1.1)	7 (3.2)	19 (7.2)
Deep vein thrombosis	4 (0.3)	15 (5.7)	19 (1.0)	1 (0.3)	4 (0.9)	0	17 (6.5)
Haematoma	8 (0.5)	1 (0.4)	9 (0.5)	1 (0.3)	6 (1.3)	2 (0.9)	0
Pallor	0	0	0	0	5 (1.1)	1 (0.5)	1 (0.4)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

(continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Metabolism and nutrition disorders	**172 (11.1)**	**70 (26.7)**	**242 (13.3)**	**23 (6.2)**	**46 (9.8)**	**44 (19.9)**	**63 (24.0)**
Hypokalaemia	52 (3.3)	13 (5.0)	65 (3.6)	13 (3.5)	12 (2.6)	10 (4.5)	8 (3.0)
Hypoglycaemia	21 (1.4)	12 (4.6)	33 (1.8)	1 (0.3)	1 (0.2)	3 (1.4)	8 (3.0)
Hyperglycaemia	21 (1.4)	7 (2.7)	28 (1.5)	4 (1.1)	11 (2.3)	5 (2.3)	6 (2.3)
Hyponatraemia	9 (0.6)	12 (4.6)	21 (1.2)	0	1 (0.2)	9 (4.1)	11 (4.2)
Dehydration	19 (1.2)	0	19 (1.0)	1 (0.3)	4 (0.9)	1 (0.5)	1 (0.4)
Hypomagnesaemia	14 (0.9)	2 (0.8)	16 (0.9)	3 (0.8)	7 (1.5)	5 (2.3)	3 (1.1)
Hyperkalaemia	9 (0.6)	4 (1.5)	13 (0.7)	0	0	4 (1.8)	8 (3.0)
Malnutrition	8 (0.5)	5 (1.9)	13 (0.7)	0	4 (0.9)	3 (1.4)	3 (1.1)
Decreased appetite	8 (0.5)	3 (1.1)	11 (0.6)	1 (0.3)	1 (0.2)	0	1 (0.4)
Hypoalbuminaemia	8 (0.5)	2 (0.8)	10 (0.6)	0	4 (0.9)	4 (1.8)	1 (0.4)
Hypernatraemia	6 (0.4)	3 (1.1)	9 (0.5)	0	0	4 (1.8)	11 (4.2)
Hypocalcaemia	7 (0.5)	2 (0.8)	9 (0.5)	1 (0.3)	6 (1.3)	2 (0.9)	3 (1.1)
Hypophosphataemia	6 (0.4)	2 (0.8)	8 (0.4)	1 (0.3)	5 (1.1)	4 (1.8)	0
Metabolic acidosis	3 (0.2)	4 (1.5)	7 (0.4)	0	2 (0.4)	0	5 (1.9)
Fluid overload	2 (0.1)	3 (1.1)	5 (0.3)	0	1 (0.2)	2 (0.9)	5 (1.9)
Hypovolaemia	3 (0.2)	1 (0.4)	4 (0.2)	0	2 (0.4)	0	3 (1.1)
Hyperphosphataemia	0	1 (0.4)	1 (0.1)	0	1 (0.2)	1 (0.5)	3 (1.1)
Hypochloraemia	0	0	0	0	0	0	3 (1.1)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0. (continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Skin and subcutaneous tissue disorders	**153 (9.8)**	**78 (29.8)**	**231 (12.7)**	**11 (3.0)**	**42 (9.0)**	**33 (14.9)**	**58 (22.1)**
Decubitus ulcer	24 (1.5)	32 (12.2)	56 (3.1)	0	2 (0.4)	11 (5.0)	19 (7.2)
Rash	30 (1.9)	21 (8.0)	51 (2.8)	1 (0.3)	5 (1.1)	3 (1.4)	13 (4.9)
Pruritus	24 (1.5)	6 (2.3)	30 (1.7)	4 (1.1)	8 (1.7)	1 (0.5)	5 (1.9)
Hyperhidrosis	17 (1.1)	0	17 (0.9)	1 (0.3)	10 (2.1)	1 (0.5)	5 (1.9)
Skin ulcer	7 (0.5)	10 (3.8)	17 (0.9)	0	0	4 (1.8)	1 (0.4)
Erythema	11 (0.7)	4 (1.5)	15 (0.8)	1 (0.3)	7 (1.5)	3 (1.4)	7 (2.7)
Skin disorder	3 (0.2)	4 (1.5)	7 (0.4)	0	1 (0.2)	2 (0.9)	4 (1.5)
Blister	3 (0.2)	2 (0.8)	5 (0.3)	0	1 (0.2)	1 (0.5)	4 (1.5)
Dermatitis	3 (0.2)	0	3 (0.2)	1 (0.3)	2 (0.4)	4 (1.8)	1 (0.4)
Skin irritation	0	2 (0.8)	2 (0.1)	0	2 (0.4)	0	3 (1.1)
Intertrigo	1 (0.1)	0	1 (0.1)	0	0	0	3 (1.1)
Psychiatric disorders	**151 (9.7)**	**68 (26.0)**	**219 (12.1)**	**21 (5.6)**	**54 (11.5)**	**23 (10.4)**	**79 (30.0)**
Insomnia	70 (4.5)	26 (9.9)	96 (5.3)	11 (3.0)	22 (4.7)	6 (2.7)	30 (11.4)
Anxiety	32 (2.1)	13 (5.0)	45 (2.5)	8 (2.2)	16 (3.4)	1 (0.5)	6 (2.3)
Agitation	16 (1.0)	18 (6.9)	34 (1.9)	0	6 (1.3)	6 (2.7)	18 (6.8)
Depression	16 (1.0)	16 (6.1)	32 (1.8)	1 (0.3)	2 (0.4)	4 (1.8)	17 (6.5)
Confusional state	14 (0.9)	6 (2.3)	20 (1.1)	0	8 (1.7)	3 (1.4)	7 (2.7)
Delirium	3 (0.2)	4 (1.5)	7 (0.4)	0	0	1 (0.5)	5 (1.9)
Restlessness	1 (0.1)	2 (0.8)	3 (0.2)	0	1 (0.2)	1 (0.5)	4 (1.5)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

(continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigations	**166 (10.7)**	**50 (19.1)**	**216 (11.9)**	**24 (6.5)**	**60 (12.8)**	**37 (16.7)**	**49 (18.6)**
GGT increased	33 (2.1)	2 (0.8)	35 (1.9)	6 (1.6)	10 (2.1)	8 (3.6)	3 (1.1)
Hepatic enzyme increased	18 (1.2)	17 (6.5)	35 (1.9)	6 (1.6)	8 (1.7)	2 (0.9)	9 (3.4)
Blood ALP increased	22 (1.4)	2 (0.8)	24 (1.3)	6 (1.6)	4 (0.9)	3 (1.4)	2 (0.8)
Alanine aminotransferase increased	18 (1.2)	2 (0.8)	20 (1.1)	7 (1.9)	4 (0.9)	6 (2.7)	1 (0.4)
Blood CPK increased	16 (1.0)	2 (0.8)	18 (1.0)	3 (0.8)	6 (1.3)	9 (4.1)	0
Platelet count increased	14 (0.9)	3 (1.1)	17 (0.9)	1 (0.3)	3 (0.6)	0	2 (0.8)
AST increased	13 (0.8)	1 (0.4)	14 (0.8)	2 (0.5)	2 (0.4)	4 (1.8)	0
Blood creatinine increased	8 (0.5)	2 (0.8)	10 (0.6)	0	0	3 (1.4)	4 (1.5)
Blood LDH increased	8 (0.5)	2 (0.8)	10 (0.6)	3 (0.8)	4 (0.9)	4 (1.8)	3 (1.1)
Blood pressure increased	9 (0.6)	0	9 (0.5)	0	6 (1.3)	2 (0.9)	0
White blood cell count increased	5 (0.3)	2 (0.8)	7 (0.4)	1 (0.3)	6 (1.3)	1 (0.5)	2 (0.8)
Blood urea increased	1 (0.1)	2 (0.8)	3 (0.2)	0	2 (0.4)	1 (0.5)	3 (1.1)
Haemoglobin decreased	2 (0.1)	1 (0.4)	3 (0.2)	0	1 (0.2)	1 (0.5)	5 (1.9)
Liver function test abnormal	0	3 (1.1)	3 (0.2)	0	0	1 (0.5)	7 (2.7)
Bacteria stool identified	0	1 (0.4)	1 (0.1)	0	0	1 (0.5)	4 (1.5)
Renal and urinary disorders	**129 (8.3)**	**26 (9.9)**	**155 (8.5)**	**15 (4.0)**	**23 (4.9)**	**19 (8.6)**	**27 (10.3)**
Haematuria	22 (1.4)	0	22 (1.2)	2 (0.5)	2 (0.4)	4 (1.8)	5 (1.9)
Urinary retention	16 (1.0)	4 (1.5)	20 (1.1)	1 (0.3)	3 (0.6)	2 (0.9)	4 (1.5)
Dysuria	13 (0.8)	4 (1.5)	17 (0.9)	4 (1.1)	4 (0.9)	0	2 (0.8)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0. GGT=gamma-glutamyltransferase; ALP=alkaline phosphatase; CPK=creatine phosphokinase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase

(continued)

Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem 500 mg			Levofloxacin 250 mg	Meropenem 1 g (bolus inj)	Piperacillin/ Tazobactam 4.5 g	Imipenem 500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Renal and urinary disorders (continued)							
Renal failure acute	11 (0.7)	6 (2.3)	17 (0.9)	0	0	3 (1.4)	4 (1.5)
Urinary incontinence	6 (0.4)	3 (1.1)	9 (0.5)	0	2 (0.4)	1 (0.5)	5 (1.9)
Renal impairment	6 (0.4)	0	6 (0.3)	0	0	3 (1.4)	3 (1.1)
Leukocyturia	3 (0.2)	1 (0.4)	4 (0.2)	1 (0.3)	0	3 (1.4)	0
Proteinuria	1 (0.1)	1 (0.4)	2 (0.1)	0	1 (0.2)	4 (1.8)	0
Blood and lymphatic system disorders	**126 (8.1)**	**27 (10.3)**	**153 (8.4)**	**9 (2.4)**	**43 (9.2)**	**41 (18.6)**	**36 (13.7)**
Anaemia	85 (5.5)	14 (5.3)	99 (5.4)	4 (1.1)	26 (5.5)	24 (10.9)	12 (4.6)
Thrombocythaemia	16 (1.0)	4 (1.5)	20 (1.1)	0	6 (1.3)	11 (5.0)	17 (6.5)
Leukocytosis	14 (0.9)	5 (1.9)	19 (1.0)	2 (0.5)	7 (1.5)	3 (1.4)	5 (1.9)
Eosinophilia	8 (0.5)	0	8 (0.4)	0	2 (0.4)	4 (1.8)	0
Thrombocytopenia	4 (0.3)	2 (0.8)	6 (0.3)	0	2 (0.4)	2 (0.9)	6 (2.3)
Injury, poisoning and procedural complications	**109 (7.0)**	**42 (16.0)**	**151 (8.3)**	**9 (2.4)**	**51 (10.9)**	**11 (5.0)**	**38 (14.4)**
Procedural pain	20 (1.3)	0	20 (1.1)	3 (0.8)	10 (2.1)	0	1 (0.4)
Wound complication	16 (1.0)	0	16 (0.9)	2 (0.5)	9 (1.9)	0	2 (0.8)
Wound dehiscence	10 (0.6)	4 (1.5)	14 (0.8)	0	6 (1.3)	3 (1.4)	3 (1.1)
Skin laceration	5 (0.3)	4 (1.5)	9 (0.5)	0	0	1 (0.5)	2 (0.8)
Excoriation	2 (0.1)	4 (1.5)	6 (0.3)	0	1 (0.2)	0	6 (2.3)
Fall	1 (0.1)	5 (1.9)	6 (0.3)	0	1 (0.2)	0	4 (1.5)
Incision site haemorrhage	1 (0.1)	4 (1.5)	5 (0.3)	0	1 (0.2)	0	1 (0.4)
Post procedural complication	3 (0.2)	2 (0.8)	5 (0.3)	0	5 (1.1)	0	7 (2.7)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

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Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem			Levofloxacin	Meropenem	Piperacillin/ Tazobactam	Imipenem
	----------500 mg ----------			250 mg	1 g (bolus inj)	4.5 g	500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Injury, poisoning and procedural complications (continued)							
Tracheostomy malfunction	1 (0.1)	3 (1.1)	4 (0.2)	0	0	0	0
Wound	1 (0.1)	3 (1.1)	4 (0.2)	0	1 (0.2)	0	1 (0.4)
Haemodilution	0	3 (1.1)	3 (0.2)	0	0	1 (0.5)	0
Haemothorax	0	0	0	0	0	1 (0.5)	4 (1.5)
Cardiac disorders	**80 (5.1)**	**39 (14.9)**	**119 (6.5)**	**7 (1.9)**	**30 (6.4)**	**32 (14.5)**	**51 (19.4)**
Tachycardia	16 (1.0)	7 (2.7)	23 (1.3)	1 (0.3)	6 (1.3)	5 (2.3)	0
Atrial fibrillation	11 (0.7)	4 (1.5)	15 (0.8)	1 (0.3)	6 (1.3)	8 (3.6)	5 (1.9)
Bradycardia	6 (0.4)	7 (2.7)	13 (0.7)	0	3 (0.6)	3 (1.4)	8 (3.0)
Angina pectoris	5 (0.3)	2 (0.8)	7 (0.4)	2 (0.5)	1 (0.2)	2 (0.9)	5 (1.9)
Arrhythmia	4 (0.3)	3 (1.1)	7 (0.4)	1 (0.3)	0	2 (0.9)	2 (0.8)
Ventricular tachycardia	3 (0.2)	4 (1.5)	7 (0.4)	0	2 (0.4)	0	4 (1.5)
Cardiac arrest	2 (0.1)	4 (1.5)	6 (0.3)	0	0	2 (0.9)	6 (2.3)
Cardio-respiratory arrest	0	4 (1.5)	4 (0.2)	0	0	2 (0.9)	5 (1.9)
Atrial flutter	2 (0.1)	1 (0.4)	3 (0.2)	0	0	0	4 (1.5)
Myocardial infarction	2 (0.1)	1 (0.4)	3 (0.2)	0	5 (1.1)	1 (0.5)	1 (0.4)
Ventricular extrasystoles	2 (0.1)	0	2 (0.1)	0	3 (0.6)	3 (1.4)	1 (0.4)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

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Attachment 9.1: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set)

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Pooled Phase 2 and 3 Studies JNJ38174942-DORI-03, 05, 06, 07, 08, 09, 10: Safety Analysis Set) (continued)

	Doripenem			Levofloxacin	Meropenem	Piperacillin/ Tazobactam	Imipenem
	----------500 mg ----------			250 mg	1 g (bolus inj)	4.5 g	500 mg/1 g
Body System or Organ Class	(N=1555)	(N=262)	(N=1817)	(N=372)	(N=469)	(N=221)	(N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Musculoskeletal and connective tissue disorders	**98 (6.3)**	**19 (7.3)**	**117 (6.4)**	**34 (9.1)**	**24 (5.1)**	**8 (3.6)**	**23 (8.7)**
Back pain	32 (2.1)	5 (1.9)	37 (2.0)	17 (4.6)	6 (1.3)	0	2 (0.8)
Pain in extremity	19 (1.2)	1 (0.4)	20 (1.1)	5 (1.3)	4 (0.9)	1 (0.5)	3 (1.1)
Muscle atrophy	4 (0.3)	3 (1.1)	7 (0.4)	0	0	2 (0.9)	2 (0.8)
Muscle spasms	2 (0.1)	2 (0.8)	4 (0.2)	0	3 (0.6)	1 (0.5)	3 (1.1)
Muscular weakness	1 (0.1)	0	2 (0.1)	0	1 (0.2)	0	3 (1.1)
Reproductive system and breast disorders	**59 (3.8)**	**7 (2.7)**	**66 (3.6)**	**7 (1.9)**	**12 (2.6)**	**4 (1.8)**	**7 (2.7)**
Scrotal oedema	3 (0.2)	3 (1.1)	6 (0.3)	0	1 (0.2)	1 (0.5)	2 (0.8)
Hepatobiliary disorders	**35 (2.3)**	**6 (2.3)**	**41 (2.3)**	**2 (0.5)**	**8 (1.7)**	**9 (4.1)**	**4 (1.5)**
Cholestasis	0	3 (1.1)	3 (0.2)	0	0	0	0
Eye disorders	**24 (1.5)**	**10 (3.8)**	**34 (1.9)**	**7 (1.9)**	**0**	**8 (3.6)**	**9 (3.4)**
Conjunctivitis	6 (0.4)	2 (0.8)	8 (0.4)	1 (0.3)	0	1 (0.5)	3 (1.1)
Endocrine disorders	**9 (0.6)**	**6 (2.3)**	**15 (0.8)**	**0**	**0**	**3 (1.4)**	**3 (1.1)**
Diabetes insipidus	1 (0.1)	3 (1.1)	4 (0.2)	0	0	1 (0.5)	2 (0.8)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent AEs were defined as those AEs with onset dates on or after the date of the start of the infusion of first dose of the study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

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Atttachment 9.2: Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

	DORI-09		DORI-10		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Infections and infestations	**65 (29.1)**	**56 (25.3)**	**123 (46.9)**	**116 (44.1)**	**188 (38.8)**
Urinary tract infection	11 (4.9)	7 (3.2)	33 (12.6)	39 (14.8)	44 (9.1)
Pneumonia	17 (7.6)	6 (2.7)	9 (3.4)	8 (3.0)	26 (5.4)
Oral candidiasis	2 (0.9)	1 (0.5)	11 (4.2)	6 (2.3)	13 (2.7)
Sepsis	5 (2.2)	5 (2.3)	8 (3.1)	7 (2.7)	13 (2.7)
Septic shock	10 (4.5)	7 (3.2)	2 (0.8)	7 (2.7)	12 (2.5)
Fungal infection	2 (0.9)	3 (1.4)	9 (3.4)	3 (1.1)	11 (2.3)
Wound infection	1 (0.4)	0	8 (3.1)	9 (3.4)	9 (1.9)
Cellulitis	1 (0.4)	0	5 (1.9)	2 (0.8)	6 (1.2)
Lung abscess	3 (1.3)	2 (0.9)	3 (1.1)	0	6 (1.2)
Bacteremia	1 (0.4)	2 (0.9)	4 (1.5)	6 (2.3)	5 (1.0)
Clostridium difficile colitis	1 (0.4)	2 (0.9)	4 (1.5)	5 (1.9)	5 (1.0)
Bronchitis	0	2 (0.9)	4 (1.5)	2 (0.8)	4 (0.8)
Catheter related infection	0	0	4 (1.5)	4 (1.5)	4 (0.8)
Central line infection	1 (0.4)	1 (0.5)	3 (1.1)	3 (1.1)	4 (0.8)
Empyema	1 (0.4)	0	3 (1.1)	4 (1.5)	4 (0.8)
Fungal skin infection	1 (0.4)	1 (0.5)	3 (1.1)	3 (1.1)	4 (0.8)
Urinary tract infection fungal	1 (0.4)	1 (0.5)	3 (1.1)	3 (1.1)	4 (0.8)
Meningitis	1 (0.4)	2 (0.9)	2 (0.8)	3 (1.1)	3 (0.6)
Oral fungal infection	0	1 (0.5)	3 (1.1)	1 (0.4)	3 (0.6)
Pseudomonas infection	0	0	3 (1.1)	0	3 (0.6)
Sinusitis	0	1 (0.5)	3 (1.1)	3 (1.1)	3 (0.6)
Staphylococcal bacteremia	0	0	3 (1.1)	3 (1.1)	3 (0.6)
Staphylococcal infection	0	1 (0.5)	3 (1.1)	0	3 (0.6)
Tracheobronchitis	1 (0.4)	1 (0.5)	2 (0.8)	3 (1.1)	3 (0.6)
Candidiasis	1 (0.4)	4 (1.8)	1 (0.4)	5 (1.9)	2 (0.4)
Eye infection	0	0	0	3 (1.1)	0
Gastrointestinal disorders	**51 (22.9)**	**59 (26.7)**	**125 (47.7)**	**117 (44.5)**	**176 (36.3)**
Diarrhea	22 (9.9)	24 (10.9)	36 (13.7)	45 (17.1)	58 (12.0)
Constipation	9 (4.0)	5 (2.3)	29 (11.1)	31 (11.8)	38 (7.8)
Vomiting	13 (5.8)	3 (1.4)	21 (8.0)	20 (7.6)	34 (7.0)
Nausea	4 (1.8)	7 (3.2)	29 (11.1)	28 (10.6)	33 (6.8)
Abdominal distension	2 (0.9)	4 (1.8)	8 (3.1)	7 (2.7)	10 (2.1)
Abdominal pain	2 (0.9)	4 (1.8)	8 (3.1)	4 (1.5)	10 (2.1)
Dysphagia	2 (0.9)	2 (0.9)	6 (2.3)	4 (1.5)	8 (1.6)
Fecal incontinence	2 (0.9)	0	3 (1.1)	2 (0.8)	5 (1.0)
Impaired gastric emptying	2 (0.9)	0	3 (1.1)	5 (1.9)	5 (1.0)
Dyspepsia	1 (0.4)	1 (0.5)	3 (1.1)	0	4 (0.8)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. Treatment-emergent adverse events were defined as those adverse events with onset dates on or after the date of the start of the infusion of first dose of study drug therapy and within 30 days after administration of the last dose of study drug therapy. AE terms were coded using MedDRA version 9.0.

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Atttachment 9.2: Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

Adverse events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set) (continued)

	--------- DORI-09 ----------		--------- DORI-10 ----------		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Gastrointestinal disorders (Cont'd)	**51 (22.9)**	**59 (26.7)**	**125 (47.7)**	**117 (44.5)**	**176 (36.3)**
Gastritis	1 (0.4)	1 (0.5)	3 (1.1)	2 (0.8)	4 (0.8)
Peritonitis	0	1 (0.5)	4 (1.5)	2 (0.8)	4 (0.8)
Ascites	1 (0.4)	2 (0.9)	2 (0.8)	3 (1.1)	3 (0.6)
Gastrointestinal hemorrhage	2 (0.9)	3 (1.4)	1 (0.4)	1 (0.4)	3 (0.6)
Ileus	0	0	3 (1.1)	5 (1.9)	3 (0.6)
Small intestinal obstruction	1 (0.4)	1 (0.5)	1 (0.4)	3 (1.1)	2 (0.4)
Gastric disorder	0	0	1 (0.4)	3 (1.1)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**56 (25.1)**	**49 (22.2)**	**75 (28.6)**	**80 (30.4)**	**131 (27.0)**
Pleural effusion	8 (3.6)	6 (2.7)	13 (5.0)	23 (8.7)	21 (4.3)
Respiratory failure	8 (3.6)	7 (3.2)	8 (3.1)	9 (3.4)	16 (3.3)
Atelectasis	5 (2.2)	2 (0.9)	6 (2.3)	5 (1.9)	11 (2.3)
Pneumothorax	3 (1.3)	5 (2.3)	5 (1.9)	4 (1.5)	8 (1.6)
Respiratory distress	3 (1.3)	4 (1.8)	4 (1.5)	5 (1.9)	7 (1.4)
Tachyon	1 (0.4)	0	6 (2.3)	2 (0.8)	7 (1.4)
Bronchospasm	2 (0.9)	3 (1.4)	4 (1.5)	3 (1.1)	6 (1.2)
Pulmonary edema	5 (2.2)	1 (0.5)	1 (0.4)	4 (1.5)	6 (1.2)
Hypoxia	1 (0.4)	0	4 (1.5)	5 (1.9)	5 (1.0)
Pleurisy	4 (1.8)	0	1 (0.4)	1 (0.4)	5 (1.0)
Aspiration	1 (0.4)	2 (0.9)	3 (1.1)	2 (0.8)	4 (0.8)
Cough	1 (0.4)	0	3 (1.1)	3 (1.1)	4 (0.8)
Dyspnea	0	3 (1.4)	4 (1.5)	3 (1.1)	4 (0.8)
Hydropneumothorax	1 (0.4)	0	3 (1.1)	0	4 (0.8)
Increased bronchial secretion	0	0	4 (1.5)	2 (0.8)	4 (0.8)
Pulmonary embolism	1 (0.4)	0	3 (1.1)	3 (1.1)	4 (0.8)
Wheezing	0	1 (0.5)	4 (1.5)	4 (1.5)	4 (0.8)
Acute respiratory distress syndrome	1 (0.4)	3 (1.4)	2 (0.8)	12 (4.6)	3 (0.6)
Acute respiratory failure	3 (1.3)	0	0	1 (0.4)	3 (0.6)
Hiccups	0	1 (0.5)	3 (1.1)	1 (0.4)	3 (0.6)
Pharyngolaryngeal pain	0	1 (0.5)	3 (1.1)	3 (1.1)	3 (0.6)
Pneumonia aspiration	3 (1.3)	2 (0.9)	0	2 (0.8)	3 (0.6)
Epistaxis	2 (0.9)	3 (1.4)	0	0	2 (0.4)
Pulmonary fibrosis	0	4 (1.8)	0	0	0

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Atttachment 9.2: Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

Adverse events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Studies JNJ38174942-DORI-09and DORI-10: Safety Analysis Set) (continued)

	---------- DORI-09 ----------		--------- DORI-10 ----------		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Skin and subcutaneous tissue disorders	**37 (16.6)**	**33 (14.9)**	**78 (29.8)**	**58 (22.1)**	**115 (23.7)**
Decubitus ulcer	10 (4.5)	11 (5.0)	32 (12.2)	19 (7.2)	42 (8.7)
Rash	5 (2.2)	3 (1.4)	21 (8.0)	13 (4.9)	26 (5.4)
Skin ulcer	5 (2.2)	4 (1.8)	10 (3.8)	1 (0.4)	15 (3.1)
Erythema	6 (2.7)	3 (1.4)	4 (1.5)	7 (2.7)	10 (2.1)
Pruritus	1 (0.4)	1 (0.5)	6 (2.3)	5 (1.9)	7 (1.4)
Skin disorder	2 (0.9)	2 (0.9)	4 (1.5)	4 (1.5)	6 (1.2)
Blister	1 (0.4)	1 (0.5)	2 (0.8)	4 (1.5)	3 (0.6)
Dry skin	3 (1.3)	1 (0.5)	0	0	3 (0.6)
Scar	3 (1.3)	2 (0.9)	0	0	3 (0.6)
Skin irritation	0	0	2 (0.8)	3 (1.1)	2 (0.4)
Dermatitis	1 (0.4)	4 (1.8)	0	1 (0.4)	1 (0.2)
Hyperhidrosis	1 (0.4)	1 (0.5)	0	5 (1.9)	1 (0.2)
Intertrigo	0	0	0	3 (1.1)	0
Metabolism and nutrition disorders	**36 (16.1)**	**44 (19.9)**	**70 (26.7)**	**63 (24.0)**	**106 (21.9)**
Hypokalemia	11 (4.9)	10 (4.5)	13 (5.0)	8 (3.0)	24 (4.9)
Hypoglycemia	7 (3.1)	3 (1.4)	12 (4.6)	8 (3.0)	19 (3.9)
Hyponatremia	2 (0.9)	9 (4.1)	12 (4.6)	11 (4.2)	14 (2.9)
Hyperglycemia	6 (2.7)	5 (2.3)	7 (2.7)	6 (2.3)	13 (2.7)
Hyperkalemia	4 (1.8)	4 (1.8)	4 (1.5)	8 (3.0)	8 (1.6)
Hypernatremia	5 (2.2)	4 (1.8)	3 (1.1)	11 (4.2)	8 (1.6)
Hypocalcemia	3 (1.3)	2 (0.9)	2 (0.8)	3 (1.1)	5 (1.0)
Hypomagnesemia	3 (1.3)	5 (2.3)	2 (0.8)	3 (1.1)	5 (1.0)
Malnutrition	0	3 (1.4)	5 (1.9)	3 (1.1)	5 (1.0)
Metabolic acidosis	1 (0.4)	0	4 (1.5)	5 (1.9)	5 (1.0)
Hypoalbuminemia	2 (0.9)	4 (1.8)	2 (0.8)	1 (0.4)	4 (0.8)
Hypophosphatemia	2 (0.9)	4 (1.8)	2 (0.8)	0	4 (0.8)
Decreased appetite	0	0	3 (1.1)	1 (0.4)	3 (0.6)
Fluid overload	0	2 (0.9)	3 (1.1)	5 (1.9)	3 (0.6)
Hyperphosphatemia	0	1 (0.5)	1 (0.4)	3 (1.1)	1 (0.2)
Hypovolemia	0	0	1 (0.4)	3 (1.1)	1 (0.2)
Hypochloremia	0	0	0	3 (1.1)	0

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Atttachment 9.2: Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

Adverse events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Studies JNJ38174942-DORI-09and DORI-10: Safety Analysis Set) (continued)

	DORI-09		DORI-10		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperaciilin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Psychiatric disorders	**27 (12.1)**	**23 (10.4)**	**68 (26.0)**	**79 (30.0)**	**95 (19.6)**
Insomnia	5 (2.2)	6 (2.7)	26 (9.9)	30 (11.4)	31 (6.4)
Agitation	9 (4.0)	6 (2.7)	18 (6.9)	18 (6.8)	27 (5.6)
Depression	3 (1.3)	4 (1.8)	16 (6.1)	17 (6.5)	19 (3.9)
Anxiety	4 (1.8)	1 (0.5)	13 (5.0)	6 (2.3)	17 (3.5)
Confusional state	5 (2.2)	3 (1.4)	6 (2.3)	7 (2.7)	11 (2.3)
Delirium	0	1 (0.5)	4 (1.5)	5 (1.9)	4 (0.8)
Restlessness	0	1 (0.5)	2 (0.8)	4 (1.5)	2 (0.4)
Investigations	**35 (15.7)**	**37 (16.7)**	**50 (19.1)**	**49 (18.6)**	**85 (17.5)**
Hepatic enzyme increased	5 (2.2)	2 (0.9)	17 (6.5)	9 (3.4)	22 (4.5)
GGT increased	10 (4.5)	8 (3.6)	2 (0.8)	3 (1.1)	12 (2.5)
Alanine aminotransferase increased	6 (2.7)	6 (2.7)	2 (0.8)	1 (0.4)	8 (1.6)
Blood alkaline phosphatase increased	6 (2.7)	3 (1.4)	2 (0.8)	2 (0.8)	8 (1.6)
Blood LDH increased	4 (1.8)	4 (1.8)	2 (0.8)	3 (1.1)	6 (1.2)
Aspartate aminotransferase increased	4 (1.8)	4 (1.8)	1 (0.4)	0	5 (1.0)
Blood CPK increased	3 (1.3)	9 (4.1)	2 (0.8)	0	5 (1.0)
Platelet count increased	2 (0.9)	0	3 (1.1)	2 (0.8)	5 (1.0)
Blood creatinine increased	2 (0.9)	3 (1.4)	2 (0.8)	4 (1.5)	4 (0.8)
Eosinophil count increased	3 (1.3)	1 (0.5)	1 (0.4)	0	4 (0.8)
Liver function test abnormal	0	1 (0.5)	3 (1.1)	7 (2.7)	3 (0.6)
Blood urea increased	0	1 (0.5)	2 (0.8)	3 (1.1)	2 (0.4)
Hemoglobin decreased	1 (0.4)	1 (0.5)	1 (0.4)	5 (1.9)	2 (0.4)
Bacteria stool identified	0	1 (0.5)	1 (0.4)	4 (1.5)	1 (0.2)
Vascular disorders	**33 (14.8)**	**36 (16.3)**	**49 (18.7)**	**48 (18.3)**	**82 (16.9)**
Hypotension	12 (5.4)	7 (3.2)	15 (5.7)	19 (7.2)	27 (5.6)
Hypertension	11 (4.9)	14 (6.3)	12 (4.6)	14 (5.3)	23 (4.7)
Deep vein thrombosis	1 (0.4)	0	15 (5.7)	17 (6.5)	16 (3.3)
Phlebitis	9 (4.0)	5 (2.3)	1 (0.4)	2 (0.8)	10 (2.1)
Nervous system disorders	**31 (13.9)**	**35 (15.8)**	**49 (18.7)**	**44 (16.7)**	**80 (16.5)**
Headache	8 (3.6)	5 (2.3)	6 (2.3)	8 (3.0)	14 (2.9)
Intracranial pressure increased	3 (1.3)	1 (0.5)	5 (1.9)	1 (0.4)	8 (1.6)
Convulsion	3 (1.3)	5 (2.3)	2 (0.8)	7 (2.7)	5 (1.0)
Hydrocephalus	3 (1.3)	1 (0.5)	2 (0.8)	2 (0.8)	5 (1.0)
Brain edema	2 (0.9)	3 (1.4)	2 (0.8)	2 (0.8)	4 (0.8)

Key: GGT=Gamma-glutamyltransferase; LDH= lactate dehydrogenase; CPK=creatine phosphokinase

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Atttachment 9.2: Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

Adverse events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Studies JNJ38174942-DORI-09and DORI-10: Safety Analysis Set) (continued)

	DORI-09		DORI-10		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Nervous system disorders	**31 (13.9)**	**35 (15.8)**	**49 (18.7)**	**44 (16.7)**	**80 (16.5)**
Cerebrovascular accident	3 (1.3)	2 (0.9)	0	0	3 (0.6)
Dizziness	0	1 (0.5)	3 (1.1)	2 (0.8)	3 (0.6)
Hemiparesis	0	1 (0.5)	2 (0.8)	4 (1.5)	2 (0.4)
Subarachnoid hemorrhage	0	0	1 (0.4)	3 (1.1)	1 (0.2)
General disorders and administration site conditions	**33 (14.8)**	**31 (14.0)**	**45 (17.2)**	**51 (19.4)**	**78 (16.1)**
Pyrexia	8 (3.6)	8 (3.6)	9 (3.4)	9 (3.4)	17 (3.5)
Edema peripheral	6 (2.7)	10 (4.5)	8 (3.1)	13 (4.9)	14 (2.9)
Generalized edema	6 (2.7)	3 (1.4)	3 (1.1)	5 (1.9)	9 (1.9)
Edema	6 (2.7)	3 (1.4)	2 (0.8)	5 (1.9)	8 (1.6)
Non-cardiac chest pain	4 (1.8)	2 (0.9)	2 (0.8)	6 (2.3)	6 (1.2)
Multi-organ failure	1 (0.4)	2 (0.9)	4 (1.5)	6(2.3)	5 (1.0)
Asthenia	3 (1.3)	0	0	4 (1.5)	3 (0.6)
Pain	1 (0.4)	3 (1.4)	1 (0.4)	2 (0.8)	2 (0.4)
Chills	0	0	1 (0.4)	3 (1.1)	1 (0.2)
Cardiac disorders	**29 (13.0)**	**32 (14.5)**	**39 (14.9)**	**51 (19.4)**	**68 (14.0)**
Bradycardia	4 (1.8)	3 (1.4)	7 (2.7)	8 (3.0)	11 (2.3)
Tachycardia	4 (1.8)	5 (2.3)	7 (2.7)	0	11 (2.3)
Arrhythmia	3 (1.3)	2 (0.9)	3 (1.1)	2 (0.8)	6 (1.2)
Atrial fibrillation	2 (0.9)	8 (3.6)	4 (1.5)	5 (1.9)	6 (1.2)
Ventricular tachycardia	2 (0.9)	0	4 (1.5)	4 (1.5)	6 (1.2)
Cardiac failure congestive	3 (1.3)	2 (0.9)	2 (0.8)	0	5 (1.0)
Cardiac arrest	0	2 (0.9)	4 (1.5)	6 (2.3)	4 (0.8)
Cardiac failure	4 (1.8)	1 (0.5)	0	2 (0.8)	4 (0.8)
Cardio-respiratory arrest	0	2 (0.9)	4 (1.5)	5 (1.9)	4 (0.8)
Cardiogenic shock	3 (1.3)	1 (0.5)	1 (0.4)	0	4 (0.8)
Angina pectoris	1 (0.4)	2 (0.9)	2 (0.8)	5 (1.9)	3 (0.6)
Atrial flutter	0	0	1 (0.4)	4 (1.5)	1 (0.2)
Ventricular extrasystoles	1 (0.4)	3 (1.4)	0	1 (0.4)	1 (0.2)

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Atttachment 9.2: Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

Adverse events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Studies JNJ38174942-DORI-09and DORI-10: Safety Analysis Set) (continued)

	---------- DORI-09 ---------		--------- DORI-10 ---------		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Blood and lymphatic system disorders	**38 (17.0)**	**41 (18.6)**	**27 (10.3)**	**36 (13.7)**	**65 (13.4)**
Anaemia	15 (6.7)	24 (10.9)	14 (5.3)	12 (4.6)	29 (6.0)
Thrombocythaemia	12 (5.4)	11 (5.0)	4 (1.5)	17 (6.5)	16 (3.3)
Leukocytosis	5 (2.2)	3 (1.4)	5 (1.9)	5 (1.9)	10 (2.1)
Eosinophilia	5 (2.2)	4 (1.8)	0	0	5 (1.0)
Thrombocytopenia	3 (1.3)	2 (0.9)	2 (0.8)	6 (2.3)	5 (1.0)
Monocytopenia	3 (1.3)	0	0	0	3 (0.6)
Injury, poisoning and procedural complications	**15 (6.7)**	**11 (5.0)**	**42 (16.0)**	**38 (14.4)**	**57 (11.8)**
Fall	1 (0.4)	0	5 (1.9)	4 (1.5)	6 (1.2)
Skin laceration	2 (0.9)	1 (0.5)	4 (1.5)	2 (0.8)	6 (1.2)
Excoriation	1 (0.4)	0	4 (1.5)	6 (2.3)	5 (1.0)
Wound dehiscence	1 (0.4)	3 (1.4)	4 (1.5)	3 (1.1)	5 (1.0)
Incision site haemorrhage	0	0	4 (1.5)	1 (0.4)	4 (0.8)
Tracheostomy malfunction	1 (0.4)	0	3 (1.1)	0	4 (0.8)
Haemodilution	0	1 (0.5)	3 (1.1)	0	3 (0.6)
Wound	0	0	3 (1.1)	1 (0.4)	3 (0.6)
Post procedural complication	0	0	2 (0.8)	7 (2.7)	2 (0.4)
Haemothorax	0	1 (0.5)	0	4 (1.5)	0
Renal and urinary disorders	**20 (9.0)**	**19 (8.6)**	**26 (9.9)**	**27 (10.3)**	**46 (9.5)**
Renal failure acute	3 (1.3)	3 (1.4)	6 (2.3)	4 (1.5)	9 (1.9)
Renal failure	5 (2.2)	2 (0.9)	2 (0.8)	2 (0.8)	7 (1.4)
Urinary retention	2 (0.9)	2 (0.9)	4 (1.5)	4 (1.5)	6 (1.2)
Urinary incontinence	2 (0.9)	1 (0.5)	3 (1.1)	5 (1.9)	5 (1.0)
Dysuria	0	0	4 (1.5)	2 (0.8)	4 (0.8)
Oliguria	3 (1.3)	1 (0.5)	1 (0.4)	2 (0.8)	4 (0.8)
Haematuria	3 (1.3)	4 (1.8)	0	5 (1.9)	3 (0.6)
Proteinuria	1 (0.4)	4 (1.8)	1 (0.4)	0	2 (0.4)
Renal impairment	2 (0.9)	3 (1.4)	0	3 (1.1)	2 (0.4)
Leukocyturia	0	3 (1.4)	1 (0.4)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	**11 (4.9)**	**8 (3.6)**	**19 (7.3)**	**23 (8.7)**	**30 (6.2)**
Back pain	3 (1.3)	0	5 (1.9)	2 (0.8)	8 (1.6)
Muscle atrophy	2 (0.9)	2 (0.9)	3 (1.1)	2 (0.8)	5 (1.0)
Pain in extremity	2 (0.9)	1 (0.5)	1 (0.4)	3 (1.1)	3 (0.6)
Muscle spasms	0	1 (0.5)	2 (0.8)	3 (1.1)	2 (0.4)
Muscular weakness	0	0	0	3 (1.1)	0
Eye disorders	**4 (1.8)**	**8 (3.6)**	**10 (3.8)**	**9 (3.4)**	**14 (2.9)**
Conjunctivitis	1 (0.4)	1 (0.5)	2 (0.8)	3 (1.1)	3 (0.6)

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Atttachment 9.2: Adverse Events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group (Studies JNJ38174942-DORI-09 and DORI-10: Safety Analysis Set)

Adverse events by System Organ Class and Preferred Term in >1% of Subjects in any Treatment Group
(Studies JNJ38174942-DORI-09and DORI-10: Safety Analysis Set) (continued)

	---------- DORI-09 ---------		--------- DORI-10 ---------		
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Piperacillin/ Tazobactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)	Total Doripenem (N=485) n (%)
Hepatobiliary disorders	**8 (3.6)**	**9 (4.1)**	**6 (2.3)**	**4 (1.5)**	**14 (2.9)**
Cholestasis	0	0	3 (1.1)	0	3 (0.6)
Endocrine disorders	**5 (2.2)**	**3 (1.4)**	**6 (2.3)**	**3 (1.1)**	**11 (2.3)**
Hypothyroidism	3 (1.3)	1 (0.5)	1 (0.4)	0	4 (0.8)
Diabetes insipidus	0	1 (0.5)	3 (1.1)	2 (0.8)	3 (0.6)
Reproductive system and breast disorders	**4 (1.8)**	**4 (1.8)**	**7 (2.7)**	**7 (2.7)**	**11 (2.3)**
Scrotal oedema	2 (0.9)	1 (0.5)	3 (1.1)	2 (0.8)	5 (1.0)

Attachment 9.3: Serious Adverse Events by System Organ Class and Preferred Term (JNJ38174942-Studies DORI-09, and DORI-10: Safety Analysis Set)

Serious Adverse Events by System Organ Class and Preferred Term
(JNJ38174942-Studies DORI-09 and DORI-10: Safety Analysis Set)

	DORI-09		DORI-10	
Body System or Organ Class Dictionary-derived Term	Doripenem (N=223) n (%)	Pipericillin/tazabactam (N=221) n (%)	Doripenem (N=262) n (%)	Imipenem (N=263) n (%)
Total no. subjects with serious adverse events	67 (30.0)	58 (26.2)	70 (26.7)	72 (27.4)
Infections and infestations	30 (13.5)	19 (8.6)	19 (7.3)	25 (9.5)
Pneumonia	12 (5.4)	3 (1.4)	2 (0.8)	5 (1.9)
Septic shock	9 (4.0)	5 (2.3)	2 (0.8)	4 (1.5)
Sepsis	3 (1.3)	2 (0.9)	6 (2.3)	6 (2.3)
Abdominal abscess	0	2 (0.9)	1 (0.4)	0
Abdominal sepsis	1 (0.4)	0	0	0
Bacteraemia	1 (0.4)	0	0	0
Bronchitis acute	1 (0.4)	1 (0.5)	0	0
Empyema	0	0	1 (0.4)	2 (0.8)
Endocarditis	1 (0.4)	0	0	0
Fungal skin infection	0	0	1 (0.4)	0
Localised infection	0	0	1 (0.4)	0
Lung abscess	0	0	1 (0.4)	0
Pneumonia fungal	1 (0.4)	0	0	0
Subcutaneous abscess	0	0	1 (0.4)	0
Thrombophlebitis septic	0	0	1 (0.4)	0
Tracheobronchitis	0	0	1 (0.4)	0
Urinary tract infection	1 (0.4)	1 (0.5)	0	0
Wound infection	0	0	1 (0.4)	1 (0.4)
Bacterial sepsis	0	1 (0.5)	0	0
Bronchitis	0	0	0	1 (0.4)
Bronchopneumonia	0	0	0	1 (0.4)

[a] Dori 500 mg 1-h i.v. infusion q8h, Piperacilin/Tazobactam 4.5 g 30-min infusion q6h
[b] Dori 500 mg 4-h i.v. infusion q8h; Imipenem 500 mg 30-min infusion q6h, or 1-g 1-h infusion q8h.
Note: At each level of summarization, a subject is counted once if the subject reported one or more events. Table includes treatment-emergent serious adverse events, defined as those serious adverse events with onset dates on or after the date of the start of the infusion of first dose of the study medication and within 30 days after administration of the last dose of the study medication. AE terms are coded using MedDRA version 9.0.

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Attachment 9.3: Serious Adverse Events by System Organ Class and Preferred Term (JNJ38174942-Studies DORI-09, and DORI-10: Safety Analysis Set)

Serious Adverse Events by System Organ Class and Preferred Term
(JNJ38174942-Studies DORI-09 and DORI-10: Safety Subject Analysis Set) (continued)

	DORI-09		DORI-10	
Body System or Organ Class	Doripenem (N=223)	Pipericillin/tazabactam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Infections and infestations (Cont'd)	30 (13.5)	19 (8.6)	19 (7.3)	25 (9.5)
Fungaemia	0	0	0	1 (0.4)
Fungal infection	0	1 (0.5)	0	0
Gangrene	0	0	0	1 (0.4)
Klebsiella infection	0	1 (0.5)	0	1 (0.4)
Meningitis	0	2 (0.9)	0	1 (0.4)
Pneumonia klebsiella	0	0	0	1 (0.4)
Pneumonia staphylococcal	0	1 (0.5)	0	1 (0.4)
Soft tissue infection	0	0	0	1 (0.4)
Urosepsis	0	0	0	1 (0.4)
Viral infection	0	1 (0.5)	0	0
Respiratory, thoracic and mediastinal disorders	22 (9.9)	14 (6.3)	19 (7.3)	18 (6.8)
Respiratory failure	5 (2.2)	3 (1.4)	6 (2.3)	6 (2.3)
Pulmonary embolism	1 (0.4)	0	3 (1.1)	0
Acute respiratory failure	3 (1.3)	0	0	1 (0.4)
Pneumonia aspiration	3 (1.3)	2 (0.9)	0	0
Pulmonary oedema	3 (1.3)	0	0	0
Respiratory distress	1 (0.4)	2 (0.9)	2 (0.8)	1 (0.4)
Aspiration	1 (0.4)	0	1 (0.4)	0
Pneumothorax	2 (0.9)	3 (1.4)	0	2 (0.8)
Respiratory arrest	1 (0.4)	1 (0.5)	1 (0.4)	0
Acute pulmonary oedema	1 (0.4)	0	0	0
Acute respiratory distress syndrome	0	2 (0.9)	1 (0.4)	4 (1.5)
Atelectasis	1 (0.4)	0	0	0
Chronic obstructive pulmonary disease	0	1 (0.5)	1 (0.4)	1 (0.4)
Emphysema	0	0	1 (0.4)	0
Haemopneumothorax	0	0	1 (0.4)	0
Hypoxia	1 (0.4)	0	0	2 (0.8)
Pleural effusion	0	1 (0.5)	1 (0.4)	0

(continued)

Attachment 9.3: Serious Adverse Events by System Organ Class and Preferred Term (JNJ38174942-Studies DORI-09, and DORI-10: Safety Analysis Set)

Serious Adverse Events by System Organ Class and Preferred Term
(JNJ38174942-Studies DORI-09 and DORI-10: Safety Subject Analysis Set) (continued)

	DORI-09		DORI-10	
Body System or Organ Class	Doripenem (N=223)	Pipericillin/tazabactam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders (Cont'd)	22 (9.9)	14 (6.3)	19 (7.3)	18 (6.8)
Pleurisy	0	0	1 (0.4)	0
Pneumonitis	1 (0.4)	0	0	0
Pulmonary artery thrombosis	1 (0.4)	0	0	0
Sputum retention	0	0	1 (0.4)	0
Bronchopleural fistula	0	0	0	1 (0.4)
Chronic respiratory failure	0	0	0	1 (0.4)
Haemoptysis	0	0	0	1 (0.4)
Obstructive airways disorder	0	0	0	1 (0.4)
Tracheal stenosis	0	0	0	1 (0.4)
Cardiac disorders	9 (4.0)	7 (3.2)	11 (4.2)	16 (6.1)
Cardio-respiratory arrest	0	2 (0.9)	4 (1.5)	5 (1.9)
Cardiogenic shock	3 (1.3)	1 (0.5)	1 (0.4)	0
Cardiac arrest	0	1 (0.5)	3 (1.1)	6 (2.3)
Cardiac failure	2 (0.9)	0	0	2 (0.8)
Acute myocardial infarction	1 (0.4)	0	0	1 (0.4)
Aortic valve incompetence	0	0	1 (0.4)	0
Arrhythmia	1 (0.4)	1 (0.5)	0	0
Atrioventricular block complete	1 (0.4)	0	0	0
Bradycardia	0	0	1 (0.4)	0
Cardiopulmonary failure	0	0	1 (0.4)	0
Myocardial ischaemia	1 (0.4)	0	0	0
Torsade de pointes	1 (0.4)	0	0	0
Ventricular fibrillation	0	1 (0.5)	1 (0.4)	1 (0.4)
Ventricular tachycardia	0	0	1 (0.4)	0
Atrial flutter	0	0	0	1 (0.4)
Myocardial infarction	0	1 (0.5)	0	1 (0.4)

(continued)

Attachment 9.3: Serious Adverse Events by System Organ Class and Preferred Term (JNJ38174942-Studies DORI-09, and DORI-10: Safety Analysis Set)

Serious Adverse Events by System Organ Class and Preferred Term
(JNJ38174942-Studies DORI-09 and DORI-10: Safety Subject Analysis Set) (continued)

	DORI-09		DORI-10	
Body System or Organ Class	Doripenem (N=223)	Pipericillin/tazabactam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Nervous system disorders	6 (2.7)	11 (5.0)	14 (5.3)	11 (4.2)
Intracranial pressure increased	1 (0.4)	1 (0.5)	4 (1.5)	0
Brain oedema	1 (0.4)	3 (1.4)	2 (0.8)	1 (0.4)
Cerebrovascular accident	2 (0.9)	2 (0.9)	0	0
Convulsion	0	1 (0.5)	2 (0.8)	3 (1.1)
Cerebral disorder	0	0	1 (0.4)	0
Cerebral haematoma	0	0	1 (0.4)	0
Cerebral haemorrhage	0	0	1 (0.4)	0
Coma	1 (0.4)	0	0	0
Hydrocephalus	0	0	1 (0.4)	0
Ischaemic stroke	1 (0.4)	2 (0.9)	0	0
Subarachnoid haemorrhage	0	0	1 (0.4)	3 (1.1)
Syncope	0	0	1 (0.4)	0
Anoxic encephalopathy	0	0	0	1 (0.4)
Cerebral infarction	0	0	0	1 (0.4)
Cerebral ischaemia	0	1 (0.5)	0	0
Cerebrovascular spasm	0	1 (0.5)	0	0
Dementia alzheimer's type	0	1 (0.5)	0	0
Monoplegia	0	0	0	1 (0.4)
Status epilepticus	0	0	0	1 (0.4)
Transient ischaemic attack	0	0	0	1 (0.4)
Gastrointestinal disorders	6 (2.7)	13 (5.9)	6 (2.3)	7 (2.7)
Peritonitis	0	1 (0.5)	3 (1.1)	2 (0.8)
Colitis ischaemic	1 (0.4)	0	1 (0.4)	0
Abdominal compartment syndrome	0	0	1 (0.4)	0
Abdominal pain	0	1 (0.5)	1 (0.4)	0
Duodenal ulcer haemorrhage	1 (0.4)	1 (0.5)	0	1 (0.4)
Gastrointestinal haemorrhage	1 (0.4)	1 (0.5)	0	0
Intestinal obstruction	1 (0.4)	0	0	0

(continued)

Attachment 9.3: Serious Adverse Events by System Organ Class and Preferred Term (JNJ38174942-Studies DORI-09, and DORI-10: Safety Analysis Set)

Serious Adverse Events by System Organ Class and Preferred Term
(JNJ38174942-Studies DORI-09 and DORI-10: Safety Subject Analysis Set) (continued)

	DORI-09		DORI-10	
Body System or Organ Class	Doripenem (N=223)	Pipericillin/tazabactam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders (Cont'd)	6 (2.7)	13 (5.9)	6 (2.3)	7 (2.7)
Large intestine perforation	0	1 (0.5)	1 (0.4)	0
Pancreatic cyst	1 (0.4)	0	0	0
Small intestinal obstruction	0	1 (0.5)	1 (0.4)	1 (0.4)
Thrombosis mesenteric vessel	1 (0.4)	0	0	0
Abdominal distension	0	1 (0.5)	0	0
Ascites	0	0	0	1 (0.4)
Diverticulitis intestinal haemorrhagic	0	1 (0.5)	0	0
Gastric ulcer	0	1 (0.5)	0	0
Gastric ulcer haemorrhage	0	2 (0.9)	0	0
Intestinal perforation	0	0	0	1 (0.4)
Pancreatitis acute	0	2 (0.9)	0	0
Pancreatitis necrotising	0	0	0	1 (0.4)
Peritoneal haemorrhage	0	0	0	1 (0.4)
Pharyngoesophageal diverticulum	0	1 (0.5)	0	0
Upper gastrointestinal haemorrhage	0	1 (0.5)	0	0
General disorders and administration site conditions	3 (1.3)	5 (2.3)	5 (1.9)	7 (2.7)
Multi-organ failure	1 (0.4)	2 (0.9)	4 (1.5)	6 (2.3)
Asthenia	1 (0.4)	0	0	0
General physical health deterioration	0	0	1 (0.4)	0
Sudden cardiac death	1 (0.4)	0	0	0
Brain death	0	0	0	1 (0.4)
Pyrexia	0	1 (0.5)	0	0
Sudden death	0	2 (0.9)	0	0
Vascular disorders	1 (0.4)	2 (0.9)	6 (2.3)	5 (1.9)
Hypotension	1 (0.4)	1 (0.5)	2 (0.8)	0
Deep vein thrombosis	0	0	2 (0.8)	2 (0.8)
Aneurysm ruptured	0	0	1 (0.4)	0

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Attachment 9.3: Serious Adverse Events by System Organ Class and Preferred Term (JNJ38174942-Studies DORI-09, and DORI-10: Safety Analysis Set)

Serious Adverse Events by System Organ Class and Preferred Term
(JNJ38174942-Studies DORI-09 and DORI-10: Safety Subject Analysis Set) (continued)

	DORI-09		DORI-10	
Body System or Organ Class	Doripenem (N=223)	Pipericillin/tazabactam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Vascular disorders (Cont'd)	1 (0.4)	2 (0.9)	6 (2.3)	5 (1.9)
Embolism	0	0	1 (0.4)	0
Venous thrombosis limb	0	0	1 (0.4)	0
Aortic aneurysm rupture	0	0	0	1 (0.4)
Neurogenic shock	0	1 (0.5)	0	0
Peripheral arterial occlusive disease	0	0	0	1 (0.4)
Thrombophlebitis	0	0	0	1 (0.4)
Renal and urinary disorders	3 (1.3)	1 (0.5)	3 (1.1)	4 (1.5)
Renal failure acute	1 (0.4)	1 (0.5)	3 (1.1)	3 (1.1)
Renal failure	2 (0.9)	0	0	1 (0.4)
Injury, poisoning and procedural complications	1 (0.4)	1 (0.5)	4 (1.5)	5 (1.9)
Wound dehiscence	0	0	2 (0.8)	0
Incision site haemorrhage	0	0	1 (0.4)	0
Shunt thrombosis	1 (0.4)	0	0	0
Tracheostomy malfunction	0	0	1 (0.4)	0
Traumatic brain injury	0	0	1 (0.4)	0
Accidental overdose	0	0	0	1 (0.4)
Decerebration	0	0	0	1 (0.4)
Gastrointestinal stoma complication	0	0	0	1 (0.4)
Haemothorax	0	1 (0.5)	0	0
Post procedural complication	0	0	0	2 (0.8)
Metabolism and nutrition disorders	2 (0.9)	1 (0.5)	0	0
Dehydration	1 (0.4)	1 (0.5)	0	0
Failure to thrive	1 (0.4)	0	0	0

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Attachment 9.3: Serious Adverse Events by System Organ Class and Preferred Term (JNJ38174942-Studies DORI-09, and DORI-10: Safety Analysis Set)

Serious Adverse Events by System Organ Class and Preferred Term
(JNJ38174942-Studies DORI-09 and DORI-10: Safety Subject Analysis Set) (continued)

	DORI-09		DORI-10	
Body System or Organ Class	Doripenem (N=223)	Pipericillin/tazabactam (N=221)	Doripenem (N=262)	Imipenem (N=263)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1 (0.5)	1 (0.4)	0
Lung neoplasm malignant	0	0	1 (0.4)	0
Oesophageal adenocarcinoma	1 (0.4)	0	0	0
Lung cancer metastatic	0	1 (0.5)	0	0
Hepatobiliary disorders	0	0	1 (0.4)	0
Cholestasis	0	0	1 (0.4)	0
Investigations	0	1 (0.5)	1 (0.4)	0
Liver function test abnormal	0	0	1 (0.4)	0
Aspiration bronchial	0	1 (0.5)	0	0
Psychiatric disorders	0	0	1 (0.4)	0
Suicide attempt	0	0	1 (0.4)	0
Skin and subcutaneous tissue disorders	0	0	1 (0.4)	3 (1.1)
Rash	0	0	1 (0.4)	1 (0.4)
Decubitus ulcer	0	0	0	1 (0.4)
Erythema multiforme	0	0	0	1 (0.4)
Blood and lymphatic system disorders	0	1 (0.5)	0	0
Lymphadenopathy	0	1 (0.5)	0	0

Attachment 9.4: Subjects With Renal-related Adverse Events in the Phase 3 Studies (JNJ J38174942-Studies DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-10

Subjects With Renal-Related Adverse Events
Phase 3 Studies JNJ38174942: DORI-05, -06, -07 –08, -09, -10

Subject Number (Age/Sex/Race)	Relevant Medical History	Adverse Event Preferred Term	Day of Onset	Course of Therapy Relationship	Doripenem	Other	Clinical Comments
Study DORI-05							
01303031 40/F/W	Hypotension Bowel obstruction Cancer of the labia/vulva Uncomplicated pyelonephritis	Renal impairment	3	Not related	Day 1 - 9	None	Mild renal impairment temporally associated with doripenem use. Resolved while still on doripenem therapy (negative rechallenge). Subject completed study thru LFU
30306011 69/M/W	Congestive heart failure Chronic Anemia Prostatic adenoma Complicated pyelonephritis	Renal failure acute*	4	Not related	Days 1 - 6	None	Post-renal renal failure most likely secondary to prostatic adenoma. The event resolved on Day 12 after placement of a urinary catheter Acute renal failure resolved on Day 13. Subject completed study through to LFU.
30704002 82/F/Hispanic	Cardiac failure Hypertension Viral pericarditis cLUTI	(worsening of basal) Renal impairment	11	Not related	Days 1 - 5	Furosemide (Day 4 to 15)	Worsening of pre-existing renal impairment 6 days after doripenem was discontinued
Study DORI-06							
35100066 73/F/Hispanic	Chronic Anemia Gram negative sepsis VAP Colon Adenocarcinoma Complicated pyelonephritis	Renal failure acute*	12	Not related	Days 1 - 5	Contrast media (Day 6 x 1 dose)	Elderly female with serious co-morbid illnesses, developed renal failure 1 week after discontinuing doripenem therapy. SAE resolved on Day 16 and subject completed study through LFU
35700366 81/F/Hispanic	Congestive heart failure Coronary artery disease Aortic stenosis Acute pulmonary edema cLUTI	Renal failure*	11	Not related	Days 1 - 11	None	Seriously ill elderly female with post renal - renal failure reported on the day doripenem was discontinued. A cystoscopy disclosed an infiltrating formation on the trigone and left lateral bladder, and a right nephrostomy was performed on Day 22. By Day 27, her creatinine vales had decreased to similar baseline values. Study drug was withdrawn but event considered by investigator to be unrelated. SAE resolved after 17 days and patient completed study through LFU

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Attachment 9.4: Subjects With Renal-related Adverse Events in the Phase 3 Studies (JNJ J38174942-Studies DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-10

Subjects With Renal-Related Adverse Events
Phase 3 Studies JNJ38174942: DORI-05, -06, -07 –08, -09, -10 (Continued)

Subject Number (Age/Sex/Race)	Relevant Medical History	Adverse Event: Preferred Term	Adverse Event: Day of Onset	Course of Therapy: Relationship	Course of Therapy: Doripenem	Course of Therapy: Other	Clinical Comments
63000035 71/F/W	Diabetes Mellitus Hypertension Renal Failure Uncomplicated pyelonephritis	(Worsening) Renal impairment*	3	Possibly related	Days 1 -2 (3 doses)	Gentamicin (Day 3 - 6) Furosemide (Day 3 x 1 dose)	Elderly female with pre-existing renal failure, had SAE report of worsening renal impairment temporally associated with administration of doripenem and probably related to sepsis and dehydration by investigator assessment.. Gentamicin and furosemide were also given on the day of the event. i.v. study drug was withdrawn on Day 2 and oral levo started. Renal impairment persisted for 12 more days despite drug withdrawal, resolving on study Day 15. Subject did not complete study per protocol (was discontinued from study on Day 36 due to renal impairment, atrial fibrillation, and increased hepatic enzymes).
63300108 61/M/W	PVD, spina bifida, type II diabetes Peripheral vascular disease Complicated pyelonephritis	Renal failure acute	4	Possibly related	Days 1 - 15	Vancomycin Days 7 - 9	Elderly male with renal failure early in doripenem treatment, before the addition of vancomycin. Renal failure resolved while on doripenem therapy (negative re-challenge). Cr_{Max}: 300.5 µmol/L on Day 3. Subject completed therapy through LFU with a positive clinical outcome
63300210 62/F/W	Intermittent diarrhea Nausea & Vomiting Uncomplicated pyelonephritis	Renal failure acute	3	Unlikely related	Day 1 - 14	None	Elderly male with history of gastrointestinal fluid loss had acute renal failure temporally associated with doripenem use. Renal failure improved while subject remained on i.v. study drug resolving fully by Day 10. Subject completed study through LFU with a positive clinical outcome
64300217 63/M/W	Aortic valve disease s/p valve surgeries Cardiomyopathy Congestive heart failure Hypotension Old history of rheumatic Fever Severe decrease in left ventricle function atrial fibrillation, mild diabetes	(worsening of) Renal failure Renal failure acute* (secondary to hypovolemia)	1 13	Not related Not related	Days 1 -2 (3 doses)	Vancomycin Days -1 to 1 Days 2 – 8	Elderly severely ill male (with cardiovascular decompensation - post-cardiac surgery complications of pericardial effusion;) on multiple inotropics for ≥ 2 weeks prior to enrollment; also concomitantly treated with vancomycin . Developed mild worsening of pre-existing renal failure on day doripenem was initiated. Doripenem therapy was continued despite AE but terminated on Day 2 following negative pre-treatment urine cultures. On Day 13 developed SAE of acute worsening of renal failure (11 days after doripenem was discontinued). Stated etiology of prerenal renal failure was hypovolemia consistent with history of very poor cardiac perfusion in this subject. Of note, this subject was discontinued from study treatment on Day 2 because of lack of a qualifying baseline culture. Cr_{Max}: 194.5 µmol/L at Baseline.

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Attachment 9.4: Subjects With Renal-related Adverse Events in the Phase 3 Studies (JNJ J38174942-Studies DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-10

Subjects With Renal-Related Adverse Events
Phase 3 Studies JNJ38174942: DORI-05, -06, -07 –08, -09, -10 (Continued)

Subject Number (Age/Sex/Race)	Relevant Medical History	Adverse Event: Preferred Term	Adverse Event: Day of Onset	Course of Therapy: Relationship	Course of Therapy: Doripenem	Course of Therapy: Other	Clinical Comments
04102020 66/M/W	Chronic Renal Insufficiency/DM Cardiac Insufficiency Renal Carcinoma s/p nephrectomy	Renal failure acute*	23	Not related	Days 1 - 4	None	This subject developed worsening renal failure 19 days after doripenem was discontinued.
04602510 61/F/W Cr_B	Congestive heart failure Diabetes Hyperlipidemia	Renal failure	14	Not related	Days 1 -6	Amikacin (Day 10 -12)	Elderly subject with CHF, developed sepsis on Day 10, and on Day 14 experienced pancreatitis, myocardial ischemia and renal failure. 8 days after doripenem was discontinued
10006028 61/M/W	Coronary artery disease Mitral valve insufficiency Diabetes Mellitus Cirrhosis of the liver	Renal failure acute*	18	Not related	Days 1 - 6	Furosemide (Days 1 – 6)	This subject developed renal failure 12 days after doripenem was discontinued; subject had a history of poor circulatory function. On Day 23 the subject's creatinine was within the normal range and the investigator considered the acute renal failure resolved. The investigator assessed the case as related to the subject's cardiac insufficiency.
		Renal failure acute	32	Unlikely related			
Study DORI-08							
02902030 71/M/W	Hypertension Kidney stones GSW to left arm	Renal failure	30	Not related	Days 1 – 6	None	This subject developed renal failure 24 days after doripenem was discontinued
12606026 69/F/W	Coronary artery disease s/p myocardial infarction Peripheral Artery disease Hyper lipoproteinemia	Renal failure*	32	Not related	Days 1 - 6	Vancomycin Days 7 -15 Gentamicin (Days 6 – 7)	This subject developed renal failure 26 days after doripenem was discontinued
12806502 51/M/W	Sepsis with organ failure Post op cardiac insufficiency	Renal failure	10	Unlikely related	Days 1 - 11	Vancomycin Days 4, 7 – 9, 14 – 24	This subject with history of sepsis and post op cardiac insufficiency developed renal failure 1 day before doripenem was discontinued. RF lasted for 2 days after discontinuation and resolved on Day 13. Subject was discontinued from study drug because of need for additional therapy Cr_{Max}: 165.0 µmol/L on Day 6.

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Attachment 9.4: Subjects With Renal-related Adverse Events in the Phase 3 Studies (JNJ J38174942-Studies DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-10

Subjects With Renal-Related Adverse Events
Phase 3 Studies JNJ38174942: DORI-05, -06, -07 –08, -09, -10 (Continued)

Subject Number (Age/Sex/Race)	Relevant Medical History	Adverse Event: Preferred Term	Adverse Event: Day of Onset	Course of Therapy: Relationship	Course of Therapy: Doripenem	Course of Therapy: Other	Clinical Comments
38304104 69/F/Hispanic	Hypertension Pre-renal failure History of stroke	Renal impairment*	16	Unlikely related	Days 1 – 6	Furosemide Days 6 - 12	This subject developed renal failure 10 days after doripenem was discontinued
Study DORI-09							
19706030 70/M/W	Pre-existing chronic renal failure-Diabetic nephropathy, hypertension, Heart failure,	Renal failure	6	Unlikely	Days 1 - 8	Amikacin Days 1 -5 Furosemide Day-1 - 12	History of left kidney abscess s/p drainage, congestive heart failure on Day 5.
30604514 90/M/Hispanic	Hypertension	Renal failure	20	Not related	Days 1 - 8	Amikacin, Days 1 – 3	Event occurred 2 weeks after doripenem therapy was discontinued.
31204035 80/M/W	Hypertension , Cardiac Failure, Type 2 diabetes	Renal impairment	9	Not related	Days 1 - 15	Vancomycin Day 1 – 7 Amikacin Day 1 – 7	Elderly male with co-morbid illnesses, developed renal impairment on Day 9. Concomitant amikacin and vancomycin also administered prior to Day 9.Creatinine on Day 9 = 1.4, and on Day 14 = 1.8.The subject did not complete the study. He died from a stroke on Day 15.
40503023 23/M/W	Multiple trauma Rhabdomyolysis	Renal failure	33	Not related	Day 1 - 11	Vancomycin Days 9 - 36 Polymyxin Day 11	Renal failure occurred more than 2 weeks after doripenem was discontinued. Creatinine <0.8mg/dL while on study drug.
40503504 72/M/W	Alcoholism Hypertension Acute renal failure	Renal failure acute	17	Not related	Day 1 – 15	Vancomycin Days 4 –13 Amikacin Days 2 – 4, Polymixin Day 14, 20-28 Amphotericin Day 24– 26, and Day 28	On Day 5 the subject experienced sepsis and renal failure on Day 17 (3 days after doripenem was discontinued). Subject received 3 other potentially nephrotoxic drugs, all of which were temporally related to the development of renal failure. Serum creatine values continue to increase despite study drug discontinuation. On Day 28 the subject died from multi organ failure CrMax: 229.8 µmol/L on Day 27.

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Attachment 9.4: Subjects With Renal-related Adverse Events in the Phase 3 Studies (JNJ J38174942-Studies DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-10

Subjects With Renal-Related Adverse Events
Phase 3 Studies JNJ38174942: DORI-05, -06, -07 –08, -09, -10 (Continued)

Subject Number (Age/Sex/Race)	Relevant Medical History	Adverse Event: Preferred Term	Adverse Event: Day of Onset	Course of Therapy: Relationship	Course of Therapy: Doripenem	Course of Therapy: Other	Clinical Comments
93001504 62/F/B	Pre-existing CRF (Cr = 2.5mg/dl at baseline), Congestive heart failure, Coronary artery disease and chronic renal insufficiency at baseline	Renal Failure*	7	Unlikely related	Day 1 – 8	Amikacin, Day 1 - 4	Renal failure preceded by an episode of documented hypotension following respiratory arrest on Day 5
93202502 64/M/W	Congestive heart failure decompensation with acute hypovolemia and pulmonary edema on Day 2.	Acute renal failure (not serious)	2	Not related	Days 1 - 9	Vancomycin Days 1 - 9	Renal failure occurred on Day 2 (not serious) again on Day 22 (SAE) after study medication had ended, and following another episode of hypotension.
		Renal failure*	22	Not related			
94101007 58/M/B	Heart failure	Renal failure acute*	9	Not related	Days 1 - 9	Vancomycin Days -3 to –2 Days 1 - 11	Renal failure immediately preceded by hypotensive episode on Day 7. Renal ultrasound on Day 8 showed pre-existing cysts
94402010 62/M/W	Pre-existing renal insufficiency at baseline (Cr @ baseline = 1.7mg/dl and on Day 11 = 0.9mg/dl), also generalized edema at baseline, hypotension on Day 2. Congestive heart failure, Hypertension	Renal impairment	11	Not related	Days 1 - 15	Vancomycin Days 2 - 20	Negative rechallenge as doripenem was continued beyond event with no worsening in serum creatinine

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Attachment 9.4: Subjects With Renal-related Adverse Events in the Phase 3 Studies (JNJ J38174942-Studies DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-10

Subjects With Renal-Related Adverse Events
Phase 3 Studies JNJ38174942: DORI-05, -06, -07 –08, -09, -10 (Continued)

Subject Number (Age/Sex/Race)	Relevant Medical History	Adverse Event: Preferred Term	Adverse Event: Day of Onset	Course of Therapy: Relationship	Course of Therapy: Doripenem	Course of Therapy: Other	Clinical Comments
Study DORI-10							
00705020 80/M/W	Renal impairment at baseline (Cr = 1.5mg/dl), Coronary artery disease, Abdominal aortic aneurysm, chronic renal insufficiency	Renal failure	11	Unlikely	Days 1 - 14	Vancomycin Days 7 – 15	This subject was very ill with severe cardiovascular disease. Renal function was impaired at baseline and worsened by septic shock and multi-organ failure beginning on Day 11. The subject died from complications of sepsis on Day 25.
12302566 77/M/B	Diabetes mellitus, Coronary artery disease, cardiovascular collapse	Renal failure acute*	18	Not related	Days 1 – 4	Vancomycin Days 1 – 2 Tobramycin Days 26 – 30	The subject experienced an AE of acute tubular necrosis on Days 7 – 17 and sepsis and renal failure on Day 18; 14 days after discontinuation of doripenem... Serum creatinine values continued to increase despite study drug discontinuation. CrMax: 397.8 µmol/L on Day 33.
12801525 21/M/B	21 year old male with gunshot wound, obesity	Renal failure acute	3	Not related	Day 1 (1 dose)	Vancomycin Day -1 to 6 Tobramycin Day 1 – 6	This subject received only one dose of doripenem before being discontinued from the study. Renal failure was reported 3 days after stopping the doripenem. The subject's outcome was indeterminate at LFU.
13401519 23/M/W	Traumatic splenic rupture, coma	Renal failure acute*	2	Unlikely	Days 1 - 3	Vancomycin Days 2 - 3	Mild renal impairment at baseline (Cr = 1.3). Developed abdominal compartment syndrome with necrotic colon on Day 2 leading to fever, sepsis, increased BUN and anuria. Had exploratory laparotomy on Day 3 and continuous renal replacement therapy (CRRT) on Day 4. Increased BUN likely due to sepsis and hypovolemia.
14402510 68/M/W	Diabetes, Coronary artery disease status post myocardial infarction with stent	Renal failure	32	Not related	Days 1 – 9	Vancomycin Days 3 - 19	Event occurred after the subject ended doripenem therapy.

(Continued)

Attachment 9.4: Subjects With Renal-related Adverse Events in the Phase 3 Studies (JNJ J38174942-Studies DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-10

Subjects With Renal-Related Adverse Events
Phase 3 Studies JNJ38174942: DORI-05, -06, -07 –08, -09, -10 (Continued)

Subject Number (Age/Sex/Race)	Relevant Medical History	Adverse Event: Preferred Term	Adverse Event: Day of Onset	Course of Therapy: Relationship	Course of Therapy: Doripenem	Course of Therapy: Other	Clinical Comments
14402546 50/M/W	Polytrauma	Renal failure acute*	8	Possibly related	Days 1 - 8	Tobramycin Days 5 – 8	Reported hypernatremia following diarrhea on Days 3 – 6. Creatinine normal at baseline but 5.7mg/dl on Day 9. Assessed by the investigator as related to study drug therapy. A nephrologist's consult that stated the most likely reason for the renal failure was rhabdomyolysis (CK values range form 1669 to 24400 at day 8 (normal range 24-195). Despite discontinuation of doripenem, acute renal failure persisted thru Day 22. Confounded case.
14502007 76/M/B	Pre-existing acute renal failure, hypertension, diabetes mellitus, metabolic acidosis, rhabdomyolysis	Renal failure acute	41	Not related	Day 1 - 12	Vancomycin Day -7, 46 Gentamicin Day –7, -5,	Event occurred after the subject ended doripenem therapy.
75005521 74/M/W	Elderly patient with complex medical history including history of cardiac arrhythmia, Coronary artery disease, pulmonary vascular disease, recent vascular bypass surgery	Renal failure acute	2	Not related	Day 1 – 2	None	Preceding events include sepsis and kidney failure Developed cardiogenic shock from ventricular fibrillation/tachycardia on Day 2 leading to worsening of acute renal failure requiring dialysis. Acute renal failure most likely secondary to hypoperfusion. Received doripenem for only 1 day.

* Serious Adverse Event
Note: B=black; F=female; M=male; SAE=serious adverse event; W=white.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
BASOPHILS (%)														
Dori 500 mg 1-h inf														
BASELINE	146	0.16	0.285	0.10	0.0	2.0								
DAY 2/3	129	0.25	0.411	0.10	0.0	2.0	0.16	94	0.07	0.047	0.451	0.00	-1.0	2.0
DAY 5	130	0.24	0.282	0.15	0.0	1.2	0.14	101	0.09	0.034	0.337	0.00	-1.0	1.2
DAY 8	83	0.23	0.264	0.10	0.0	1.0	0.11	67	0.10	0.033	0.273	0.00	-0.6	1.0
DAY 11	40	0.24	0.349	0.10	0.0	1.6	0.08	32	0.11	0.046	0.260	0.00	-0.3	0.9
DAY 14	12	0.30	0.252	0.20	0.0	0.7	0.10	6	0.15	0.092	0.226	0.10	0.0	0.6
END IV THERAPY	159	0.31	0.406	0.20	0.0	3.0	0.16	115	0.15	0.042	0.445	0.00	-1.0	2.5
EARLY FOLLOW-UP	178	0.37	0.441	0.30	0.0	3.4	0.16	127	0.20	0.039	0.435	0.00	-1.4	2.0
LATE FOLLOW-UP	88	0.35	0.410	0.30	0.0	3.0	0.14	59	0.14	0.038	0.296	0.10	-0.7	1.3
Dori 500 mg 4-h inf														
BASELINE	221	0.20	0.335	0.00	0.0	1.6								
DAY 2/3	214	0.28	0.499	0.10	0.0	3.0	0.20	188	0.09	0.046	0.626	0.00	-1.4	3.0
DAY 5	189	0.29	0.548	0.10	0.0	5.7	0.18	162	0.13	0.050	0.637	0.00	-1.4	5.7
DAY 8	122	0.41	0.565	0.20	0.0	4.0	0.17	102	0.24	0.068	0.689	0.10	-1.0	4.0
DAY 11	47	0.41	0.520	0.20	0.0	2.0	0.23	37	0.18	0.108	0.658	0.00	-1.0	2.0
DAY 14	19	0.50	0.561	0.30	0.0	2.0	0.22	15	0.34	0.146	0.564	0.10	-0.3	2.0
END IV THERAPY	212	0.40	0.571	0.20	0.0	4.0	0.21	179	0.19	0.048	0.646	0.00	-1.1	4.0
EARLY FOLLOW-UP	230	0.34	0.410	0.25	0.0	2.0	0.19	197	0.15	0.034	0.483	0.10	-1.1	2.0
LATE FOLLOW-UP	85	0.41	0.357	0.30	0.0	1.6	0.19	78	0.24	0.057	0.505	0.20	-1.0	1.3
Dori 500 mg														
BASELINE	367	0.18	0.316	0.00	0.0	2.0								
DAY 2/3	343	0.27	0.467	0.10	0.0	3.0	0.18	282	0.08	0.034	0.573	0.00	-1.4	3.0
DAY 5	319	0.27	0.459	0.10	0.0	5.7	0.17	263	0.11	0.033	0.541	0.00	-1.4	5.7
DAY 8	205	0.34	0.475	0.20	0.0	4.0	0.15	169	0.18	0.043	0.565	0.10	-1.0	4.0
DAY 11	87	0.33	0.455	0.10	0.0	2.0	0.16	69	0.14	0.062	0.511	0.00	-1.0	2.0
DAY 14	31	0.42	0.471	0.20	0.0	2.0	0.19	21	0.29	0.108	0.493	0.10	-0.3	2.0
END IV THERAPY	371	0.36	0.508	0.20	0.0	4.0	0.19	294	0.17	0.034	0.576	0.00	-1.1	4.0

Dori 500 mg 1-h inf: Doripenem 500 mg 1-h infusion q8h, Dori 500 mg 4-h inf: Doripenem 500 mg 4-h infusion q8h,
Dori 500 mg: Doripenem 500 mg 1-h + 4-h infusion q8h, Pip/Taz: Piperacilin/Tazobactam 4.5 g 30-min infusion q6h,
Imi: Imipenem 500 mg 30-min infusion q6h, or 1-g 1-h infusion q8h.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
BASOPHILS (%)														
Dori 500 mg														
EARLY FOLLOW-UP	408	0.35	0.424	0.30	0.0	3.4	0.18	324	0.17	0.026	0.465	0.05	-1.4	2.0
LATE FOLLOW-UP	173	0.38	0.385	0.30	0.0	3.0	0.17	137	0.20	0.037	0.429	0.10	-1.0	1.3
Pip/Taz														
BASELINE	139	0.11	0.202	0.00	0.0	1.1								
DAY 2/3	129	0.20	0.302	0.10	0.0	1.7	0.09	99	0.09	0.029	0.284	0.00	-0.5	1.7
DAY 5	101	0.24	0.332	0.10	0.0	2.0	0.12	74	0.09	0.036	0.311	0.00	-1.0	1.0
DAY 8	66	0.19	0.260	0.10	0.0	1.0	0.12	51	0.04	0.046	0.326	0.00	-1.0	1.0
DAY 11	38	0.20	0.234	0.15	0.0	0.8	0.11	27	0.08	0.056	0.294	0.00	-1.0	0.7
DAY 14	20	0.22	0.336	0.05	0.0	1.3	0.10	16	0.14	0.082	0.326	0.00	-0.3	1.1
END IV THERAPY	137	0.25	0.335	0.10	0.0	2.0	0.11	110	0.11	0.035	0.363	0.00	-1.0	2.0
EARLY FOLLOW-UP	160	0.34	0.391	0.30	0.0	3.0	0.11	112	0.18	0.041	0.430	0.00	-0.6	3.0
LATE FOLLOW-UP	91	0.32	0.328	0.20	0.0	1.8	0.07	64	0.23	0.045	0.360	0.00	-0.3	1.5
Imi														
BASELINE	222	0.23	0.425	0.00	0.0	3.0								
DAY 2/3	211	0.36	0.512	0.10	0.0	3.0	0.22	183	0.11	0.042	0.569	0.00	-2.0	3.0
DAY 5	188	0.31	0.526	0.10	0.0	4.0	0.23	167	0.09	0.052	0.678	0.00	-2.0	4.0
DAY 8	125	0.36	0.504	0.10	0.0	2.0	0.23	109	0.14	0.060	0.626	0.00	-2.0	2.0
DAY 11	41	0.35	0.465	0.20	0.0	2.0	0.18	38	0.17	0.108	0.663	0.00	-1.0	2.0
DAY 14	8	0.35	0.351	0.30	0.0	1.0	0.30	5	0.00	0.235	0.524	0.00	-0.7	0.6
END IV THERAPY	211	0.33	0.465	0.10	0.0	2.0	0.23	182	0.12	0.043	0.577	0.00	-2.0	2.0
EARLY FOLLOW-UP	236	0.39	0.520	0.20	0.0	3.0	0.24	201	0.16	0.044	0.624	0.00	-2.0	3.0
LATE FOLLOW-UP	106	0.36	0.358	0.30	0.0	2.0	0.25	91	0.12	0.058	0.553	0.10	-1.8	2.0
BASOPHILS, ABS (X10E9/L)														
Dori 500 mg 1-h inf														
BASELINE	146	0.02	0.029	0.01	0.0	0.2								
DAY 2/3	129	0.03	0.050	0.01	0.0	0.3	0.01	94	0.01	0.006	0.055	0.00	-0.1	0.3
DAY 5	130	0.03	0.033	0.01	0.0	0.2	0.01	101	0.01	0.004	0.037	0.00	-0.2	0.1
DAY 8	83	0.03	0.035	0.02	0.0	0.2	0.01	67	0.02	0.005	0.039	0.00	-0.1	0.2
DAY 11	40	0.03	0.034	0.01	0.0	0.1	0.01	32	0.01	0.005	0.027	0.00	-0.0	0.1

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
BASOPHILS, ABS (X10E9/L)														
Dori 500 mg 1-h inf														
DAY 14	12	0.04	0.028	0.03	0.0	0.1	0.01	6	0.02	0.011	0.026	0.01	0.0	0.1
END IV THERAPY	159	0.03	0.037	0.02	0.0	0.2	0.02	115	0.01	0.004	0.042	0.00	-0.1	0.2
EARLY FOLLOW-UP	178	0.03	0.045	0.02	0.0	0.3	0.02	127	0.02	0.004	0.050	0.01	-0.2	0.3
LATE FOLLOW-UP	88	0.03	0.045	0.02	0.0	0.4	0.01	59	0.01	0.003	0.024	0.00	-0.1	0.1
Dori 500 mg 4-h inf														
BASELINE	184	0.02	0.047	0.00	0.0	0.3								
DAY 2/3	180	0.04	0.076	0.01	0.0	0.5	0.02	155	0.01	0.007	0.092	0.00	-0.3	0.5
DAY 5	157	0.04	0.073	0.02	0.0	0.6	0.02	131	0.02	0.006	0.074	0.00	-0.1	0.6
DAY 8	107	0.05	0.073	0.02	0.0	0.4	0.02	87	0.03	0.009	0.087	0.01	-0.2	0.4
DAY 11	44	0.05	0.074	0.02	0.0	0.4	0.03	34	0.02	0.017	0.099	0.00	-0.2	0.4
DAY 14	17	0.05	0.045	0.03	0.0	0.2	0.02	13	0.03	0.016	0.057	0.02	-0.1	0.2
END IV THERAPY	177	0.05	0.078	0.03	0.0	0.5	0.03	145	0.02	0.007	0.090	0.00	-0.2	0.5
EARLY FOLLOW-UP	194	0.04	0.057	0.02	0.0	0.4	0.02	162	0.01	0.005	0.065	0.01	-0.2	0.4
LATE FOLLOW-UP	67	0.03	0.028	0.02	0.0	0.1	0.02	62	0.01	0.005	0.042	0.01	-0.1	0.1
Dori 500 mg														
BASELINE	330	0.02	0.041	0.01	0.0	0.3								
DAY 2/3	309	0.03	0.067	0.01	0.0	0.5	0.02	249	0.01	0.005	0.080	0.00	-0.3	0.5
DAY 5	287	0.03	0.058	0.02	0.0	0.6	0.02	232	0.02	0.004	0.061	0.00	-0.2	0.6
DAY 8	190	0.04	0.060	0.02	0.0	0.4	0.02	154	0.02	0.006	0.070	0.01	-0.2	0.4
DAY 11	84	0.04	0.059	0.02	0.0	0.4	0.02	66	0.02	0.009	0.073	0.00	-0.2	0.4
DAY 14	29	0.04	0.039	0.03	0.0	0.2	0.02	19	0.03	0.011	0.049	0.02	-0.1	0.2
END IV THERAPY	336	0.04	0.063	0.02	0.0	0.5	0.02	260	0.02	0.005	0.073	0.00	-0.2	0.5
EARLY FOLLOW-UP	372	0.04	0.051	0.02	0.0	0.4	0.02	289	0.02	0.003	0.059	0.01	-0.2	0.4
LATE FOLLOW-UP	155	0.03	0.038	0.02	0.0	0.4	0.02	121	0.01	0.003	0.034	0.01	-0.1	0.1
Pip/Taz														
BASELINE	139	0.01	0.034	0.00	0.0	0.3								
DAY 2/3	129	0.02	0.037	0.01	0.0	0.3	0.01	99	0.01	0.004	0.036	0.00	-0.1	0.3
DAY 5	101	0.02	0.039	0.01	0.0	0.3	0.02	74	0.00	0.005	0.040	0.00	-0.2	0.1
DAY 8	66	0.02	0.029	0.01	0.0	0.1	0.02	51	-0.00	0.008	0.060	0.00	-0.3	0.1
DAY 11	38	0.02	0.023	0.02	0.0	0.1	0.02	27	0.00	0.013	0.068	0.00	-0.3	0.1

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
BASOPHILS, ABS (X10E9/L)														
Pip/Taz														
DAY 14	20	0.02	0.030	0.01	0.0	0.1	0.01	16	0.01	0.008	0.031	0.00	-0.0	0.1
END IV THERAPY	137	0.02	0.036	0.01	0.0	0.2	0.01	110	0.01	0.005	0.048	0.00	-0.3	0.2
EARLY FOLLOW-UP	160	0.03	0.041	0.02	0.0	0.4	0.01	112	0.01	0.005	0.052	0.00	-0.3	0.4
LATE FOLLOW-UP	91	0.02	0.026	0.02	0.0	0.1	0.01	64	0.01	0.003	0.028	0.00	-0.0	0.1
Imi														
BASELINE	193	0.03	0.067	0.00	0.0	0.6								
DAY 2/3	182	0.04	0.071	0.02	0.0	0.5	0.03	158	0.01	0.006	0.079	0.00	-0.2	0.5
DAY 5	159	0.04	0.066	0.01	0.0	0.4	0.03	140	0.01	0.008	0.097	0.00	-0.6	0.4
DAY 8	111	0.05	0.082	0.01	0.0	0.5	0.03	97	0.02	0.012	0.115	0.00	-0.6	0.5
DAY 11	38	0.04	0.067	0.01	0.0	0.3	0.03	35	0.01	0.017	0.102	0.00	-0.2	0.3
DAY 14	8	0.04	0.036	0.04	0.0	0.1	0.04	5	-0.00	0.034	0.075	0.00	-0.1	0.1
END IV THERAPY	180	0.04	0.071	0.02	0.0	0.4	0.03	156	0.01	0.007	0.088	0.00	-0.2	0.4
EARLY FOLLOW-UP	204	0.04	0.070	0.02	0.0	0.4	0.03	174	0.01	0.006	0.085	0.00	-0.2	0.4
LATE FOLLOW-UP	93	0.03	0.030	0.02	0.0	0.2	0.04	79	-0.00	0.009	0.081	0.01	-0.5	0.2
EOSINOPHILS (%)														
Dori 500 mg 1-h inf														
BASELINE	146	1.59	2.525	0.85	0.0	18.0								
DAY 2/3	129	2.32	2.260	1.90	0.0	13.0	1.47	94	0.72	0.244	2.370	0.60	-8.0	9.2
DAY 5	130	2.81	2.855	2.45	0.0	22.3	1.52	101	1.29	0.272	2.736	1.00	-5.2	16.5
DAY 8	83	2.40	2.806	1.60	0.0	14.0	1.35	67	0.78	0.274	2.245	0.50	-4.0	8.9
DAY 11	40	3.05	3.906	1.55	0.0	17.3	1.50	32	0.62	0.639	3.613	0.00	-15.0	6.2
DAY 14	12	3.86	4.550	2.40	0.0	15.0	1.68	6	0.32	0.280	0.685	0.15	-0.5	1.5
END IV THERAPY	159	2.72	2.989	2.00	0.0	16.0	1.66	115	0.83	0.299	3.210	0.70	-16.0	9.9
EARLY FOLLOW-UP	178	3.32	3.188	2.55	0.0	19.6	1.63	127	1.65	0.322	3.633	1.30	-16.0	12.0
LATE FOLLOW-UP	88	3.41	3.942	2.30	0.0	24.7	1.58	59	1.85	0.515	3.959	1.30	-7.6	18.7
Dori 500 mg 4-h inf														
BASELINE	221	1.75	2.243	1.00	0.0	18.7								
DAY 2/3	214	2.35	2.447	1.90	0.0	20.8	1.76	188	0.68	0.204	2.792	0.60	-17.2	15.8
DAY 5	189	2.33	2.651	1.90	0.0	21.7	1.86	162	0.44	0.222	2.825	0.45	-16.4	16.7

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
EOSINOPHILS (%)														
Dori 500 mg 4-h inf														
DAY 8	122	2.03	1.882	1.50	0.0	8.8	1.76	102	0.30	0.272	2.752	0.20	-16.7	8.0
DAY 11	47	2.22	2.072	2.00	0.0	9.0	1.81	37	0.54	0.453	2.758	0.50	-8.0	8.0
DAY 14	19	2.88	4.634	1.60	0.0	20.2	2.25	15	1.21	1.385	5.364	0.20	-10.0	15.2
END IV THERAPY	212	2.30	2.503	1.90	0.0	20.2	1.86	179	0.51	0.201	2.684	0.50	-13.6	15.2
EARLY FOLLOW-UP	230	2.57	2.486	2.00	0.0	20.2	1.80	197	0.82	0.196	2.748	0.90	-13.1	15.2
LATE FOLLOW-UP	85	2.93	2.543	2.10	0.0	14.7	1.79	78	1.16	0.306	2.707	1.10	-7.6	8.6
Dori 500 mg														
BASELINE	367	1.69	2.357	1.00	0.0	18.7								
DAY 2/3	343	2.34	2.375	1.90	0.0	20.8	1.66	282	0.69	0.158	2.654	0.60	-17.2	15.8
DAY 5	319	2.53	2.742	2.00	0.0	22.3	1.73	263	0.76	0.174	2.817	0.70	-16.4	16.7
DAY 8	205	2.18	2.302	1.50	0.0	14.0	1.60	169	0.49	0.197	2.566	0.40	-16.7	8.9
DAY 11	87	2.60	3.064	1.70	0.0	17.3	1.67	69	0.58	0.380	3.159	0.30	-15.0	8.0
DAY 14	31	3.26	4.551	2.00	0.0	20.2	2.09	21	0.96	0.986	4.520	0.20	-10.0	15.2
END IV THERAPY	371	2.48	2.726	1.90	0.0	20.2	1.78	294	0.64	0.169	2.900	0.60	-16.0	15.2
EARLY FOLLOW-UP	408	2.90	2.835	2.15	0.0	20.2	1.73	324	1.14	0.175	3.146	1.00	-16.0	15.2
LATE FOLLOW-UP	173	3.17	3.327	2.20	0.0	24.7	1.70	137	1.46	0.283	3.309	1.20	-7.6	18.7
Pip/Taz														
BASELINE	139	1.43	1.876	1.00	0.0	15.0								
DAY 2/3	129	2.83	3.133	2.00	0.0	22.0	1.38	99	1.26	0.274	2.722	1.00	-11.0	15.0
DAY 5	101	3.54	3.642	2.60	0.0	26.0	1.53	74	1.89	0.426	3.669	1.40	-15.0	19.0
DAY 8	66	2.54	2.561	2.00	0.0	12.0	1.17	51	1.35	0.355	2.535	1.00	-3.0	11.9
DAY 11	38	2.89	2.567	2.00	0.0	10.0	1.18	27	2.01	0.616	3.200	1.00	-3.0	9.1
DAY 14	20	3.90	3.862	3.00	0.0	12.8	1.85	16	2.08	0.960	3.840	1.65	-4.1	9.7
END IV THERAPY	137	3.16	3.046	2.50	0.0	20.0	1.46	110	1.74	0.319	3.343	1.15	-15.0	13.0
EARLY FOLLOW-UP	160	3.39	3.011	2.70	0.0	15.6	1.50	112	1.76	0.340	3.598	1.30	-15.0	14.4
LATE FOLLOW-UP	91	3.30	2.739	2.70	0.0	13.0	1.08	64	2.11	0.350	2.802	1.85	-2.6	12.0
Imi														
BASELINE	222	1.56	1.994	1.00	0.0	12.0								
DAY 2/3	211	2.09	2.097	1.70	0.0	13.0	1.55	183	0.59	0.155	2.100	0.70	-7.3	6.7
DAY 5	188	2.30	2.207	2.00	0.0	11.0	1.56	167	0.73	0.166	2.141	0.40	-7.0	8.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
EOSINOPHILS (%)														
Imi														
DAY 8	126	2.24	2.494	1.60	0.0	15.0	1.51	110	0.76	0.222	2.333	0.40	-9.0	12.0
DAY 11	41	1.82	2.581	1.10	0.0	12.0	1.47	38	0.12	0.419	2.584	0.05	-10.0	7.0
DAY 14	8	1.61	1.562	1.30	0.1	4.0	0.26	5	1.18	0.761	1.702	1.00	-0.9	3.7
END IV THERAPY	211	2.21	2.401	1.90	0.0	23.0	1.47	182	0.69	0.191	2.579	0.50	-6.9	20.0
EARLY FOLLOW-UP	236	2.82	2.820	2.05	0.0	25.3	1.52	201	1.35	0.219	3.098	1.00	-6.9	22.3
LATE FOLLOW-UP	106	3.03	2.553	2.40	0.0	14.7	1.52	91	1.60	0.299	2.849	1.40	-4.9	14.7
EOSINOPHILS, ABS (X10E9/L)														
Dori 500 mg 1-h inf														
BASELINE	146	0.18	0.331	0.10	0.0	3.2								
DAY 2/3	129	0.26	0.269	0.19	0.0	1.9	0.18	94	0.08	0.030	0.292	0.08	-1.7	0.8
DAY 5	130	0.32	0.390	0.25	0.0	2.7	0.19	101	0.16	0.033	0.331	0.09	-0.5	2.1
DAY 8	83	0.27	0.354	0.18	0.0	2.3	0.18	67	0.09	0.036	0.292	0.07	-1.0	1.3
DAY 11	40	0.36	0.432	0.22	0.0	1.9	0.23	32	0.05	0.104	0.586	0.02	-2.7	1.1
DAY 14	12	0.41	0.458	0.25	0.0	1.4	0.17	6	0.06	0.033	0.082	0.03	0.0	0.2
END IV THERAPY	159	0.27	0.330	0.18	0.0	2.2	0.18	115	0.08	0.038	0.412	0.04	-2.9	1.5
EARLY FOLLOW-UP	178	0.33	0.376	0.23	0.0	2.1	0.18	127	0.16	0.042	0.468	0.09	-2.9	1.6
LATE FOLLOW-UP	88	0.29	0.437	0.16	0.0	3.0	0.16	59	0.12	0.053	0.411	0.06	-0.7	2.5
Dori 500 mg 4-h inf														
BASELINE	184	0.20	0.245	0.11	0.0	1.3								
DAY 2/3	180	0.29	0.289	0.21	0.0	1.5	0.21	155	0.09	0.023	0.285	0.06	-1.0	1.1
DAY 5	157	0.28	0.312	0.22	0.0	2.4	0.22	131	0.05	0.025	0.286	0.06	-1.3	0.9
DAY 8	107	0.23	0.252	0.19	0.0	1.5	0.19	87	0.05	0.034	0.319	0.05	-1.0	1.5
DAY 11	44	0.23	0.181	0.20	0.0	0.6	0.21	34	0.03	0.040	0.230	0.03	-0.5	0.6
DAY 14	17	0.33	0.497	0.12	0.0	1.8	0.17	13	0.23	0.121	0.438	0.07	-0.3	1.1
END IV THERAPY	177	0.26	0.303	0.19	0.0	2.4	0.22	145	0.05	0.024	0.289	0.05	-1.3	1.1
EARLY FOLLOW-UP	194	0.24	0.266	0.19	0.0	2.4	0.21	162	0.04	0.023	0.296	0.03	-1.3	1.1
LATE FOLLOW-UP	67	0.23	0.212	0.17	0.0	1.3	0.21	62	0.02	0.032	0.255	0.07	-1.0	0.5
Dori 500 mg														
BASELINE	330	0.19	0.286	0.11	0.0	3.2								

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
EOSINOPHILS, ABS (X10E9/L)														
Dori 500 mg														
DAY 2/3	309	0.27	0.281	0.19	0.0	1.9	0.19	249	0.09	0.018	0.287	0.07	-1.7	1.1
DAY 5	287	0.30	0.349	0.22	0.0	2.7	0.20	232	0.10	0.020	0.310	0.07	-1.3	2.1
DAY 8	190	0.25	0.301	0.19	0.0	2.3	0.18	154	0.07	0.025	0.307	0.05	-1.0	1.5
DAY 11	84	0.29	0.330	0.20	0.0	1.9	0.22	66	0.04	0.054	0.437	0.02	-2.7	1.1
DAY 14	29	0.36	0.475	0.14	0.0	1.8	0.17	19	0.17	0.084	0.368	0.04	-0.3	1.1
END IV THERAPY	336	0.27	0.315	0.19	0.0	2.4	0.20	260	0.06	0.022	0.349	0.04	-2.9	1.5
EARLY FOLLOW-UP	372	0.28	0.326	0.21	0.0	2.4	0.20	289	0.09	0.023	0.386	0.07	-2.9	1.6
LATE FOLLOW-UP	155	0.27	0.358	0.16	0.0	3.0	0.18	121	0.07	0.031	0.342	0.06	-1.0	2.5
Pip/Taz														
BASELINE	139	0.16	0.189	0.12	0.0	1.4								
DAY 2/3	129	0.28	0.307	0.21	0.0	1.9	0.16	99	0.13	0.031	0.306	0.09	-1.1	1.3
DAY 5	101	0.35	0.365	0.26	0.0	2.1	0.17	74	0.19	0.043	0.371	0.16	-1.4	1.6
DAY 8	66	0.28	0.315	0.19	0.0	1.6	0.14	51	0.16	0.045	0.320	0.07	-0.3	1.2
DAY 11	38	0.31	0.287	0.23	0.0	1.1	0.15	27	0.20	0.068	0.355	0.14	-0.7	0.9
DAY 14	20	0.36	0.408	0.29	0.0	1.8	0.22	16	0.15	0.106	0.425	0.09	-0.6	1.1
END IV THERAPY	137	0.30	0.295	0.23	0.0	1.9	0.17	110	0.15	0.033	0.344	0.11	-1.4	1.3
EARLY FOLLOW-UP	160	0.29	0.258	0.25	0.0	1.6	0.17	112	0.11	0.029	0.302	0.08	-1.4	0.9
LATE FOLLOW-UP	91	0.26	0.262	0.20	0.0	2.0	0.13	64	0.14	0.039	0.311	0.10	-0.3	1.9
Imi														
BASELINE	193	0.21	0.313	0.12	0.0	2.5								
DAY 2/3	182	0.26	0.289	0.19	0.0	1.8	0.20	158	0.07	0.024	0.301	0.06	-1.1	1.3
DAY 5	159	0.31	0.323	0.22	0.0	2.3	0.21	140	0.10	0.026	0.302	0.10	-0.9	1.7
DAY 8	112	0.30	0.413	0.19	0.0	2.7	0.20	98	0.11	0.038	0.375	0.04	-0.9	2.1
DAY 11	38	0.23	0.352	0.13	0.0	1.8	0.17	35	0.05	0.051	0.302	0.01	-0.7	1.2
DAY 14	8	0.20	0.177	0.17	0.0	0.5	0.02	5	0.16	0.085	0.191	0.13	-0.0	0.5
END IV THERAPY	180	0.27	0.381	0.19	0.0	4.2	0.19	156	0.09	0.033	0.408	0.06	-0.9	3.6
EARLY FOLLOW-UP	204	0.33	0.433	0.22	0.0	3.9	0.19	174	0.15	0.036	0.475	0.12	-1.1	3.3
LATE FOLLOW-UP	93	0.28	0.253	0.21	0.0	1.6	0.20	79	0.09	0.038	0.342	0.10	-0.9	1.6

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
HAEMATOCRIT (V/V)														
Dori 500 mg 1-h inf														
BASELINE	142	0.33	0.067	0.33	0.2	0.5								
DAY 2/3	127	0.33	0.051	0.33	0.2	0.5	0.33	93	-0.00	0.004	0.040	-0.01	-0.1	0.1
DAY 5	131	0.33	0.055	0.32	0.2	0.5	0.32	103	0.00	0.005	0.047	0.01	-0.1	0.1
DAY 8	82	0.33	0.056	0.33	0.2	0.5	0.32	66	0.00	0.006	0.048	-0.00	-0.1	0.1
DAY 11	40	0.34	0.046	0.34	0.2	0.4	0.33	34	0.01	0.010	0.057	0.02	-0.1	0.1
DAY 14	15	0.32	0.050	0.32	0.2	0.4	0.32	11	0.01	0.020	0.066	0.03	-0.1	0.1
END IV THERAPY	162	0.34	0.055	0.34	0.2	0.5	0.33	114	0.01	0.005	0.049	0.01	-0.1	0.1
EARLY FOLLOW-UP	175	0.35	0.055	0.35	0.2	0.5	0.33	124	0.02	0.006	0.063	0.02	-0.1	0.2
LATE FOLLOW-UP	91	0.38	0.057	0.39	0.2	0.5	0.33	57	0.05	0.011	0.083	0.06	-0.2	0.3
Dori 500 mg 4-h inf														
BASELINE	206	0.30	0.051	0.29	0.2	0.5								
DAY 2/3	211	0.29	0.044	0.29	0.2	0.4	0.29	171	-0.00	0.003	0.034	-0.00	-0.1	0.1
DAY 5	189	0.30	0.049	0.30	0.2	0.4	0.29	148	0.01	0.003	0.042	0.00	-0.1	0.1
DAY 8	123	0.30	0.054	0.29	0.2	0.5	0.30	100	0.01	0.004	0.044	0.01	-0.1	0.1
DAY 11	47	0.29	0.036	0.29	0.2	0.4	0.29	32	-0.00	0.009	0.051	-0.00	-0.1	0.1
DAY 14	18	0.29	0.036	0.29	0.2	0.3	0.29	13	-0.00	0.013	0.047	0.02	-0.1	0.0
END IV THERAPY	215	0.31	0.049	0.31	0.2	0.5	0.30	169	0.01	0.004	0.047	0.01	-0.1	0.1
EARLY FOLLOW-UP	233	0.32	0.053	0.31	0.2	0.5	0.29	183	0.02	0.004	0.057	0.02	-0.1	0.2
LATE FOLLOW-UP	84	0.36	0.045	0.37	0.3	0.5	0.29	71	0.07	0.007	0.060	0.07	-0.1	0.2
Dori 500 mg														
BASELINE	348	0.31	0.061	0.30	0.2	0.5								
DAY 2/3	338	0.31	0.050	0.30	0.2	0.5	0.31	264	-0.00	0.002	0.036	-0.00	-0.1	0.1
DAY 5	320	0.31	0.053	0.31	0.2	0.5	0.31	251	0.00	0.003	0.044	0.00	-0.1	0.1
DAY 8	205	0.31	0.056	0.30	0.2	0.5	0.31	166	0.00	0.004	0.046	0.00	-0.1	0.1
DAY 11	87	0.31	0.047	0.31	0.2	0.4	0.31	66	0.00	0.007	0.054	0.01	-0.1	0.1
DAY 14	33	0.30	0.047	0.31	0.2	0.4	0.30	24	0.00	0.011	0.055	0.02	-0.1	0.1
END IV THERAPY	377	0.32	0.054	0.32	0.2	0.5	0.31	283	0.01	0.003	0.048	0.01	-0.1	0.1
EARLY FOLLOW-UP	408	0.33	0.057	0.33	0.2	0.5	0.31	307	0.02	0.003	0.059	0.02	-0.1	0.2
LATE FOLLOW-UP	175	0.37	0.052	0.38	0.2	0.5	0.31	128	0.06	0.006	0.072	0.07	-0.2	0.3

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
HAEMATOCRIT (V/V)														
Pip/Taz														
BASELINE	135	0.34	0.063	0.34	0.2	0.5								
DAY 2/3	128	0.33	0.056	0.32	0.2	0.5	0.33	101	-0.00	0.004	0.044	-0.01	-0.1	0.2
DAY 5	101	0.33	0.052	0.32	0.2	0.5	0.33	73	-0.01	0.006	0.052	-0.01	-0.1	0.2
DAY 8	64	0.33	0.052	0.31	0.2	0.5	0.33	50	-0.01	0.006	0.040	-0.01	-0.1	0.1
DAY 11	42	0.32	0.049	0.31	0.2	0.4	0.33	29	-0.01	0.010	0.055	-0.02	-0.2	0.1
DAY 14	21	0.31	0.043	0.31	0.2	0.4	0.34	16	-0.03	0.020	0.079	-0.01	-0.2	0.1
END IV THERAPY	137	0.34	0.058	0.33	0.2	0.5	0.34	110	-0.00	0.006	0.060	-0.00	-0.2	0.2
EARLY FOLLOW-UP	158	0.36	0.059	0.36	0.2	0.5	0.34	110	0.01	0.006	0.065	0.01	-0.2	0.2
LATE FOLLOW-UP	89	0.38	0.057	0.39	0.2	0.5	0.34	61	0.04	0.009	0.070	0.05	-0.1	0.2
Imi														
BASELINE	214	0.29	0.053	0.29	0.2	0.6								
DAY 2/3	210	0.29	0.051	0.29	0.2	0.6	0.30	175	-0.01	0.003	0.034	-0.01	-0.1	0.1
DAY 5	191	0.30	0.049	0.30	0.2	0.5	0.30	163	-0.00	0.003	0.043	0.00	-0.1	0.1
DAY 8	124	0.31	0.054	0.30	0.2	0.5	0.30	106	0.01	0.005	0.054	0.00	-0.2	0.2
DAY 11	39	0.30	0.049	0.29	0.2	0.4	0.30	34	0.00	0.010	0.057	0.01	-0.1	0.1
DAY 14	7	0.29	0.042	0.27	0.2	0.4	0.27	5	0.03	0.020	0.045	0.03	-0.0	0.1
END IV THERAPY	213	0.30	0.050	0.30	0.2	0.5	0.30	178	0.01	0.004	0.049	0.01	-0.2	0.1
EARLY FOLLOW-UP	234	0.32	0.056	0.31	0.2	0.5	0.30	194	0.02	0.004	0.059	0.03	-0.2	0.2
LATE FOLLOW-UP	107	0.35	0.061	0.36	0.2	0.5	0.30	90	0.06	0.008	0.075	0.06	-0.2	0.3
HAEMOGLOBIN (G/L)														
Dori 500 mg 1-h inf														
BASELINE	157	108.62	20.984	107.00	59.0	170.0								
DAY 2/3	138	107.63	17.124	107.00	78.0	164.0	108.64	107	-1.37	1.192	12.335	-2.00	-29.0	35.0
DAY 5	137	106.77	18.352	105.00	65.0	168.0	105.22	112	-0.21	1.381	14.612	0.00	-40.0	34.0
DAY 8	85	105.65	18.575	104.00	60.0	143.0	104.67	73	-0.45	1.869	15.969	-2.00	-34.0	41.0
DAY 11	41	108.78	15.717	110.00	78.0	138.0	106.86	36	1.17	3.056	18.334	0.00	-35.0	43.0
DAY 14	15	104.87	17.200	100.00	77.0	133.0	103.09	11	2.91	6.092	20.206	9.00	-39.0	26.0
END IV THERAPY	168	110.14	18.193	108.00	65.0	166.0	107.75	129	1.09	1.292	14.674	1.00	-44.0	35.0
EARLY FOLLOW-UP	181	114.42	18.609	115.00	69.0	158.0	107.62	138	5.81	1.668	19.596	4.50	-41.0	74.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
HAEMOGLOBIN (G/L)														
Dori 500 mg 1-h inf														
LATE FOLLOW-UP	93	122.97	19.795	125.00	75.0	167.0	107.89	66	14.68	2.995	24.331	15.00	-60.0	81.0
Dori 500 mg 4-h inf														
BASELINE	233	96.95	15.956	95.00	54.0	150.0								
DAY 2/3	225	96.19	14.523	95.00	66.0	141.0	96.54	205	-0.48	0.740	10.597	-1.00	-21.0	39.0
DAY 5	198	98.91	15.790	98.00	66.0	153.0	96.61	175	2.29	1.002	13.249	1.00	-35.0	39.0
DAY 8	128	98.52	17.797	96.00	64.0	152.0	98.34	112	0.80	1.372	14.516	1.00	-40.0	42.0
DAY 11	50	94.38	11.462	92.50	76.0	121.0	94.86	42	-0.81	2.347	15.208	0.00	-38.0	34.0
DAY 14	19	92.58	10.731	95.00	71.0	110.0	93.75	16	-1.50	3.373	13.491	2.00	-29.0	18.0
END IV THERAPY	224	100.20	16.111	99.50	64.0	152.0	96.79	198	3.12	1.074	15.108	3.00	-39.0	39.0
EARLY FOLLOW-UP	234	103.53	17.475	103.00	52.0	155.0	96.55	208	7.21	1.208	17.418	6.00	-36.0	50.0
LATE FOLLOW-UP	88	118.57	15.591	119.00	82.0	156.0	95.79	81	23.06	2.097	18.872	26.00	-17.0	62.0
Dori 500 mg														
BASELINE	390	101.65	19.008	99.00	54.0	170.0								
DAY 2/3	363	100.54	16.506	98.00	66.0	164.0	100.69	312	-0.79	0.635	11.211	-1.50	-29.0	39.0
DAY 5	335	102.13	17.297	101.00	65.0	168.0	99.97	287	1.31	0.816	13.826	1.00	-40.0	39.0
DAY 8	213	101.36	18.404	99.00	60.0	152.0	100.84	185	0.31	1.108	15.075	-1.00	-40.0	42.0
DAY 11	91	100.87	15.272	100.00	76.0	138.0	100.40	78	0.10	1.884	16.641	0.00	-38.0	43.0
DAY 14	34	98.00	15.055	98.50	71.0	133.0	97.56	27	0.30	3.144	16.337	4.00	-39.0	26.0
END IV THERAPY	392	104.46	17.710	102.50	64.0	166.0	101.11	327	2.32	0.827	14.949	2.00	-44.0	39.0
EARLY FOLLOW-UP	415	108.28	18.752	107.00	52.0	158.0	100.97	346	6.65	0.984	18.303	6.00	-41.0	74.0
LATE FOLLOW-UP	181	120.83	17.962	122.00	75.0	167.0	101.22	147	19.30	1.800	21.822	21.00	-60.0	81.0
Pip/Taz														
BASELINE	146	111.16	20.467	112.00	62.0	156.0								
DAY 2/3	137	107.55	18.067	105.00	71.0	167.0	108.34	110	-0.50	1.412	14.807	-2.00	-38.0	57.0
DAY 5	104	106.41	17.254	102.50	76.0	158.0	108.13	80	-3.43	1.871	16.731	-3.50	-39.0	58.0
DAY 8	66	106.92	17.654	104.50	71.0	157.0	107.40	53	-3.87	1.881	13.692	-6.00	-28.0	31.0
DAY 11	43	103.51	16.840	103.00	67.0	137.0	106.28	32	-4.25	3.173	17.952	-4.00	-64.0	25.0
DAY 14	21	100.76	16.370	97.00	77.0	144.0	107.89	18	-7.56	5.937	25.187	-1.00	-54.0	37.0
END IV THERAPY	143	111.48	19.392	109.00	74.0	158.0	109.63	119	-1.08	1.659	18.095	0.00	-54.0	52.0
EARLY FOLLOW-UP	163	116.11	20.616	116.00	73.0	169.0	109.93	121	2.67	1.885	20.730	2.00	-63.0	54.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
HAEMOGLOBIN (G/L)														
Pip/Taz														
LATE FOLLOW-UP	93	124.20	19.659	124.00	80.0	167.0	111.28	68	10.34	2.767	22.818	12.00	-51.0	71.0
Imi														
BASELINE	232	97.33	16.832	95.00	63.0	187.0								
DAY 2/3	221	96.15	15.817	94.00	63.0	188.0	97.60	198	-2.51	0.783	11.017	-4.00	-29.0	29.0
DAY 5	201	97.58	15.979	98.00	63.0	159.0	97.50	183	-0.74	1.013	13.698	-1.00	-44.0	36.0
DAY 8	128	100.02	16.560	98.00	67.0	161.0	98.79	119	0.69	1.546	16.870	-1.00	-52.0	54.0
DAY 11	42	98.50	15.153	96.00	67.0	137.0	98.44	39	-0.90	2.765	17.267	1.00	-54.0	34.0
DAY 14	8	103.00	26.252	91.50	80.0	159.0	88.67	6	6.83	5.930	14.525	5.00	-11.0	32.0
END IV THERAPY	221	99.30	16.591	97.00	61.0	178.0	97.57	196	1.43	1.072	15.007	0.50	-55.0	37.0
EARLY FOLLOW-UP	241	104.07	17.955	102.00	69.0	165.0	97.44	214	6.48	1.263	18.476	8.00	-80.0	50.0
LATE FOLLOW-UP	107	114.96	20.244	115.00	61.0	161.0	97.27	97	18.46	2.333	22.981	20.00	-50.0	79.0
LYMPHOCYTES (%)														
Dori 500 mg 1-h inf														
BASELINE	146	10.88	6.578	9.45	1.0	35.9								
DAY 2/3	129	12.64	7.846	10.10	1.0	48.9	10.41	94	1.17	0.710	6.882	1.20	-24.0	18.4
DAY 5	130	14.80	8.403	13.00	1.6	50.0	10.94	101	3.00	0.748	7.519	2.40	-19.0	27.0
DAY 8	83	13.26	7.720	10.90	1.0	35.5	9.87	67	2.19	0.898	7.349	0.60	-17.9	26.7
DAY 11	40	11.16	6.743	10.00	1.0	27.1	8.52	32	1.38	1.041	5.887	0.25	-8.8	18.0
DAY 14	12	14.26	6.150	13.95	3.6	26.7	10.65	6	0.95	3.000	7.348	-1.80	-5.4	10.2
END IV THERAPY	159	16.55	9.033	15.80	1.0	40.5	10.97	115	4.49	0.806	8.638	3.30	-17.9	35.0
EARLY FOLLOW-UP	178	19.42	9.927	18.60	1.0	45.0	11.03	127	7.20	0.876	9.868	4.80	-8.7	39.6
LATE FOLLOW-UP	88	25.85	10.565	26.30	5.0	52.5	11.89	59	13.62	1.363	10.470	13.30	-6.3	40.8
Dori 500 mg 4-h inf														
BASELINE	221	10.89	6.398	10.00	1.0	44.0								
DAY 2/3	214	11.95	5.815	11.25	1.0	35.0	11.04	188	0.97	0.471	6.457	1.00	-29.0	22.0
DAY 5	189	12.55	6.035	12.00	1.7	39.0	10.96	162	1.26	0.544	6.920	2.00	-26.0	21.7
DAY 8	122	13.56	6.948	12.30	1.8	42.0	10.63	102	2.86	0.697	7.043	2.00	-13.6	22.3
DAY 11	47	14.01	7.019	13.00	0.0	38.0	11.08	37	2.96	1.150	6.997	3.00	-11.0	19.1
DAY 14	19	17.54	8.159	16.00	6.0	39.0	14.94	15	4.23	1.600	6.197	4.00	-5.0	13.8

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
LYMPHOCYTES (%)														
Dori 500 mg 4-h inf														
END IV THERAPY	212	14.21	7.004	13.85	2.6	40.4	10.99	179	3.01	0.534	7.148	2.40	-14.0	22.5
EARLY FOLLOW-UP	230	16.06	7.801	15.20	2.6	47.0	10.69	197	5.25	0.582	8.173	5.00	-29.0	36.1
LATE FOLLOW-UP	85	23.83	10.138	23.10	4.8	51.0	11.00	78	13.26	1.387	12.246	12.40	-24.2	40.6
Dori 500 mg														
BASELINE	367	10.89	6.461	10.00	1.0	44.0								
DAY 2/3	343	12.21	6.649	11.00	1.0	48.9	10.83	282	1.04	0.392	6.590	1.00	-29.0	22.0
DAY 5	319	13.47	7.170	12.00	1.6	50.0	10.96	263	1.93	0.443	7.192	2.00	-26.0	27.0
DAY 8	205	13.44	7.253	12.00	1.0	42.0	10.33	169	2.59	0.550	7.152	1.70	-17.9	26.7
DAY 11	87	12.70	7.001	12.00	0.0	38.0	9.89	69	2.22	0.783	6.508	2.40	-11.0	19.1
DAY 14	31	16.27	7.514	15.00	3.6	39.0	13.71	21	3.30	1.426	6.534	2.40	-5.4	13.8
END IV THERAPY	371	15.21	8.010	14.10	1.0	40.5	10.98	294	3.59	0.454	7.784	2.50	-17.9	35.0
EARLY FOLLOW-UP	408	17.53	8.938	16.00	1.0	47.0	10.82	324	6.01	0.495	8.912	5.00	-29.0	39.6
LATE FOLLOW-UP	173	24.86	10.377	24.90	4.8	52.5	11.38	137	13.41	0.980	11.476	13.00	-24.2	40.8
Pip/Taz														
BASELINE	139	10.72	6.803	9.00	1.0	44.5								
DAY 2/3	129	13.36	8.023	11.50	2.0	43.0	9.76	99	1.94	0.511	5.084	2.00	-8.3	19.3
DAY 5	101	14.03	6.977	12.00	2.0	33.8	9.75	74	2.98	0.727	6.252	2.70	-9.0	19.0
DAY 8	66	11.57	5.677	10.85	3.0	25.9	8.40	51	2.77	0.839	5.993	2.10	-9.3	19.3
DAY 11	38	14.01	7.453	13.10	2.6	30.0	8.57	27	4.06	1.453	7.550	2.50	-12.8	25.1
DAY 14	20	11.89	5.691	11.65	3.0	23.6	8.68	16	3.32	1.971	7.884	3.85	-14.1	18.1
END IV THERAPY	137	15.35	7.684	14.50	3.0	38.2	10.26	110	4.07	0.669	7.015	3.90	-14.1	23.2
EARLY FOLLOW-UP	160	20.40	10.952	19.25	3.0	55.3	10.96	112	7.52	0.916	9.694	6.45	-16.3	32.0
LATE FOLLOW-UP	91	27.42	11.282	28.00	2.5	56.8	9.59	64	16.62	1.451	11.609	16.65	-12.0	42.9
Imi														
BASELINE	222	9.29	5.533	8.00	1.0	40.0								
DAY 2/3	211	11.25	6.785	10.00	1.0	43.6	9.23	183	1.90	0.440	5.952	1.80	-17.6	32.8
DAY 5	188	11.82	6.541	10.00	2.0	36.1	9.21	167	2.60	0.523	6.753	2.10	-24.0	21.8
DAY 8	125	12.32	7.849	11.80	1.0	56.2	9.60	109	2.47	0.693	7.232	1.00	-20.0	37.2
DAY 11	41	12.17	6.314	11.20	3.0	26.3	7.75	38	3.73	0.884	5.448	4.90	-6.0	17.3
DAY 14	8	13.14	4.182	13.05	8.1	20.7	8.64	5	4.34	3.114	6.963	6.00	-7.6	10.7

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
LYMPHOCYTES (%)														
Imi														
END IV THERAPY	211	12.00	6.090	11.80	1.0	36.0	9.29	182	2.55	0.451	6.089	2.75	-22.0	20.3
EARLY FOLLOW-UP	236	15.88	8.768	14.35	1.0	50.0	9.20	201	6.40	0.546	7.743	5.90	-15.0	28.5
LATE FOLLOW-UP	106	23.18	10.872	22.05	4.0	65.2	9.75	91	12.90	1.075	10.250	12.40	-15.0	32.8
LYMPHOCYTES, ABS (X10E9/L)														
Dori 500 mg 1-h inf														
BASELINE	146	1.20	0.647	1.10	0.1	3.5								
DAY 2/3	129	1.37	0.672	1.33	0.1	4.9	1.19	94	0.16	0.075	0.729	0.14	-2.0	3.7
DAY 5	130	1.57	0.795	1.48	0.3	5.4	1.24	101	0.34	0.070	0.700	0.26	-1.8	2.6
DAY 8	83	1.43	0.636	1.40	0.2	3.2	1.12	67	0.31	0.084	0.684	0.20	-1.0	2.3
DAY 11	40	1.31	0.742	1.18	0.2	3.5	1.05	32	0.23	0.136	0.769	0.10	-0.8	2.1
DAY 14	12	1.60	0.631	1.61	0.7	2.6	1.20	6	0.19	0.314	0.769	0.27	-0.8	1.2
END IV THERAPY	159	1.61	0.773	1.56	0.2	5.4	1.20	115	0.36	0.069	0.736	0.29	-1.8	2.4
EARLY FOLLOW-UP	178	1.75	0.808	1.68	0.3	5.7	1.22	127	0.51	0.077	0.868	0.41	-1.5	3.8
LATE FOLLOW-UP	88	2.10	0.986	1.91	0.5	5.5	1.25	59	0.86	0.138	1.057	0.82	-1.0	4.4
Dori 500 mg 4-h inf														
BASELINE	184	1.31	0.777	1.16	0.3	4.6								
DAY 2/3	180	1.44	0.740	1.25	0.1	4.4	1.32	155	0.11	0.064	0.799	0.11	-3.0	3.0
DAY 5	157	1.56	0.916	1.42	0.4	8.3	1.30	131	0.21	0.072	0.826	0.31	-2.8	2.2
DAY 8	107	1.62	0.824	1.41	0.3	4.8	1.25	87	0.33	0.099	0.924	0.39	-2.4	3.4
DAY 11	44	1.50	0.627	1.43	0.0	3.2	1.22	34	0.29	0.142	0.825	0.27	-2.0	2.6
DAY 14	17	1.71	0.941	1.45	0.7	4.5	1.46	13	0.40	0.230	0.831	0.39	-1.3	2.2
END IV THERAPY	177	1.66	0.889	1.52	0.1	8.4	1.30	145	0.37	0.084	1.014	0.35	-2.8	6.4
EARLY FOLLOW-UP	194	1.63	0.814	1.52	0.1	6.5	1.28	162	0.37	0.071	0.910	0.43	-2.4	4.6
LATE FOLLOW-UP	67	1.91	0.748	1.82	0.5	4.0	1.23	62	0.67	0.112	0.879	0.66	-1.8	2.5
Dori 500 mg														
BASELINE	330	1.26	0.724	1.12	0.1	4.6								
DAY 2/3	309	1.41	0.712	1.29	0.1	4.9	1.27	249	0.13	0.049	0.772	0.14	-3.0	3.7
DAY 5	287	1.57	0.862	1.43	0.3	8.3	1.28	232	0.27	0.051	0.775	0.28	-2.8	2.6
DAY 8	190	1.53	0.752	1.41	0.2	4.8	1.19	154	0.32	0.067	0.826	0.26	-2.4	3.4

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
LYMPHOCYTES, ABS (X10E9/L)														
Dori 500 mg														
DAY 11	84	1.41	0.687	1.35	0.0	3.5	1.14	66	0.26	0.098	0.793	0.19	-2.0	2.6
DAY 14	29	1.67	0.816	1.45	0.7	4.5	1.38	19	0.33	0.183	0.797	0.36	-1.3	2.2
END IV THERAPY	336	1.64	0.835	1.55	0.1	8.4	1.26	260	0.36	0.056	0.900	0.33	-2.8	6.4
EARLY FOLLOW-UP	372	1.69	0.812	1.60	0.1	6.5	1.25	289	0.43	0.053	0.893	0.42	-2.4	4.6
LATE FOLLOW-UP	155	2.02	0.894	1.86	0.5	5.5	1.24	121	0.77	0.088	0.971	0.73	-1.8	4.4
Pip/Taz														
BASELINE	139	1.25	0.625	1.12	0.2	4.1								
DAY 2/3	129	1.32	0.650	1.19	0.3	4.2	1.26	99	0.04	0.062	0.619	0.08	-1.4	2.4
DAY 5	101	1.40	0.676	1.25	0.2	3.7	1.22	74	0.13	0.075	0.643	0.04	-1.5	2.2
DAY 8	66	1.24	0.576	1.17	0.3	3.1	1.10	51	0.20	0.088	0.628	0.23	-1.3	2.0
DAY 11	38	1.44	0.714	1.43	0.3	2.7	1.06	27	0.31	0.125	0.648	0.19	-1.1	1.3
DAY 14	20	1.16	0.745	0.94	0.4	3.3	1.00	16	0.23	0.164	0.657	0.27	-1.0	1.6
END IV THERAPY	137	1.45	0.680	1.35	0.4	4.5	1.28	110	0.14	0.070	0.729	0.18	-2.9	2.8
EARLY FOLLOW-UP	160	1.74	0.822	1.63	0.4	4.6	1.31	112	0.35	0.070	0.745	0.30	-1.7	2.6
LATE FOLLOW-UP	91	2.15	0.884	2.07	0.3	4.9	1.22	64	0.97	0.136	1.090	0.93	-1.6	3.4
Imi														
BASELINE	193	1.27	1.051	1.01	0.1	11.3								
DAY 2/3	182	1.40	0.803	1.28	0.2	4.2	1.21	158	0.18	0.060	0.759	0.15	-1.8	2.9
DAY 5	159	1.54	0.798	1.37	0.4	4.8	1.27	140	0.31	0.096	1.133	0.32	-8.7	3.9
DAY 8	111	1.59	1.152	1.38	0.1	7.4	1.30	97	0.25	0.098	0.961	0.29	-3.9	3.8
DAY 11	38	1.63	0.899	1.45	0.4	3.8	1.10	35	0.55	0.151	0.896	0.40	-1.0	2.8
DAY 14	8	1.84	0.434	1.82	1.3	2.5	1.15	5	0.60	0.233	0.520	0.78	-0.3	0.9
END IV THERAPY	180	1.44	0.749	1.31	0.3	3.5	1.23	156	0.23	0.063	0.783	0.21	-2.4	1.9
EARLY FOLLOW-UP	204	1.63	0.958	1.46	0.1	9.6	1.23	174	0.40	0.063	0.834	0.36	-2.1	3.4
LATE FOLLOW-UP	93	1.99	0.889	1.82	0.5	5.1	1.27	79	0.71	0.125	1.115	0.70	-6.2	2.8
MCH (PG/CELL)														
Dori 500 mg 1-h inf														
BASELINE	157	30.43	1.865	30.00	23.0	35.0								
DAY 2/3	138	29.97	2.171	30.00	22.0	35.0	30.32	107	-0.13	0.068	0.702	0.00	-2.0	2.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MCH (PG/CELL)														
Dori 500 mg 1-h inf														
DAY 5	137	30.19	1.857	30.00	23.0	36.0	30.34	112	-0.13	0.076	0.800	0.00	-2.0	2.0
DAY 8	85	30.15	2.056	30.00	23.0	35.0	30.36	73	-0.12	0.085	0.725	0.00	-1.0	2.0
DAY 11	41	29.85	1.982	30.00	22.0	34.0	30.28	36	-0.36	0.160	0.961	0.00	-3.0	1.0
DAY 14	15	30.27	1.438	30.00	28.0	33.0	30.45	11	0.00	0.191	0.632	0.00	-1.0	1.0
END IV THERAPY	168	30.02	2.057	30.00	22.0	35.0	30.37	129	-0.19	0.071	0.811	0.00	-2.0	2.0
EARLY FOLLOW-UP	181	29.78	2.104	30.00	21.0	35.0	30.39	138	-0.43	0.090	1.053	0.00	-5.0	4.0
LATE FOLLOW-UP	93	29.80	2.366	30.00	22.0	36.0	30.56	66	-0.68	0.172	1.394	-1.00	-4.0	5.0
Dori 500 mg 4-h inf														
BASELINE	233	30.99	1.903	31.00	24.0	40.0								
DAY 2/3	225	30.78	1.736	31.00	24.0	36.0	30.99	205	-0.22	0.057	0.816	0.00	-5.0	2.0
DAY 5	198	30.67	1.785	31.00	24.0	36.0	30.95	175	-0.29	0.063	0.838	0.00	-5.0	2.0
DAY 8	128	30.58	1.855	31.00	24.0	35.0	30.86	112	-0.38	0.078	0.830	0.00	-3.0	1.0
DAY 11	50	30.36	1.770	30.00	27.0	35.0	30.83	42	-0.52	0.157	1.018	-1.00	-3.0	2.0
DAY 14	19	30.05	1.580	30.00	27.0	34.0	30.13	16	-0.38	0.239	0.957	-0.50	-2.0	2.0
END IV THERAPY	223	30.57	1.581	31.00	24.0	35.0	30.99	197	-0.43	0.067	0.937	0.00	-5.0	2.0
EARLY FOLLOW-UP	234	30.36	1.539	30.00	25.0	34.0	30.93	208	-0.55	0.074	1.062	0.00	-6.0	2.0
LATE FOLLOW-UP	88	29.72	1.813	30.00	25.0	34.0	30.44	81	-0.70	0.170	1.528	-1.00	-7.0	2.0
Dori 500 mg														
BASELINE	390	30.76	1.905	31.00	23.0	40.0								
DAY 2/3	363	30.47	1.950	31.00	22.0	36.0	30.76	312	-0.19	0.044	0.778	0.00	-5.0	2.0
DAY 5	335	30.47	1.828	30.00	23.0	36.0	30.71	287	-0.23	0.049	0.825	0.00	-5.0	2.0
DAY 8	213	30.41	1.944	30.00	23.0	35.0	30.66	185	-0.28	0.059	0.799	0.00	-3.0	2.0
DAY 11	91	30.13	1.875	30.00	22.0	35.0	30.58	78	-0.45	0.112	0.989	-0.50	-3.0	2.0
DAY 14	34	30.15	1.500	30.00	27.0	34.0	30.26	27	-0.22	0.163	0.847	0.00	-2.0	2.0
END IV THERAPY	391	30.33	1.819	30.00	22.0	35.0	30.75	326	-0.33	0.050	0.895	0.00	-5.0	2.0
EARLY FOLLOW-UP	415	30.11	1.828	30.00	21.0	35.0	30.71	346	-0.50	0.057	1.058	0.00	-6.0	4.0
LATE FOLLOW-UP	181	29.76	2.110	30.00	22.0	36.0	30.50	147	-0.69	0.121	1.465	-1.00	-7.0	5.0
Pip/Taz														
BASELINE	146	30.42	2.409	30.00	20.0	38.0								
DAY 2/3	137	30.06	2.281	30.00	21.0	37.0	30.35	110	-0.20	0.067	0.701	0.00	-3.0	1.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MCH (PG/CELL)														
Pip/Taz														
DAY 5	104	29.97	2.083	30.00	26.0	36.0	30.16	80	-0.26	0.073	0.651	0.00	-2.0	1.0
DAY 8	66	30.12	2.019	30.00	26.0	36.0	30.49	53	-0.42	0.095	0.692	0.00	-2.0	1.0
DAY 11	43	29.86	1.934	30.00	25.0	34.0	30.19	32	-0.34	0.153	0.865	0.00	-2.0	1.0
DAY 14	21	29.71	1.875	29.00	27.0	34.0	29.72	18	-0.11	0.212	0.900	0.00	-2.0	1.0
END IV THERAPY	143	30.25	2.263	30.00	21.0	37.0	30.39	119	-0.24	0.080	0.873	0.00	-2.0	3.0
EARLY FOLLOW-UP	163	29.96	2.274	30.00	20.0	36.0	30.37	121	-0.34	0.106	1.166	0.00	-4.0	4.0
LATE FOLLOW-UP	93	29.78	1.999	30.00	23.0	35.0	30.44	68	-0.78	0.211	1.744	-1.00	-7.0	5.0
Imi														
BASELINE	232	30.81	1.740	31.00	24.0	37.0								
DAY 2/3	221	30.69	1.728	31.00	23.0	36.0	30.84	198	-0.16	0.056	0.794	0.00	-3.0	3.0
DAY 5	201	30.54	1.691	31.00	23.0	36.0	30.84	183	-0.30	0.060	0.814	0.00	-3.0	3.0
DAY 8	128	30.48	2.485	30.00	24.0	53.0	30.59	119	-0.08	0.219	2.394	0.00	-3.0	24.0
DAY 11	42	30.57	1.399	30.50	28.0	34.0	30.74	39	-0.18	0.132	0.823	0.00	-2.0	2.0
DAY 14	8	30.00	1.195	30.50	28.0	31.0	29.17	6	0.50	0.224	0.548	0.50	0.0	1.0
END IV THERAPY	221	30.49	1.568	31.00	23.0	34.0	30.84	196	-0.33	0.069	0.970	0.00	-3.0	2.0
EARLY FOLLOW-UP	241	30.33	1.653	30.00	23.0	35.0	30.85	214	-0.49	0.077	1.121	0.00	-4.0	3.0
LATE FOLLOW-UP	107	29.71	1.858	30.00	23.0	36.0	30.46	97	-0.85	0.157	1.543	-1.00	-5.0	4.0
MCHC (GHB/L)														
Dori 500 mg 1-h inf														
BASELINE	142	328.80	13.500	330.00	290.0	360.0								
DAY 2/3	127	326.77	13.445	330.00	280.0	350.0	328.39	93	-2.04	1.219	11.755	0.00	-40.0	30.0
DAY 5	131	327.10	12.057	330.00	280.0	370.0	328.74	103	-2.43	1.175	11.920	0.00	-40.0	30.0
DAY 8	82	326.10	13.945	330.00	280.0	350.0	327.58	66	-2.42	1.465	11.905	0.00	-30.0	20.0
DAY 11	40	323.25	12.066	320.00	290.0	350.0	327.35	34	-4.12	2.158	12.581	-10.00	-30.0	20.0
DAY 14	15	322.67	12.228	320.00	310.0	350.0	325.45	11	-3.64	3.377	11.201	0.00	-30.0	10.0
END IV THERAPY	162	325.06	13.010	330.00	280.0	350.0	329.12	114	-5.09	1.235	13.187	0.00	-40.0	30.0
EARLY FOLLOW-UP	175	324.17	11.904	330.00	280.0	350.0	328.23	124	-4.92	1.182	13.159	0.00	-40.0	20.0
LATE FOLLOW-UP	91	324.29	12.662	330.00	280.0	350.0	327.54	57	-3.51	1.553	11.725	0.00	-30.0	20.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MCHC (GHB/L)														
Dori 500 mg 4-h inf														
BASELINE	206	330.05	12.973	330.00	280.0	360.0								
DAY 2/3	211	328.53	11.760	330.00	290.0	350.0	329.94	171	-1.58	0.883	11.549	0.00	-40.0	30.0
DAY 5	189	328.84	11.747	330.00	300.0	350.0	329.86	148	-1.15	0.985	11.982	0.00	-40.0	40.0
DAY 8	123	327.64	11.879	330.00	280.0	350.0	329.50	100	-1.90	1.134	11.344	0.00	-30.0	30.0
DAY 11	47	325.11	9.526	330.00	300.0	350.0	330.31	32	-4.38	2.005	11.341	0.00	-30.0	30.0
DAY 14	18	323.89	11.448	325.00	300.0	340.0	323.08	13	0.77	3.093	11.152	0.00	-20.0	20.0
END IV THERAPY	215	326.60	12.001	330.00	280.0	350.0	329.29	169	-2.60	0.936	12.163	0.00	-30.0	30.0
EARLY FOLLOW-UP	233	327.30	11.024	330.00	290.0	360.0	329.95	183	-2.30	0.959	12.974	0.00	-30.0	40.0
LATE FOLLOW-UP	84	325.60	11.858	320.00	280.0	350.0	327.89	71	-1.55	1.972	16.617	0.00	-60.0	40.0
Dori 500 mg														
BASELINE	348	329.54	13.185	330.00	280.0	360.0								
DAY 2/3	338	327.87	12.430	330.00	280.0	350.0	329.39	264	-1.74	0.714	11.602	0.00	-40.0	30.0
DAY 5	320	328.13	11.887	330.00	280.0	370.0	329.40	251	-1.67	0.754	11.949	0.00	-40.0	40.0
DAY 8	205	327.02	12.735	330.00	280.0	350.0	328.73	166	-2.11	0.895	11.537	0.00	-30.0	30.0
DAY 11	87	324.25	10.744	320.00	290.0	350.0	328.79	66	-4.24	1.465	11.905	-5.00	-30.0	30.0
DAY 14	33	323.33	11.637	320.00	300.0	350.0	324.17	24	-1.25	2.277	11.156	0.00	-30.0	20.0
END IV THERAPY	377	325.94	12.451	330.00	280.0	350.0	329.22	283	-3.60	0.750	12.622	0.00	-40.0	30.0
EARLY FOLLOW-UP	408	325.96	11.500	330.00	280.0	360.0	329.25	307	-3.36	0.747	13.091	0.00	-40.0	40.0
LATE FOLLOW-UP	175	324.91	12.265	330.00	280.0	350.0	327.73	128	-2.42	1.292	14.621	0.00	-60.0	40.0
Pip/Taz														
BASELINE	134	327.46	16.392	330.00	270.0	370.0								
DAY 2/3	128	327.19	14.469	330.00	270.0	350.0	326.70	100	0.50	1.192	11.924	0.00	-50.0	30.0
DAY 5	101	325.94	15.309	330.00	270.0	350.0	326.81	72	-1.53	1.198	10.162	0.00	-30.0	20.0
DAY 8	64	327.19	12.783	330.00	290.0	350.0	327.40	50	0.20	1.840	13.013	0.00	-30.0	50.0
DAY 11	42	323.57	13.937	330.00	290.0	350.0	326.55	29	-3.10	1.992	10.725	0.00	-20.0	30.0
DAY 14	21	322.38	13.002	320.00	300.0	340.0	322.50	16	-1.88	3.561	14.245	0.00	-20.0	30.0
END IV THERAPY	137	324.16	16.344	330.00	280.0	380.0	326.42	109	-3.30	1.188	12.402	0.00	-40.0	40.0
EARLY FOLLOW-UP	158	324.05	14.932	330.00	270.0	360.0	326.15	109	-3.21	1.322	13.803	0.00	-40.0	40.0
LATE FOLLOW-UP	89	323.60	15.539	330.00	280.0	350.0	326.23	61	-5.25	1.820	14.213	0.00	-40.0	30.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MCHC (GHB/L)														
Imi														
BASELINE	214	330.79	12.365	330.00	290.0	350.0								
DAY 2/3	210	329.29	12.753	330.00	290.0	350.0	330.40	175	-0.74	0.773	10.228	0.00	-30.0	30.0
DAY 5	191	327.49	12.522	330.00	280.0	360.0	330.00	163	-3.19	0.952	12.157	0.00	-30.0	40.0
DAY 8	124	327.74	21.483	330.00	280.0	520.0	330.47	106	-2.36	2.249	23.158	0.00	-30.0	200.0
DAY 11	39	327.69	8.099	330.00	310.0	340.0	331.18	34	-4.12	2.199	12.820	-10.00	-30.0	30.0
DAY 14	7	330.00	8.165	330.00	320.0	340.0	332.00	5	-4.00	5.099	11.402	0.00	-20.0	10.0
END IV THERAPY	213	326.85	12.475	330.00	290.0	350.0	330.51	178	-3.65	0.938	12.516	0.00	-30.0	30.0
EARLY FOLLOW-UP	234	326.50	11.995	330.00	290.0	350.0	330.93	194	-4.02	0.914	12.727	0.00	-30.0	40.0
LATE FOLLOW-UP	107	325.89	11.570	330.00	290.0	350.0	331.44	90	-5.11	1.501	14.241	-10.00	-40.0	50.0
MCV (FL)														
Dori 500 mg 1-h inf														
BASELINE	142	92.42	5.593	92.50	69.0	108.0								
DAY 2/3	127	91.61	6.453	92.00	71.0	108.0	92.09	93	-0.08	0.283	2.728	0.00	-10.0	7.0
DAY 5	131	92.34	6.289	92.00	69.0	111.0	92.45	103	0.17	0.288	2.928	0.00	-10.0	8.0
DAY 8	82	92.66	6.296	92.00	71.0	108.0	92.71	66	0.20	0.365	2.968	0.00	-5.0	9.0
DAY 11	40	92.30	5.889	92.50	70.0	104.0	92.41	34	0.09	0.533	3.108	0.00	-5.0	9.0
DAY 14	15	93.67	5.367	94.00	86.0	104.0	93.73	11	0.82	0.998	3.311	0.00	-4.0	9.0
END IV THERAPY	162	92.36	6.181	93.00	70.0	109.0	92.27	114	0.63	0.310	3.308	0.00	-9.0	11.0
EARLY FOLLOW-UP	175	91.85	5.744	92.00	67.0	107.0	92.38	124	0.10	0.347	3.867	0.00	-12.0	9.0
LATE FOLLOW-UP	91	91.98	6.141	91.00	74.0	108.0	92.89	57	-1.28	0.586	4.427	-1.00	-12.0	13.0
Dori 500 mg 4-h inf														
BASELINE	206	93.98	5.935	93.00	77.0	116.0								
DAY 2/3	211	93.53	5.229	93.00	77.0	109.0	93.76	171	-0.25	0.229	2.989	0.00	-13.0	7.0
DAY 5	189	93.37	5.552	93.00	78.0	109.0	93.93	148	-0.43	0.253	3.076	0.00	-11.0	8.7
DAY 8	123	93.47	5.820	93.00	77.0	117.0	93.77	100	-0.47	0.358	3.577	0.00	-12.4	13.5
DAY 11	47	93.00	4.862	93.00	85.0	106.0	94.23	32	-0.77	0.569	3.217	-0.50	-8.0	4.7
DAY 14	18	92.33	3.605	91.00	87.0	101.0	93.18	13	-1.48	0.833	3.003	-2.00	-5.8	4.0
END IV THERAPY	215	93.55	4.941	93.00	77.0	108.0	94.21	169	-0.53	0.284	3.698	0.00	-12.0	13.5
EARLY FOLLOW-UP	233	92.88	4.663	92.00	79.0	106.0	93.84	183	-0.92	0.285	3.850	0.00	-18.0	11.1

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MCV (FL)														
Dori 500 mg 4-h inf														
LATE FOLLOW-UP	84	91.13	4.745	91.40	78.0	102.0	92.41	71	-1.55	0.563	4.740	-1.00	-13.3	8.0
Dori 500 mg														
BASELINE	348	93.34	5.841	93.00	69.0	116.0								
DAY 2/3	338	92.81	5.786	92.00	71.0	109.0	93.17	264	-0.19	0.178	2.896	0.00	-13.0	7.0
DAY 5	320	92.95	5.877	93.00	69.0	111.0	93.32	251	-0.18	0.191	3.024	0.00	-11.0	8.7
DAY 8	205	93.15	6.013	93.00	71.0	117.0	93.35	166	-0.21	0.260	3.355	0.00	-12.4	13.5
DAY 11	87	92.68	5.338	93.00	70.0	106.0	93.29	66	-0.33	0.390	3.166	0.00	-8.0	9.0
DAY 14	33	92.94	4.468	92.00	86.0	104.0	93.43	24	-0.43	0.672	3.293	-0.50	-5.8	9.0
END IV THERAPY	377	93.04	5.532	93.00	70.0	109.0	93.43	283	-0.06	0.213	3.586	0.00	-12.0	13.5
EARLY FOLLOW-UP	408	92.44	5.173	92.00	67.0	107.0	93.25	307	-0.51	0.222	3.883	0.00	-18.0	11.1
LATE FOLLOW-UP	175	91.57	5.516	91.00	74.0	108.0	92.63	128	-1.43	0.405	4.587	-1.00	-13.3	13.0
Pip/Taz														
BASELINE	135	92.96	6.334	92.00	74.0	118.0								
DAY 2/3	128	92.07	5.892	92.00	73.0	111.0	92.69	101	-0.61	0.289	2.902	0.00	-11.0	12.0
DAY 5	101	91.91	5.669	91.00	78.0	106.0	92.55	73	-0.56	0.301	2.571	-1.00	-10.0	7.0
DAY 8	64	92.17	5.611	91.00	79.0	105.0	93.14	50	-1.06	0.479	3.389	-1.00	-12.0	5.0
DAY 11	42	92.26	4.884	91.00	81.0	101.0	92.28	29	-0.17	0.581	3.129	-1.00	-6.0	6.0
DAY 14	21	91.90	4.085	91.00	86.0	102.0	92.19	16	-0.69	1.098	4.393	0.50	-11.0	5.0
END IV THERAPY	137	93.20	5.726	93.00	73.0	110.0	93.05	110	-0.08	0.347	3.635	0.00	-12.0	12.0
EARLY FOLLOW-UP	158	92.47	5.801	92.00	73.0	111.0	93.09	110	-0.39	0.387	4.059	0.00	-13.0	14.0
LATE FOLLOW-UP	89	92.01	5.127	92.00	80.0	111.0	92.84	61	-0.72	0.711	5.550	0.00	-14.0	12.0
Imi														
BASELINE	214	93.24	5.495	93.00	71.7	116.0								
DAY 2/3	210	93.24	5.614	93.00	68.8	115.0	93.37	175	-0.26	0.189	2.499	0.00	-9.0	7.0
DAY 5	191	93.30	5.357	93.00	70.5	116.0	93.45	163	0.06	0.228	2.916	0.00	-11.0	8.0
DAY 8	124	92.99	5.382	92.20	69.1	109.0	92.58	106	0.42	0.302	3.108	0.00	-8.4	11.0
DAY 11	39	93.03	4.090	93.00	85.0	105.0	93.60	34	-0.13	0.604	3.519	0.00	-11.5	5.0
DAY 14	7	89.14	3.436	89.00	84.0	95.0	89.40	5	0.60	1.122	2.510	2.00	-3.0	3.0
END IV THERAPY	213	93.43	5.564	93.00	69.1	114.0	93.39	178	0.10	0.231	3.083	0.00	-11.4	9.0
EARLY FOLLOW-UP	234	93.18	5.379	92.00	68.1	114.0	93.30	194	-0.07	0.249	3.472	0.00	-17.0	9.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MCV (FL)														
Imi														
LATE FOLLOW-UP	107	91.08	5.378	91.00	68.1	107.0	91.96	90	-0.89	0.492	4.664	-1.00	-14.0	11.0
MONOCYTES (%)														
Dori 500 mg 1-h inf														
BASELINE	146	6.11	4.206	5.55	0.0	25.7								
DAY 2/3	129	6.31	3.679	6.00	0.0	19.0	6.50	94	0.21	0.381	3.694	0.00	-10.0	10.7
DAY 5	130	6.09	3.032	6.00	0.0	16.1	6.47	101	-0.19	0.423	4.248	0.00	-20.8	11.4
DAY 8	83	5.18	2.994	5.00	0.1	12.6	6.13	67	-0.85	0.491	4.017	-1.00	-12.1	12.2
DAY 11	40	5.73	2.860	5.90	0.5	11.5	6.84	32	-1.18	0.863	4.882	-1.20	-19.9	8.3
DAY 14	12	7.23	4.405	6.40	0.9	14.9	9.23	6	-3.27	3.811	9.335	-3.30	-18.4	10.6
END IV THERAPY	159	6.18	3.514	6.00	0.0	22.3	5.98	115	0.02	0.476	5.108	1.00	-20.5	10.0
EARLY FOLLOW-UP	178	6.69	3.740	6.30	0.0	23.0	6.09	127	0.74	0.438	4.935	1.00	-20.5	11.2
LATE FOLLOW-UP	88	7.00	3.401	7.00	0.0	19.6	5.32	59	1.23	0.549	4.219	1.30	-12.4	13.5
Dori 500 mg 4-h inf														
BASELINE	221	5.14	3.313	5.00	0.0	14.3								
DAY 2/3	214	4.99	3.084	5.00	0.0	14.0	5.27	188	-0.36	0.251	3.441	0.00	-9.6	8.0
DAY 5	189	4.92	3.284	5.00	0.0	22.0	5.11	162	-0.18	0.315	4.006	0.00	-11.7	15.1
DAY 8	122	5.05	2.836	4.80	0.0	15.0	5.24	102	-0.25	0.370	3.740	-0.10	-12.1	9.0
DAY 11	47	5.37	3.580	5.00	0.0	16.0	5.09	37	0.32	0.658	4.000	0.00	-8.3	11.4
DAY 14	19	6.25	3.570	6.10	0.4	16.0	5.72	15	0.79	0.960	3.720	0.80	-7.9	5.9
END IV THERAPY	212	5.45	2.884	5.20	0.0	16.0	5.04	179	0.49	0.282	3.767	0.80	-12.1	13.0
EARLY FOLLOW-UP	230	5.61	2.783	5.65	0.0	13.9	5.15	197	0.50	0.256	3.598	1.00	-12.1	8.4
LATE FOLLOW-UP	85	6.55	2.612	6.50	0.9	15.2	5.12	78	1.49	0.363	3.206	1.50	-6.0	9.0
Dori 500 mg														
BASELINE	367	5.52	3.719	5.00	0.0	25.7								
DAY 2/3	343	5.49	3.376	5.20	0.0	19.0	5.68	282	-0.17	0.210	3.531	0.00	-10.0	10.7
DAY 5	319	5.40	3.230	5.20	0.0	22.0	5.64	263	-0.18	0.252	4.093	0.00	-20.8	15.1
DAY 8	205	5.10	2.895	4.80	0.0	15.0	5.59	169	-0.49	0.296	3.852	-0.20	-12.1	12.2
DAY 11	87	5.53	3.256	5.10	0.0	16.0	5.90	69	-0.38	0.537	4.460	0.00	-19.9	11.4
DAY 14	31	6.63	3.873	6.10	0.4	16.0	6.72	21	-0.37	1.291	5.915	-0.20	-18.4	10.6

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MONOCYTES (%)														
Dori 500 mg														
END IV THERAPY	371	5.76	3.185	5.40	0.0	22.3	5.41	294	0.31	0.253	4.339	0.85	-20.5	13.0
EARLY FOLLOW-UP	408	6.08	3.275	6.00	0.0	23.0	5.52	324	0.60	0.232	4.168	1.00	-20.5	11.2
LATE FOLLOW-UP	173	6.78	3.038	6.90	0.0	19.6	5.21	137	1.38	0.313	3.664	1.40	-12.4	13.5
Pip/Taz														
BASELINE	139	5.99	3.705	5.40	0.0	24.7								
DAY 2/3	129	6.20	3.409	5.90	0.0	18.5	5.96	99	0.25	0.380	3.783	0.40	-15.8	9.0
DAY 5	101	6.99	3.569	7.00	0.0	17.7	6.24	74	0.74	0.447	3.842	1.00	-13.7	9.4
DAY 8	66	5.95	2.543	5.80	0.0	12.0	5.99	51	-0.09	0.547	3.905	0.80	-16.6	6.3
DAY 11	38	6.39	2.580	6.00	1.3	11.2	7.29	27	-0.84	0.837	4.349	0.00	-13.5	6.0
DAY 14	20	7.12	3.399	6.20	2.0	12.9	7.01	16	0.10	1.443	5.771	1.00	-13.7	7.9
END IV THERAPY	137	6.57	3.579	6.00	0.0	19.2	6.17	110	0.53	0.426	4.464	0.70	-13.7	13.8
EARLY FOLLOW-UP	160	6.95	3.161	6.65	0.2	19.2	6.16	112	0.77	0.405	4.291	1.00	-18.5	12.9
LATE FOLLOW-UP	91	6.75	3.117	7.00	0.0	18.7	5.15	64	1.84	0.549	4.396	1.20	-8.0	18.7
Imi														
BASELINE	222	5.27	3.651	4.95	0.0	17.0								
DAY 2/3	211	5.10	3.338	5.00	0.0	14.2	5.39	183	-0.26	0.323	4.375	0.00	-12.0	11.2
DAY 5	188	4.80	3.205	4.55	0.0	15.0	5.19	167	-0.27	0.302	3.909	0.10	-11.0	10.0
DAY 8	125	4.84	2.896	4.70	0.0	15.0	5.39	109	-0.49	0.426	4.445	0.00	-14.0	12.0
DAY 11	41	4.74	3.330	4.70	0.0	13.6	4.98	38	-0.39	0.779	4.800	-0.90	-12.2	11.0
DAY 14	8	5.41	2.549	5.20	0.4	8.5	6.86	5	-1.26	2.640	5.903	-0.60	-10.6	4.4
END IV THERAPY	211	5.31	3.329	5.00	0.0	24.1	5.26	182	0.01	0.320	4.323	0.05	-14.0	11.0
EARLY FOLLOW-UP	236	5.99	3.481	6.00	0.0	24.1	5.39	201	0.67	0.300	4.259	0.90	-11.0	15.0
LATE FOLLOW-UP	106	6.31	2.988	6.30	0.0	20.0	5.15	91	1.27	0.441	4.203	1.00	-9.0	15.0
MONOCYTES, ABS (X10E9/L)														
Dori 500 mg 1-h inf														
BASELINE	146	0.72	0.504	0.64	0.0	2.8								
DAY 2/3	129	0.77	0.537	0.67	0.0	2.7	0.77	94	0.08	0.057	0.555	0.00	-1.1	2.0
DAY 5	130	0.76	0.527	0.65	0.0	3.2	0.77	101	0.05	0.063	0.632	0.01	-1.9	2.1
DAY 8	83	0.63	0.420	0.54	0.0	1.9	0.76	67	-0.07	0.067	0.551	0.06	-2.1	1.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MONOCYTES, ABS (X10E9/L)														
Dori 500 mg 1-h inf														
DAY 11	40	0.71	0.396	0.65	0.1	2.2	0.80	32	-0.06	0.110	0.622	-0.03	-1.3	1.4
DAY 14	12	0.81	0.440	0.74	0.1	1.4	1.19	6	-0.44	0.532	1.304	-0.30	-2.7	1.3
END IV THERAPY	159	0.66	0.429	0.58	0.0	2.7	0.70	115	-0.02	0.061	0.650	-0.01	-2.7	2.0
EARLY FOLLOW-UP	178	0.67	0.498	0.56	0.0	3.4	0.71	127	0.02	0.059	0.660	0.02	-2.8	2.0
LATE FOLLOW-UP	88	0.59	0.338	0.54	0.0	2.0	0.64	59	-0.11	0.077	0.590	-0.05	-2.2	1.2
Dori 500 mg 4-h inf														
BASELINE	184	0.71	0.495	0.64	0.0	3.1								
DAY 2/3	180	0.65	0.476	0.52	0.0	2.8	0.74	155	-0.09	0.047	0.582	-0.08	-2.2	2.5
DAY 5	157	0.68	0.532	0.56	0.0	3.0	0.71	131	-0.01	0.051	0.580	-0.01	-1.7	2.4
DAY 8	107	0.65	0.424	0.55	0.0	2.3	0.69	87	-0.04	0.054	0.502	0.01	-1.7	1.2
DAY 11	44	0.64	0.482	0.50	0.0	2.2	0.66	34	-0.02	0.097	0.566	-0.04	-1.5	1.7
DAY 14	17	0.61	0.369	0.49	0.0	1.3	0.59	13	0.04	0.155	0.560	0.04	-1.2	0.8
END IV THERAPY	177	0.67	0.447	0.54	0.0	3.0	0.71	145	-0.00	0.046	0.550	0.04	-2.1	2.4
EARLY FOLLOW-UP	194	0.64	0.460	0.54	0.0	3.2	0.72	162	-0.06	0.043	0.549	-0.06	-2.1	2.4
LATE FOLLOW-UP	67	0.55	0.285	0.53	0.1	1.6	0.70	62	-0.15	0.050	0.397	-0.09	-1.4	0.6
Dori 500 mg														
BASELINE	330	0.71	0.498	0.64	0.0	3.1								
DAY 2/3	309	0.70	0.504	0.57	0.0	2.8	0.75	249	-0.03	0.037	0.577	-0.06	-2.2	2.5
DAY 5	287	0.71	0.530	0.60	0.0	3.2	0.74	232	0.02	0.040	0.602	0.01	-1.9	2.4
DAY 8	190	0.64	0.421	0.54	0.0	2.3	0.72	154	-0.05	0.042	0.523	0.02	-2.1	1.2
DAY 11	84	0.67	0.442	0.59	0.0	2.2	0.73	66	-0.04	0.073	0.590	-0.03	-1.5	1.7
DAY 14	29	0.70	0.405	0.67	0.0	1.4	0.78	19	-0.11	0.197	0.858	0.03	-2.7	1.3
END IV THERAPY	336	0.67	0.438	0.56	0.0	3.0	0.70	260	-0.01	0.037	0.595	0.01	-2.7	2.4
EARLY FOLLOW-UP	372	0.66	0.478	0.55	0.0	3.4	0.72	289	-0.02	0.035	0.601	-0.03	-2.8	2.4
LATE FOLLOW-UP	155	0.57	0.316	0.53	0.0	2.0	0.67	121	-0.13	0.045	0.499	-0.08	-2.2	1.2
Pip/Taz														
BASELINE	139	0.74	0.495	0.65	0.0	2.6								
DAY 2/3	129	0.69	0.438	0.57	0.0	2.0	0.78	99	-0.03	0.052	0.514	0.02	-2.2	1.2
DAY 5	101	0.75	0.491	0.64	0.0	2.6	0.79	74	-0.00	0.053	0.457	0.02	-1.4	1.3
DAY 8	66	0.68	0.346	0.63	0.0	1.6	0.79	51	-0.06	0.053	0.381	-0.04	-1.3	0.7

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
MONOCYTES, ABS (X10E9/L)														
Pip/Taz														
DAY 11	38	0.72	0.395	0.70	0.1	1.7	0.89	27	-0.12	0.092	0.478	-0.19	-1.4	0.9
DAY 14	20	0.65	0.340	0.58	0.2	1.7	0.74	16	-0.05	0.121	0.484	-0.08	-1.1	1.1
END IV THERAPY	137	0.65	0.420	0.55	0.0	2.4	0.79	110	-0.10	0.055	0.581	-0.06	-2.0	1.8
EARLY FOLLOW-UP	160	0.64	0.359	0.56	0.0	2.1	0.77	112	-0.09	0.046	0.489	-0.05	-1.6	1.4
LATE FOLLOW-UP	91	0.57	0.383	0.51	0.0	2.4	0.69	64	-0.06	0.073	0.587	-0.04	-2.0	2.4
Imi														
BASELINE	193	0.76	0.552	0.68	0.0	3.1								
DAY 2/3	182	0.69	0.475	0.60	0.0	2.5	0.78	158	-0.07	0.052	0.660	-0.01	-3.1	1.8
DAY 5	159	0.70	0.540	0.59	0.0	2.9	0.77	140	-0.03	0.054	0.637	-0.00	-1.9	2.5
DAY 8	111	0.65	0.449	0.59	0.0	2.9	0.76	97	-0.09	0.069	0.682	-0.02	-2.3	2.5
DAY 11	38	0.59	0.437	0.63	0.0	2.2	0.78	35	-0.18	0.121	0.717	-0.09	-1.9	1.2
DAY 14	8	0.76	0.388	0.70	0.1	1.4	0.74	5	0.03	0.151	0.338	-0.07	-0.3	0.6
END IV THERAPY	180	0.68	0.416	0.62	0.0	2.0	0.77	156	-0.08	0.049	0.615	-0.02	-2.3	1.6
EARLY FOLLOW-UP	204	0.67	0.396	0.60	0.0	1.9	0.76	174	-0.07	0.043	0.570	-0.00	-2.0	1.6
LATE FOLLOW-UP	93	0.57	0.338	0.51	0.0	2.1	0.67	79	-0.08	0.058	0.516	-0.08	-1.9	1.5
NEUTROPHILS (%)														
Dori 500 mg 1-h inf														
BASELINE	146	79.23	10.946	81.00	30.0	95.7								
DAY 2/3	129	76.80	9.663	77.80	38.6	95.0	79.38	94	-1.85	1.041	10.097	-1.70	-26.2	53.0
DAY 5	130	74.73	10.414	75.50	39.0	96.5	78.96	101	-3.64	1.041	10.460	-3.00	-30.1	42.0
DAY 8	83	77.70	9.793	79.00	49.6	95.4	79.97	67	-0.91	1.375	11.253	0.00	-25.3	51.8
DAY 11	40	78.50	9.780	80.50	59.4	95.4	82.15	32	-1.68	1.758	9.944	-2.00	-21.0	17.3
DAY 14	12	74.36	10.051	73.90	59.3	92.5	78.33	6	1.85	3.802	9.312	4.90	-12.1	10.0
END IV THERAPY	159	72.89	11.202	74.20	37.5	96.5	79.17	115	-4.72	1.178	12.636	-5.60	-40.0	38.9
EARLY FOLLOW-UP	178	69.24	12.142	67.00	40.4	97.0	79.17	127	-8.92	1.230	13.862	-8.90	-43.7	24.6
LATE FOLLOW-UP	88	63.07	11.915	62.95	33.2	88.5	79.21	59	-15.39	1.908	14.658	-13.80	-45.4	18.0
Dori 500 mg 4-h inf														
BASELINE	191	75.55	12.911	77.00	8.0	97.0								
DAY 2/3	190	75.12	10.684	76.00	39.0	97.7	75.46	157	-0.70	0.901	11.287	-1.70	-41.6	37.4

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
NEUTROPHILS (%)														
Dori 500 mg 4-h inf														
DAY 5	170	75.87	10.859	77.90	36.0	97.9	75.10	135	1.48	1.110	12.899	0.20	-28.2	46.0
DAY 8	113	75.10	10.519	77.00	35.0	94.4	75.95	91	-0.41	1.219	11.630	-1.00	-31.0	34.2
DAY 11	45	73.54	11.362	75.50	32.0	87.8	74.89	35	-0.96	2.397	14.181	-2.60	-24.8	28.0
DAY 14	18	67.37	15.535	68.55	28.0	86.2	72.36	14	-7.90	3.050	11.411	-9.95	-23.2	20.0
END IV THERAPY	195	73.95	9.856	75.20	28.0	94.2	75.80	150	-1.74	1.016	12.446	-2.35	-31.0	44.0
EARLY FOLLOW-UP	222	72.95	9.758	73.75	26.0	95.5	75.73	169	-2.90	1.101	14.315	-3.60	-54.0	70.0
LATE FOLLOW-UP	81	65.50	10.848	67.00	26.9	93.5	76.10	64	-11.23	2.155	17.239	-12.60	-44.1	62.0
Dori 500 mg														
BASELINE	337	77.14	12.219	79.00	8.0	97.0								
DAY 2/3	319	75.80	10.301	76.80	38.6	97.7	76.93	251	-1.13	0.685	10.851	-1.70	-41.6	53.0
DAY 5	300	75.38	10.666	76.90	36.0	97.9	76.75	236	-0.71	0.792	12.160	-1.25	-30.1	46.0
DAY 8	196	76.20	10.273	77.75	35.0	95.4	77.65	158	-0.63	0.910	11.438	-1.00	-31.0	51.8
DAY 11	85	75.87	10.873	78.00	32.0	95.4	78.36	67	-1.30	1.497	12.255	-2.60	-24.8	28.0
DAY 14	30	70.17	13.853	70.20	28.0	92.5	74.16	20	-4.98	2.578	11.530	-6.80	-23.2	20.0
END IV THERAPY	354	73.47	10.480	74.55	28.0	96.5	77.26	265	-3.03	0.774	12.593	-3.40	-40.0	44.0
EARLY FOLLOW-UP	400	71.30	11.025	72.00	26.0	97.0	77.21	296	-5.48	0.838	14.411	-5.10	-54.0	70.0
LATE FOLLOW-UP	169	64.23	11.447	64.30	26.9	93.5	77.59	123	-13.23	1.454	16.123	-13.00	-45.4	62.0
Pip/Taz														
BASELINE	139	79.10	10.233	80.60	39.6	95.0								
DAY 2/3	129	75.87	10.432	76.00	40.5	94.0	79.90	99	-2.38	0.890	8.860	-2.90	-21.9	25.0
DAY 5	101	73.99	9.422	75.00	52.3	90.3	80.26	74	-4.93	1.123	9.658	-5.85	-28.9	22.0
DAY 8	66	78.39	9.125	79.75	52.0	93.0	80.91	51	-2.06	1.531	10.933	-3.00	-37.1	26.0
DAY 11	38	75.66	9.370	75.90	58.3	92.0	77.86	27	-0.72	2.597	13.494	-3.00	-24.0	29.0
DAY 14	20	76.44	9.698	76.60	51.1	90.0	78.99	16	-2.82	3.435	13.739	-6.00	-21.3	31.0
END IV THERAPY	137	73.68	10.243	74.00	46.0	92.7	79.26	110	-4.95	1.128	11.827	-5.10	-35.0	39.3
EARLY FOLLOW-UP	160	68.40	12.682	69.70	31.6	92.7	78.68	112	-8.36	1.354	14.332	-9.00	-43.3	39.3
LATE FOLLOW-UP	91	62.09	13.030	61.50	29.8	96.4	81.67	64	-18.52	1.856	14.849	-17.25	-51.2	19.0
Imi														
BASELINE	200	76.81	12.333	78.00	35.0	97.3								
DAY 2/3	195	76.75	10.156	77.00	34.0	95.9	77.02	162	-0.33	0.924	11.766	-1.65	-32.6	55.5

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
NEUTROPHILS (%)														
Imi														
DAY 5	169	76.40	9.738	77.00	45.0	97.1	78.02	146	-1.51	0.917	11.076	-1.85	-29.0	45.0
DAY 8	119	76.37	10.628	77.10	39.2	95.6	77.77	99	-1.47	1.207	12.010	-0.10	-35.3	26.0
DAY 11	41	76.44	11.148	76.00	43.0	95.3	77.62	36	-0.22	1.760	10.560	2.50	-27.0	30.2
DAY 14	8	78.74	6.159	77.95	69.6	87.0	71.14	5	7.34	7.689	17.193	14.90	-15.5	24.0
END IV THERAPY	197	76.14	10.817	77.00	37.0	95.0	77.24	161	-0.89	1.039	13.178	-2.00	-32.2	48.1
EARLY FOLLOW-UP	225	71.90	11.945	73.00	33.0	95.0	76.86	180	-4.67	1.029	13.804	-4.90	-38.9	55.4
LATE FOLLOW-UP	104	65.40	12.196	67.30	21.3	87.0	77.01	82	-11.51	1.874	16.966	-12.00	-46.9	29.8
NEUTROPHILS, ABS (X10E9/L)														
Dori 500 mg 1-h inf														
BASELINE	146	10.36	5.071	9.86	0.4	31.0								
DAY 2/3	129	9.91	5.085	9.15	1.8	32.4	10.60	94	-0.17	0.578	5.608	-0.42	-14.1	20.5
DAY 5	130	9.59	5.180	8.52	1.6	28.9	10.48	101	-0.24	0.627	6.300	-0.82	-14.5	21.6
DAY 8	83	10.09	4.853	9.76	1.8	27.4	10.60	67	0.34	0.805	6.587	0.95	-15.4	21.2
DAY 11	40	10.78	5.263	9.99	3.9	26.3	11.29	32	0.46	1.196	6.764	1.43	-18.7	12.4
DAY 14	12	8.96	3.220	7.97	5.6	17.4	9.26	6	1.25	1.157	2.833	1.43	-3.0	5.6
END IV THERAPY	159	8.63	4.627	7.82	1.6	28.9	10.24	115	-1.21	0.571	6.120	-0.68	-25.0	21.6
EARLY FOLLOW-UP	178	7.73	5.109	6.19	1.4	40.4	10.22	127	-1.96	0.594	6.695	-1.66	-24.8	27.5
LATE FOLLOW-UP	88	5.44	2.382	4.84	2.0	13.9	9.80	59	-4.33	0.627	4.813	-3.95	-16.7	3.8
Dori 500 mg 4-h inf														
BASELINE	184	10.57	5.517	9.36	0.1	40.9								
DAY 2/3	180	9.86	4.370	9.32	1.9	32.0	10.31	155	-0.55	0.390	4.851	-0.50	-25.6	11.6
DAY 5	157	10.52	5.366	9.44	2.0	44.0	10.48	131	0.32	0.602	6.889	0.07	-33.3	23.5
DAY 8	107	10.02	4.698	8.95	1.6	24.8	10.31	87	-0.47	0.613	5.719	-0.60	-16.3	12.7
DAY 11	44	9.09	4.654	8.11	2.7	23.6	10.57	34	-1.35	1.018	5.935	-0.42	-14.9	11.3
DAY 14	17	6.87	3.329	6.38	2.0	13.1	9.50	13	-3.28	1.278	4.610	-3.43	-15.7	1.9
END IV THERAPY	177	9.52	4.786	8.58	1.6	44.0	10.56	145	-0.91	0.548	6.605	-0.78	-33.3	23.5
EARLY FOLLOW-UP	194	8.74	5.188	7.62	1.6	44.0	10.52	162	-1.65	0.553	7.043	-1.83	-35.5	26.7
LATE FOLLOW-UP	67	5.81	3.164	4.93	2.0	18.6	10.42	62	-4.75	0.860	6.772	-3.53	-36.8	8.1

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
NEUTROPHILS, ABS (X10E9/L)														
Dori 500 mg														
BASELINE	330	10.47	5.317	9.60	0.1	40.9								
DAY 2/3	309	9.88	4.674	9.28	1.8	32.4	10.42	249	-0.41	0.326	5.142	-0.46	-25.6	20.5
DAY 5	287	10.10	5.294	8.97	1.6	44.0	10.48	232	0.08	0.435	6.631	-0.27	-33.3	23.5
DAY 8	190	10.05	4.754	9.12	1.6	27.4	10.44	154	-0.12	0.492	6.105	-0.08	-16.3	21.2
DAY 11	84	9.90	4.996	9.02	2.7	26.3	10.92	66	-0.48	0.784	6.367	0.27	-18.7	12.4
DAY 14	29	7.73	3.391	7.41	2.0	17.4	9.42	19	-1.85	1.053	4.591	-0.80	-15.7	5.6
END IV THERAPY	336	9.10	4.725	8.20	1.6	44.0	10.42	260	-1.04	0.396	6.385	-0.72	-33.3	23.5
EARLY FOLLOW-UP	372	8.26	5.168	6.81	1.4	44.0	10.38	289	-1.79	0.405	6.882	-1.82	-35.5	27.5
LATE FOLLOW-UP	155	5.60	2.744	4.90	2.0	18.6	10.12	121	-4.54	0.534	5.878	-3.64	-36.8	8.1
Pip/Taz														
BASELINE	139	10.86	5.466	10.20	1.2	29.4								
DAY 2/3	129	9.14	4.955	7.88	1.1	24.6	11.66	99	-1.74	0.515	5.123	-1.17	-19.5	13.2
DAY 5	101	8.57	5.064	7.10	2.0	34.5	11.28	74	-2.29	0.699	6.017	-2.26	-21.3	20.8
DAY 8	66	9.22	4.035	8.47	2.9	22.9	12.16	51	-2.21	0.873	6.235	-1.40	-18.9	11.3
DAY 11	38	8.49	3.658	7.81	3.2	16.1	10.35	27	-1.18	0.949	4.929	-0.62	-15.9	9.6
DAY 14	20	7.61	3.017	6.96	3.0	13.7	9.88	16	-1.99	1.128	4.513	-3.12	-7.4	8.3
END IV THERAPY	137	8.20	4.546	7.02	1.9	29.8	11.14	110	-2.44	0.539	5.652	-2.05	-21.3	14.1
EARLY FOLLOW-UP	160	7.07	4.334	5.84	1.3	29.8	10.87	112	-3.21	0.551	5.831	-2.82	-24.7	14.1
LATE FOLLOW-UP	91	5.60	3.131	4.72	1.6	16.1	11.52	64	-5.46	0.694	5.555	-4.98	-20.8	4.6
Imi														
BASELINE	193	11.25	5.223	10.08	1.3	36.8								
DAY 2/3	182	11.04	5.325	9.83	2.6	32.9	11.25	158	-0.03	0.450	5.660	-0.37	-19.0	21.1
DAY 5	159	11.34	5.125	10.06	1.4	33.0	11.76	140	-0.15	0.508	6.009	-0.74	-18.2	18.0
DAY 8	111	10.84	4.679	9.64	3.1	34.4	11.14	97	-0.16	0.602	5.928	0.14	-13.7	18.6
DAY 11	38	11.10	5.013	10.91	3.3	31.7	12.19	35	-0.51	0.979	5.794	-0.19	-10.1	15.1
DAY 14	8	12.02	4.931	9.88	6.5	20.6	11.46	5	0.06	4.645	10.386	-3.58	-11.4	16.3
END IV THERAPY	180	10.32	4.887	9.17	2.3	34.4	11.29	156	-0.87	0.505	6.305	-0.98	-19.7	20.5
EARLY FOLLOW-UP	204	8.60	4.270	7.53	1.3	26.8	11.10	174	-2.47	0.453	5.980	-1.96	-26.5	16.1
LATE FOLLOW-UP	93	6.33	2.979	5.67	0.6	14.8	10.50	79	-4.16	0.626	5.560	-3.61	-17.5	7.5

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
PLATELET COUNT (X10E9/L)														
Dori 500 mg 1-h inf														
BASELINE	148	268.87	174.620	230.50	56.0	1311.0								
DAY 2/3	135	322.73	162.484	296.00	97.0	982.0	259.44	99	52.94	11.533	114.756	41.00	-382.0	566.0
DAY 5	132	379.96	193.307	324.00	65.0	1424.0	275.00	101	102.16	18.625	187.179	76.00	-739.0	1008.0
DAY 8	84	419.42	175.196	404.50	50.0	914.0	267.52	67	161.63	27.033	221.272	137.00	-908.0	596.0
DAY 11	40	436.53	195.731	424.00	138.0	901.0	220.25	32	208.59	38.649	218.633	142.50	-112.0	672.0
DAY 14	14	481.50	147.895	414.00	346.0	806.0	288.13	8	177.25	67.510	190.947	135.00	56.0	635.0
END IV THERAPY	167	430.24	202.030	396.00	70.0	1367.0	275.02	121	154.44	20.390	224.293	133.00	-908.0	951.0
EARLY FOLLOW-UP	178	386.98	169.333	363.00	70.0	912.0	269.38	128	118.48	19.772	223.690	117.00	-863.0	610.0
LATE FOLLOW-UP	90	331.94	132.718	310.00	57.0	803.0	282.31	62	42.92	29.548	232.663	73.00	-960.0	565.0
Dori 500 mg 4-h inf														
BASELINE	218	274.48	162.772	238.00	56.0	1279.0								
DAY 2/3	212	333.75	177.283	295.50	58.0	1110.0	268.93	183	65.13	6.177	83.563	55.00	-196.0	566.0
DAY 5	191	415.37	197.850	377.00	62.0	1166.0	277.71	160	142.28	11.032	139.543	120.50	-139.0	592.0
DAY 8	123	490.50	218.181	453.00	53.0	1163.0	256.01	105	235.72	20.914	214.303	217.00	-157.0	1033.0
DAY 11	46	525.87	229.322	518.00	52.0	1224.0	259.95	37	280.46	40.220	244.652	244.00	-156.0	918.0
DAY 14	17	428.94	185.611	442.00	50.0	726.0	225.07	15	233.73	45.132	174.794	180.00	-34.0	542.0
END IV THERAPY	210	509.90	246.215	474.00	50.0	1687.0	284.24	178	229.39	18.147	242.114	181.00	-205.0	1436.0
EARLY FOLLOW-UP	225	450.13	199.564	425.00	50.0	1294.0	277.86	190	179.69	16.547	228.090	157.00	-608.0	1128.0
LATE FOLLOW-UP	86	373.43	139.230	338.00	143.0	868.0	277.44	75	100.55	20.325	176.019	105.00	-502.0	480.0
Dori 500 mg														
BASELINE	366	272.21	167.451	236.00	56.0	1311.0								
DAY 2/3	347	329.47	171.523	296.00	58.0	1110.0	265.60	282	60.85	5.696	95.653	50.00	-382.0	566.0
DAY 5	323	400.90	196.479	348.00	62.0	1424.0	276.66	261	126.75	9.936	160.520	109.00	-739.0	1008.0
DAY 8	207	461.66	204.410	433.00	50.0	1163.0	260.49	172	206.86	16.730	219.413	169.00	-908.0	1033.0
DAY 11	86	484.31	217.780	467.00	52.0	1224.0	241.54	69	247.13	28.177	234.056	217.00	-156.0	918.0
DAY 14	31	452.68	168.995	431.00	50.0	806.0	247.00	23	214.09	37.184	178.327	148.00	-34.0	635.0
END IV THERAPY	377	474.61	230.839	431.00	50.0	1687.0	280.51	299	199.06	13.738	237.557	154.00	-908.0	1436.0
EARLY FOLLOW-UP	403	422.24	189.215	393.00	50.0	1294.0	274.44	318	155.06	12.784	227.966	140.00	-863.0	1128.0
LATE FOLLOW-UP	176	352.22	137.135	328.00	57.0	868.0	279.64	137	74.47	17.502	204.858	89.00	-960.0	565.0

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
PLATELET COUNT (X10E9/L)														
Pip/Taz														
BASELINE	141	257.11	131.262	230.00	55.0	901.0								
DAY 2/3	131	322.45	156.504	302.00	61.0	865.0	250.12	102	55.39	9.905	100.033	38.00	-202.0	479.0
DAY 5	101	367.13	155.363	347.00	84.0	804.0	245.27	77	106.18	14.202	124.619	90.00	-167.0	464.0
DAY 8	66	409.11	202.271	371.00	129.0	958.0	254.29	51	166.76	26.184	186.994	127.00	-97.0	671.0
DAY 11	41	497.10	248.498	448.00	51.0	993.0	204.03	29	279.62	45.244	243.647	260.00	-65.0	851.0
DAY 14	19	397.47	221.098	327.00	115.0	941.0	175.50	16	237.31	62.389	249.558	136.00	-3.0	823.0
END IV THERAPY	138	420.33	202.062	381.50	50.0	973.0	247.28	111	179.26	19.352	203.888	148.00	-183.0	823.0
EARLY FOLLOW-UP	157	363.78	162.477	326.00	50.0	1092.0	261.92	113	120.65	18.023	191.586	80.00	-578.0	918.0
LATE FOLLOW-UP	92	321.00	146.632	288.50	80.0	924.0	261.67	67	77.40	22.671	185.570	64.00	-682.0	750.0
Imi														
BASELINE	219	275.10	172.264	241.00	45.0	1584.0								
DAY 2/3	208	331.18	188.541	297.00	21.0	1482.0	274.87	179	63.88	6.952	93.008	62.00	-425.0	413.0
DAY 5	191	403.49	199.542	378.00	18.0	1320.0	272.37	169	144.50	11.866	154.254	137.00	-575.0	614.0
DAY 8	120	500.32	217.454	493.00	74.0	1268.0	271.90	106	227.79	20.314	209.147	243.50	-345.0	774.0
DAY 11	41	572.20	272.548	578.00	119.0	1156.0	241.86	37	345.11	45.856	278.934	304.00	-47.0	913.0
DAY 14	8	575.63	238.520	623.00	251.0	878.0	241.33	6	366.50	114.732	281.036	254.00	115.0	802.0
END IV THERAPY	210	490.24	262.612	443.50	47.0	1626.0	273.33	180	225.79	18.917	253.803	194.00	-610.0	989.0
EARLY FOLLOW-UP	233	435.60	212.448	400.00	47.0	1626.0	270.66	199	166.13	15.788	222.712	152.00	-711.0	989.0
LATE FOLLOW-UP	103	399.19	147.387	376.00	110.0	938.0	269.55	89	132.06	21.609	203.859	131.00	-913.0	673.0
RBC (X10E12/L)														
Dori 500 mg 1-h inf														
BASELINE	157	3.59	0.716	3.50	2.0	5.9								
DAY 2/3	138	3.61	0.570	3.60	2.6	5.4	3.60	107	-0.02	0.041	0.423	0.00	-1.0	1.3
DAY 5	137	3.55	0.625	3.50	2.2	5.5	3.48	112	0.01	0.046	0.492	0.00	-1.4	1.3
DAY 8	85	3.52	0.639	3.50	2.0	4.9	3.46	73	0.01	0.062	0.532	0.00	-1.1	1.3
DAY 11	41	3.65	0.520	3.60	2.8	4.8	3.56	36	0.06	0.105	0.628	0.05	-1.5	1.4
DAY 14	15	3.49	0.593	3.40	2.4	4.4	3.42	11	0.10	0.209	0.694	0.20	-1.4	0.9
END IV THERAPY	168	3.69	0.601	3.60	2.3	5.5	3.56	129	0.06	0.044	0.498	0.10	-2.0	1.3
EARLY FOLLOW-UP	181	3.86	0.636	3.90	2.0	5.4	3.56	138	0.24	0.056	0.662	0.20	-1.6	2.7

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
RBC (X10E12/L)														
Dori 500 mg 1-h inf														
LATE FOLLOW-UP	93	4.15	0.670	4.30	2.5	5.3	3.54	66	0.58	0.102	0.828	0.60	-2.0	2.6
Dori 500 mg 4-h inf														
BASELINE	198	3.13	0.554	3.10	1.7	4.9								
DAY 2/3	192	3.15	0.522	3.10	2.1	5.0	3.13	175	0.01	0.027	0.354	0.00	-0.7	1.4
DAY 5	167	3.24	0.573	3.20	2.0	5.0	3.13	147	0.11	0.037	0.449	0.10	-1.0	1.3
DAY 8	113	3.25	0.648	3.10	2.0	5.2	3.21	97	0.08	0.048	0.474	0.10	-1.3	1.5
DAY 11	47	3.14	0.418	3.10	2.5	4.2	3.09	39	0.05	0.083	0.520	0.10	-1.3	1.3
DAY 14	17	3.11	0.408	3.10	2.3	3.6	3.09	14	0.04	0.105	0.392	0.15	-0.6	0.6
END IV THERAPY	189	3.30	0.579	3.30	2.0	5.2	3.13	166	0.17	0.041	0.526	0.20	-1.3	1.4
EARLY FOLLOW-UP	198	3.44	0.606	3.40	2.2	5.2	3.13	175	0.32	0.047	0.622	0.40	-1.3	1.9
LATE FOLLOW-UP	71	4.05	0.540	4.00	3.0	5.4	3.14	67	0.90	0.078	0.639	1.00	-0.4	2.3
Dori 500 mg														
BASELINE	355	3.33	0.670	3.20	1.7	5.9								
DAY 2/3	330	3.34	0.588	3.30	2.1	5.4	3.31	282	-0.00	0.023	0.382	0.00	-1.0	1.4
DAY 5	304	3.38	0.616	3.40	2.0	5.5	3.28	259	0.06	0.029	0.470	0.00	-1.4	1.3
DAY 8	198	3.37	0.657	3.30	2.0	5.2	3.32	170	0.05	0.038	0.499	0.00	-1.3	1.5
DAY 11	88	3.38	0.531	3.30	2.5	4.8	3.32	75	0.06	0.066	0.570	0.10	-1.5	1.4
DAY 14	32	3.28	0.531	3.30	2.3	4.4	3.24	25	0.07	0.107	0.534	0.20	-1.4	0.9
END IV THERAPY	357	3.48	0.619	3.40	2.0	5.5	3.32	295	0.12	0.030	0.516	0.10	-2.0	1.4
EARLY FOLLOW-UP	379	3.64	0.655	3.60	2.0	5.4	3.32	313	0.29	0.036	0.640	0.30	-1.6	2.7
LATE FOLLOW-UP	164	4.11	0.617	4.10	2.5	5.4	3.34	133	0.74	0.065	0.753	0.70	-2.0	2.6
Pip/Taz														
BASELINE	146	3.67	0.668	3.70	2.0	5.1								
DAY 2/3	137	3.60	0.606	3.50	2.4	5.3	3.58	110	0.01	0.048	0.501	0.00	-1.4	1.9
DAY 5	104	3.56	0.579	3.50	2.5	5.7	3.59	80	-0.08	0.061	0.549	-0.10	-1.3	2.1
DAY 8	66	3.56	0.564	3.50	2.3	5.6	3.55	53	-0.09	0.062	0.453	-0.20	-1.0	1.1
DAY 11	43	3.48	0.530	3.40	2.4	4.8	3.54	32	-0.11	0.106	0.602	-0.10	-2.2	0.8
DAY 14	21	3.39	0.485	3.30	2.6	4.4	3.62	18	-0.24	0.208	0.883	-0.10	-1.9	1.3
END IV THERAPY	143	3.69	0.621	3.70	2.4	5.6	3.63	119	-0.02	0.057	0.617	0.00	-1.9	1.8
EARLY FOLLOW-UP	163	3.89	0.652	3.90	2.4	5.7	3.64	121	0.13	0.062	0.685	0.10	-2.2	1.8

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
RBC (X10E12/L)														
Pip/Taz														
LATE FOLLOW-UP	93	4.18	0.630	4.30	2.5	5.5	3.68	68	0.43	0.091	0.750	0.60	-1.7	2.2
Imi														
BASELINE	204	3.19	0.601	3.10	2.0	6.3								
DAY 2/3	192	3.17	0.552	3.10	2.1	6.3	3.20	174	-0.06	0.028	0.372	-0.10	-1.1	1.0
DAY 5	172	3.22	0.573	3.20	2.1	5.6	3.20	157	-0.01	0.037	0.463	0.00	-1.4	1.2
DAY 8	114	3.29	0.614	3.25	1.8	5.7	3.26	108	0.02	0.057	0.588	0.00	-1.8	1.9
DAY 11	39	3.21	0.528	3.20	2.2	4.4	3.24	37	-0.04	0.092	0.561	0.00	-1.7	1.2
DAY 14	8	3.46	0.848	3.15	2.6	5.2	3.05	6	0.20	0.218	0.533	0.15	-0.4	1.1
END IV THERAPY	190	3.27	0.583	3.20	2.0	5.9	3.19	171	0.06	0.039	0.507	0.00	-1.9	1.2
EARLY FOLLOW-UP	209	3.44	0.629	3.40	2.1	5.5	3.19	188	0.24	0.046	0.637	0.20	-2.5	1.7
LATE FOLLOW-UP	94	3.92	0.707	4.00	2.0	5.7	3.22	85	0.73	0.087	0.802	0.80	-1.7	2.9
WBC (X10E9/L)														
Dori 500 mg 1-h inf														
BASELINE	155	12.66	5.382	11.80	1.4	33.9								
DAY 2/3	137	12.55	5.697	11.50	4.0	39.2	13.09	105	0.28	0.615	6.302	-0.20	-14.8	22.5
DAY 5	135	12.43	5.937	11.00	3.0	39.7	12.76	108	0.32	0.676	7.027	-0.20	-18.0	21.0
DAY 8	84	12.55	5.275	12.16	3.6	32.2	12.89	71	0.49	0.867	7.307	0.55	-16.6	24.1
DAY 11	40	13.41	5.675	12.40	5.1	31.1	13.44	33	0.70	1.283	7.369	1.23	-19.0	15.7
DAY 14	12	11.81	2.723	11.31	9.1	18.8	11.75	7	0.67	1.256	3.323	1.27	-4.9	4.5
END IV THERAPY	167	11.34	5.124	10.10	3.5	39.2	12.61	127	-0.63	0.611	6.882	-0.40	-24.8	22.0
EARLY FOLLOW-UP	180	10.69	5.766	9.10	2.5	44.6	12.59	136	-1.27	0.634	7.391	-1.33	-24.6	30.7
LATE FOLLOW-UP	91	8.47	2.722	8.00	4.2	17.6	12.13	64	-3.65	0.647	5.179	-3.25	-17.5	6.6
Dori 500 mg 4-h inf														
BASELINE	233	14.17	6.696	12.70	1.4	45.2								
DAY 2/3	225	13.14	5.123	12.90	3.5	32.7	13.91	205	-0.58	0.373	5.344	-0.70	-25.1	12.6
DAY 5	198	13.63	5.803	12.75	3.3	48.9	13.97	175	-0.07	0.562	7.436	0.20	-31.8	25.8
DAY 8	129	13.22	5.488	11.80	2.8	26.3	13.28	112	-0.16	0.629	6.661	-0.70	-19.6	17.0
DAY 11	50	12.25	5.875	10.35	4.2	30.3	13.13	42	-0.82	1.113	7.216	-1.40	-14.7	18.4
DAY 14	19	10.39	4.710	8.80	6.0	21.5	11.63	16	-1.20	1.413	5.653	-1.00	-15.4	7.1

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
WBC (X10E9/L)														
Dori 500 mg 4-h inf														
END IV THERAPY	224	12.74	5.600	11.80	2.8	48.9	14.05	198	-1.16	0.530	7.452	-0.70	-32.0	25.8
EARLY FOLLOW-UP	234	11.75	5.942	10.70	2.8	48.9	13.94	208	-1.96	0.545	7.861	-1.85	-35.7	34.1
LATE FOLLOW-UP	88	8.71	3.478	8.10	3.8	19.9	13.19	81	-4.55	0.756	6.801	-3.50	-36.8	10.3
Dori 500 mg														
BASELINE	388	13.57	6.241	12.50	1.4	45.2								
DAY 2/3	362	12.92	5.347	12.10	3.5	39.2	13.63	310	-0.29	0.323	5.691	-0.40	-25.1	22.5
DAY 5	333	13.14	5.878	12.30	3.0	48.9	13.51	283	0.08	0.432	7.273	0.00	-31.8	25.8
DAY 8	213	12.95	5.402	12.00	2.8	32.2	13.13	183	0.09	0.511	6.906	-0.10	-19.6	24.1
DAY 11	90	12.77	5.783	11.55	4.2	31.1	13.26	75	-0.15	0.840	7.274	-0.10	-19.0	18.4
DAY 14	31	10.94	4.065	9.59	6.0	21.5	11.67	23	-0.63	1.054	5.057	-0.50	-15.4	7.1
END IV THERAPY	391	12.14	5.439	11.10	2.8	48.9	13.49	325	-0.95	0.401	7.229	-0.66	-32.0	25.8
EARLY FOLLOW-UP	414	11.29	5.883	9.85	2.5	48.9	13.40	344	-1.69	0.414	7.675	-1.55	-35.7	34.1
LATE FOLLOW-UP	179	8.59	3.110	8.10	3.8	19.9	12.72	145	-4.16	0.509	6.135	-3.40	-36.8	10.3
Pip/Taz														
BASELINE	145	13.61	6.367	12.61	2.7	36.8								
DAY 2/3	135	11.54	5.603	10.14	2.6	27.2	14.51	107	-1.97	0.548	5.665	-1.20	-20.1	15.8
DAY 5	103	11.20	5.789	9.60	3.1	38.2	13.96	78	-2.34	0.766	6.761	-2.15	-24.3	23.7
DAY 8	66	11.61	4.363	10.55	3.8	25.4	15.04	52	-2.62	0.983	7.085	-1.45	-20.3	11.8
DAY 11	41	10.89	4.137	9.61	4.4	18.5	13.91	29	-2.15	1.176	6.335	-1.97	-16.5	9.8
DAY 14	20	9.85	3.414	9.45	4.7	16.6	12.91	17	-2.58	1.204	4.966	-3.70	-11.0	9.3
END IV THERAPY	141	10.75	5.098	9.60	3.4	36.3	14.04	116	-2.61	0.591	6.362	-2.25	-23.2	14.9
EARLY FOLLOW-UP	162	9.82	4.749	8.45	3.3	36.3	13.67	119	-3.16	0.583	6.361	-2.60	-26.5	13.0
LATE FOLLOW-UP	92	8.57	3.477	7.70	3.5	19.2	14.04	67	-4.97	0.775	6.342	-4.50	-22.6	7.7
Imi														
BASELINE	232	14.59	5.943	13.40	1.1	39.3								
DAY 2/3	221	13.86	6.027	12.80	3.9	36.2	14.69	198	-0.51	0.410	5.775	-1.15	-19.1	22.4
DAY 5	202	14.27	5.702	13.35	4.8	41.8	14.87	184	-0.32	0.475	6.447	-0.70	-20.8	19.6
DAY 8	128	13.84	5.299	13.00	5.4	40.0	14.42	119	-0.51	0.630	6.875	0.20	-18.9	21.6
DAY 11	42	13.87	5.100	13.50	4.3	33.5	15.29	39	-0.88	1.157	7.224	-1.00	-21.3	15.5
DAY 14	8	14.96	5.075	12.70	9.3	23.7	16.60	6	-3.03	5.786	14.174	-2.85	-26.7	17.3

See footnotes on the first page of the table.

Attachment 10: Summary of Mean Changes From Baseline Over Time for Hematology Analytes (Studies JNJ38174942-DORI-09, DORI-10)

Study: JNJ38174942-ISSNP01

Output DLABNP01: Hematology: Means and Mean Changes from Baseline Over Time
NP Study Group - Studies JNJ38174942-DORI-09, 10 (continued)

Analysis Set: Safety Subject

							Base	change from baseline						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
WBC (X10E9/L)														
Imi														
END IV THERAPY	221	13.16	5.215	12.00	4.4	40.0	14.60	196	-1.23	0.486	6.801	-1.00	-26.7	21.6
EARLY FOLLOW-UP	241	11.62	4.925	10.10	2.9	29.5	14.51	214	-2.75	0.454	6.637	-2.10	-26.3	16.1
LATE FOLLOW-UP	107	9.28	3.453	8.60	2.8	22.2	13.52	97	-4.25	0.578	5.694	-3.80	-17.2	14.9

See footnotes on the first page of the table.

Attachment 11.1: Shift From Baseline to Maximum Post-Baseline Grade in ALT and AST - Using Sponsor Defined Ranges (Study JNJ-38174942-DORI-09: ITT Analysis Set)

Shift From Baseline to Maximum Post-Baseline Grade in ALT and AST - Using Sponsor Defined Ranges
(Study JNJ-38174942-DORI-09: ITT Analysis Set)

	Treatment Group and Evaluation at Baseline									
	DORIPENEM					PIPERACILLIN/ TAZOBACTAM				
	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total
ALT (SGPT)										
End point (IV)										
≤ ULN	70(44.0)	17(10.7)	0	0	87(54.7)	75(53.2)	13(9.2)	2(1.4)	0	90(63.8)
>ULN-3xULN	35(22.0)	20(12.6)	2(1.3)	3(1.9)	60(37.7)	22(15.6)	18(12.8)	1(0.7)	0	41(29.1)
>3xULN-5xULN	5(3.1)	4(2.5)	0	0	9(5.7)	5(3.5)	2(1.4)	1(0.7)	1(0.7)	9(6.4)
>5xULN	2(1.3)	1(0.6)	0	0	3(1.9)	0	1(0.7)	0	0	1(0.7)
Total	112(70.4)	42(26.4)	2(1.3)	3(1.9)	159(100)	102(72.3)	34(24.1)	4(2.8)	1(0.7)	141(100)
End IV therapy										
≤ ULN	63(43.2)	16(11.0)	0	0	79(54.1)	69(52.3)	13(9.8)	2(1.5)	0	84(63.6)
>ULN-3xULN	34(23.3)	21(14.4)	2(1.4)	3(2.1)	60(41.1)	20(15.2)	17(12.9)	1(0.8)	0	38(28.8)
>3xULN-5xULN	3(2.1)	2(1.4)	0	0	5(3.4)	5(3.8)	2(1.5)	1(0.8)	1(0.8)	9(6.8)
>5xULN	2(1.4)	0	0	0	2(1.4)	0	1(0.8)	0	0	1(0.8)
Total	102(69.9)	39(26.7)	2(1.4)	3(2.1)	146(100)	94(71.2)	33(25.0)	4(3.0)	1(0.8)	132(100)
Test of cure										
≤ ULN	70(55.1)	17(13.4)	0	0	87(68.5)	61(58.1)	17(16.2)	2(1.9)	0	80(76.2)
>ULN-3xULN	17(13.4)	11(8.7)	1(0.8)	1(0.8)	30(23.6)	10(9.5)	9(8.6)	1(1.0)	0	20(19.0)
>3xULN-5xULN	3(2.4)	1(0.8)	1(0.8)	1(0.8)	6(4.7)	3(2.9)	1(1.0)	0	0	4(3.8)
>5xULN	4(3.1)	0	0	0	4(3.1)	1(1.0)	0	0	0	1(1.0)
Total	94(74.0)	29(22.8)	2(1.6)	2(1.6)	127(100)	75(71.4)	27(25.7)	3(2.9)	0	105(100)

Note: ULN = Upper limit of the normal range for the regional laboratory where the sample was processed. The denominator of the percentage is the number of subjects whose baseline grade and at least one post-baseline grade are not missing.

(continued)

Attachment 11.1: Shift From Baseline to Maximum Post-Baseline Grade in ALT and AST - Using Sponsor Defined Ranges (Study JNJ-38174942-DORI-09: ITT Analysis Set)

Shift From Baseline to Maximum Post-Baseline Grade in ALT and AST - Using Sponsor Defined Ranges
(Study JNJ-38174942-DORI-09: ITT Analysis Set) (continued)

	Treatment Group and Evaluation at Baseline									
	DORIPENEM					PIPERACILLIN/ TAZOBACTAM				
	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total
AST (SGOT)										
End point (IV)										
≤ ULN	63(39.6)	32(20.1)	2(1.3)	0	97(61.0)	81(57.0)	20(14.1)	1(0.7)	1(0.7)	103(72.5)
>ULN-3xULN	19(11.9)	34(21.4)	1(0.6)	1(0.6)	55(34.6)	13(9.2)	18(12.7)	3(2.1)	1(0.7)	35(24.6)
>3xULN-5xULN	2(1.3)	1(0.6)	0	1(0.6)	4(2.5)	0	1(0.7)	0	1(0.7)	2(1.4)
>5xULN	2(1.3)	1(0.6)	0	0	3(1.9)	2(1.4)	0	0	0	2(1.4)
Total	86(54.1)	68(42.8)	3(1.9)	2(1.3)	159(100)	96(67.6)	39(27.5)	4(2.8)	3(2.1)	142(100)
End IV therapy										
≤ ULN	55(37.7)	31(21.2)	2(1.4)	0	88(60.3)	74(56.1)	21(15.9)	1(0.8)	1(0.8)	97(73.5)
>ULN-3xULN	18(12.3)	33(22.6)	1(0.7)	1(0.7)	53(36.3)	12(9.1)	15(11.4)	3(2.3)	1(0.8)	31(23.5)
>3xULN-5xULN	0	1(0.7)	0	1(0.7)	2(1.4)	0	1(0.8)	0	1(0.8)	2(1.5)
>5xULN	1(0.7)	1(0.7)	0	1(0.7)	3(2.1)	2(1.5)	0	0	0	2(1.5)
Total	74(50.7)	66(45.2)	3(2.1)	3(2.1)	146(100)	88(66.7)	37(28.0)	4(3.0)	3(2.3)	132(100)
Test of cure										
≤ ULN	58(45.7)	38(29.9)	0	0	96(75.6)	60(56.6)	21(19.8)	3(2.8)	1(0.9)	85(80.2)
>ULN-3xULN	10(7.9)	14(11.0)	1(0.8)	1(0.8)	26(20.5)	8(7.5)	9(8.5)	0	0	17(16.0)
>3xULN-5xULN	0	2(1.6)	0	1(0.8)	3(2.4)	2(1.9)	1(0.9)	0	0	3(2.8)
>5xULN	1(0.8)	1(0.8)	0	0	2(1.6)	1(0.9)	0	0	0	1(0.9)
Total	69(54.3)	55(43.3)	1(0.8)	2(1.6)	127(100)	71(67.0)	31(29.2)	3(2.8)	1(0.9)	106(100)

Attachment 11.2: Shift From Baseline to Post-Baseline Grade in ALT and AST - Using Sponsor Defined Ranges (Study JNJ-38174942-Dori-10: ITT Analysis Set)

Shift From Baseline to Post-Baseline Grade in ALT and AST - Using Sponsor Defined Ranges
(Study JNJ-38174942-Dori-10: ITT Analysis Set)

	Treatment Group and Evaluation at Baseline									
	DORIPENEM					IMIPENEM				
	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total
ALT (SGPT)										
End point (IV)										
≤ ULN	64(27.0)	16(6.8)	0	0	80(33.8)	82(35.0)	32(13.7)	1(0.4)	0	115(49.1)
>ULN-3xULN	57(24.1)	54(22.8)	6(2.5)	5(2.1)	122(51.5)	47(20.1)	40(17.1)	7(3.0)	6(2.6)	100(42.7)
>3xULN-5xULN	8(3.4)	9(3.8)	3(1.3)	1(0.4)	21(8.9)	7(3.0)	2(0.9)	1(0.4)	1(0.4)	11(4.7)
>5xULN	6(2.5)	8(3.4)	0	0	14(5.9)	3(1.3)	0	2(0.9)	3(1.3)	8(3.4)
Total	135(57.0)	87(36.7)	9(3.8)	6(2.5)	237(100)	139(59.4)	74(31.6)	11(4.7)	10(4.3)	234(100)
End IV Therapy										
≤ ULN	58(27.1)	15(7.0)	0	0	73(34.1)	72(34.8)	29(14.0)	1(0.5)	0	102(49.3)
>ULN-3xULN	50(23.4)	52(24.3)	6(2.8)	5(2.3)	113(52.8)	38(18.4)	38(18.4)	5(2.4)	5(2.4)	86(41.5)
>3xULN-5xULN	5(2.3)	6(2.8)	3(1.4)	1(0.5)	15(7.0)	8(3.9)	2(1.0)	1(0.5)	1(0.5)	12(5.8)
>5xULN	6(2.8)	7(3.3)	0	0	13(6.1)	4(1.9)	0	2(1.0)	1(0.5)	7(3.4)
Total	119(55.6)	80(37.4)	9(4.2)	6(2.8)	214(100)	122(58.9)	69(33.3)	9(4.3)	7(3.4)	207(100)
Test of cure										
≤ ULN	56(35.2)	30(18.9)	2(1.3)	5(3.1)	93(58.5)	56(36.4)	28(18.2)	4(2.6)	3(1.9)	91(59.1)
>ULN-3xULN	27(17.0)	18(11.3)	3(1.9)	1(0.6)	49(30.8)	28(18.2)	14(9.1)	4(2.6)	3(1.9)	49(31.8)
>3xULN-5xULN	4(2.5)	5(3.1)	0	0	9(5.7)	8(5.2)	4(2.6)	0	1(0.6)	13(8.4)
>5xULN	5(3.1)	2(1.3)	1(0.6)	0	8(5.0)	1(0.6)	0	0	0	1(0.6)
Total	92(57.9)	55(34.6)	6(3.8)	6(3.8)	159(100)	93(60.4)	46(29.9)	8(5.2)	7(4.5)	154(100)

Note: ULN = Upper limit of the normal range for the regional laboratory where the sample was processed. The denominator of the percentage is the number of subjects whose baseline grade and at least one post-baseline grade are not missing. Endpoint i.v. therapy was defined as the last available value measured during i.v. therapy. End i.v. therapy was defined as the value measured between the day before and the after the day of last i.v. dose. (continued)

Attachment 11.2: Shift From Baseline to Post-Baseline Grade in ALT and AST - Using Sponsor Defined Ranges (Study JNJ-38174942-Dori-10: ITT Analysis Set)

Shift From Baseline to Post-Baseline Grade in ALT and AST – Using Sponsor Defined Ranges
(Study JNJ-38174942-Dori-10: ITT Analysis Set) (continued)

	Treatment Group and Evaluation at Baseline									
	DORIPENEM					IMIPENEM				
	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total	≤ ULN	>ULN-3xULN	>3xULN-5xULN	>5xULN	Total
AST (SGOT)										
End point (IV)										
≤ ULN	70(29.4)	31(13.0)	2(0.8)	2(0.8)	105(44.1)	77(32.9)	45(19.2)	2(0.9)	2(0.9)	126(53.8)
>ULN-3xULN	46(19.3)	57(23.9)	7(2.9)	1(0.4)	111(46.6)	45(19.2)	42(17.9)	6(2.6)	4(1.7)	97(41.5)
>3xULN-5xULN	4(1.7)	8(3.4)	2(0.8)	0	14(5.9)	2(0.9)	2(0.9)	2(0.9)	2(0.9)	8(3.4)
>5xULN	3(1.3)	5(2.1)	0	0	8(3.4)	1(0.4)	1(0.4)	1(0.4)	0	3(1.3)
Total	123(51.7)	101(42.4)	11(4.6)	3(1.3)	238(100)	125(53.4)	90(38.5)	11(4.7)	8(3.4)	234(100)
End IV Therapy										
≤ ULN	67(31.2)	31(14.4)	2(0.9)	2(0.9)	102(47.4)	66(31.9)	43(20.8)	2(1.0)	2(1.0)	113(54.6)
>ULN-3xULN	40(18.6)	47(21.9)	7(3.3)	1(0.5)	95(44.2)	40(19.3)	33(15.9)	5(2.4)	4(1.9)	82(39.6)
>3xULN-5xULN	2(0.9)	5(2.3)	2(0.9)	0	9(4.2)	4(1.9)	2(1.0)	2(1.0)	1(0.5)	9(4.3)
>5xULN	4(1.9)	5(2.3)	0	0	9(4.2)	1(0.5)	1(0.5)	1(0.5)	0	3(1.4)
Total	113(52.6)	88(40.9)	11(5.1)	3(1.4)	215(100)	111(53.6)	79(38.2)	10(4.8)	7(3.4)	207(100)
Test of cure										
≤ ULN	70(44.0)	39(24.5)	7(4.4)	2(1.3)	118(74.2)	65(42.2)	42(27.3)	4(2.6)	2(1.3)	113(73.4)
>ULN-3xULN	16(10.1)	19(11.9)	1(0.6)	1(0.6)	37(23.3)	19(12.3)	14(9.1)	2(1.3)	3(1.9)	38(24.7)
>3xULN-5xULN	2(1.3)	1(0.6)	0	0	3(1.9)	1(0.6)	1(0.6)	0	0	2(1.3)
>5xULN	1(0.6)	0	0	0	1(0.6)	0	1(0.6)	0	0	1(0.6)
Total	89(56.0)	59(37.1)	8(5.0)	3(1.9)	159(100)	85(55.2)	58(37.7)	6(3.9)	5(3.2)	154(100)