CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-106

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-106
Submission Date	December 12, 2006
Brand Name	TBD
Generic Name	Doripenem for Injection
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OCP Division	DCP4
OND Division	DAIOP
Applicant	Johnson & Johnson
Relevant IND(s)	66,416
Submission Type; Code	Original NDA (NME)
Formulation; Strength	Doripenem for Injection, 500 mg single-use vial
Indication(s)	Treatment of adults with complicated intra-abdominal infections or complicated urinary tract infections, including [redacted] pyelonephritis, caused by susceptible bacteria.

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1. EXECUTIVE SUMMARY

Doripenem is an injectable, synthetic carbapenem (β-lactam) antibacterial agent with broad-spectrum activity against gram-positive and gram-negative pathogenic bacteria, including anaerobic organisms. The compound was discovered by Shionogi & Co., Ltd. (Osaka, Japan). In 2003, Peninsula Pharmaceuticals, Inc. (PPI) obtained an exclusive license for the development of doripenem in North America, South America, and Europe. PPI has subsequently transferred all sponsor obligations to Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&J). Doripenem for Injection (Finibax®), 250 mg, 2 or 3 times a day, has been registered for commercial use in Japan since 2005. Doripenem was studied in comprehensive preclinical testing and in Phase 1, 2 and 3 clinical studies by Shionogi & Co. in Japan, as well as Phase 1, 2 and 3 clinical studies conducted by PPI and Johnson & Johnson in North America, South America and Europe. The safety, tolerability and pharmacokinetics (PK) of doripenem by intravenous infusion have been evaluated in a total of 48 clinical studies in adults – 16 Phase 1 studies, 10 Phase 2 studies and 22 Phase 3 studies. In this New Drug Application (NDA), the Sponsor proposes a doripenem dose of 500 mg IV every 8 hours (q8h) in adults for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including [redacted] pyelonephritis caused by susceptible bacteria.

Doripenem shares the same bactericidal mechanism of action of other β-lactam antibiotics by targeting penicillin-binding proteins (PBPs) to inhibit the biosynthesis of the bacterial cell wall. It has demonstrated a high affinity for multiple PBPs of susceptible species. Doripenem is resistant to hydrolysis by a variety of β-lactamases, including penicillinases, cephalosporinases, and extended spectrum β-lactamases, and thereby retains activity against most cephalosporin-resistant gram-negative bacilli. Doripenem's *in vitro* antibacterial spectrum of activity includes methicillin-susceptible *staphylococci*, *streptococci* spp. (including penicillin-resistant *Streptococcus pneumoniae* [PRSP]), Enterobacteriaceae, *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis,* ceftazidime-susceptible *Acinetobacter* spp., *Neisseria* spp., *Bordetella* spp., *Bacteroides* spp., *Prevotella* spp., *Clostridium* spp., and other gram-positive anaerobes.

A summary of the components submitted by the Sponsor in support of the NDA are as follows:

- Seven *in vitro* studies performed with human biomaterials (cells, tissues, or related materials) that are pertinent to characterizing human pharmacokinetics (metabolism, protein binding, etc.) have been submitted.
- Eight Phase 1 studies sponsored by J&J and PPI and conducted in Western populations have been submitted. These include 3 PK studies conducted in healthy subjects and 3 conducted in special populations (subjects with varying degrees of renal impairment, subjects on hemodialysis, and elderly subjects), as well as one pharmacodynamic (PD) study (a thorough QT/QTc study). A clinical study of an aerosolized form of doripenem was also conducted to evaluate its potential use for the management of chronic pulmonary infections in patients with cystic fibrosis; however, the inhaled program was subsequently terminated.
- A total of 33 Phase 1, 2 and 3 Japanese studies have been submitted. The studies include a drug interaction study conducted with probenecid in healthy subjects and multiple studies evaluating initial tolerability, safety and drug distribution in various patient populations.
- Four Phase 3 trials have been submitted in support of the efficacy and safety of doripenem in the treatment of cIAI and cUTI, including complicated and uncomplicated pyelonephritis (DORI-05, DORI-06, DORI-07 and DORI-08).

1.1. Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant in the NDA submission is acceptable. Labeling comments will be communicated to the Applicant.

1.2. Phase IV Commitments

No Phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Doripenem is a synthetic broad-spectrum antibacterial agent that belongs to the carbapenem class of β-lactam antibiotics. Doripenem achieves bactericidal activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria by inhibiting the transpeptidation process required to complete peptidoglycan biosynthesis. Its *in vitro* antimicrobial spectrum includes methicillin susceptible Staphylococci, Streptococci (including penicillin-resistant *Streptococcus pneumoniae*), Enterobacteriaceae spp., *Haemophilus influenzae*, *Moraxella catarrhalis*, Neisseria spp., Bordetella spp., *Bacteroides fragilis*, Clostridium spp., Peptostreptococcus spp. and *Pseudomonas aeruginosa*. Like other carbapenems, doripenem is stable toward most plasma- or chromosomally-mediated β-lactamases, conferring activity against β -lactamase producing pathogens.

The clinical pharmacology characteristics of doripenem have been examined in Japanese healthy subjects and Japanese patients with urologic infections and surgical patients. A number of studies evaluating the pharmacology of doripenem have also been conducted in Western populations of healthy subjects, including subjects with impaired renal function and the elderly. Doripenem dose selection was based on the exposure-response (E/R) relationship defined by *in vitro* time-kill studies, *in vivo* animal models of infection, and Monte-Carlo simulations. In addition, a population PK analysis was performed using pooled data from healthy subjects with varying degrees of renal impairment and from patients with cUTI or pyelonephritis from a total of 7 studies (n = 285). The population PK analysis assessed the effect of various subject covariates on doripenem PK parameters and exposure. Monte Carlo simulations were performed to estimate the expected PK/PD target attainment rates in patients with cUTI or cIAI for a given dose. Additionally, target attainment rates and relative exposure ratios were determined for varying degrees of renal impairment to support the recommendation for dosage adjustment in renal impairment. The studies conducted show doripenem demonstrates the following clinical pharmacology characteristics:

Exposure-Response:

- Animal models of infection established T > MIC as the primary PK/PD parameter related to efficacy. Efficacy studies for doripenem in the neutropenic mouse thigh infection model were conducted with penicillin-susceptible (PSSP), penicillin-resistant (PRSP) and quinolone-resistant strains of *S. pneumoniae*, methicillin-susceptible and –resistant strains of *S. aureus*, and cephalosporin and ESBL-producing strains of Gram-negative bacilli (GNB). The %T>MIC required to produce a static effect ranged from of 2.3 to 38% among the individual pathogens studied. GNB and *S. aureus* required the longest %T>MIC for a static effect, with mean values of 29%. For *S. pneumonia* the mean %T>MIC for a static effect was 12.4%.

- There was no major difference in %T>MIC determinations for PSSP, PRSP and quinolone-resistant strains of *S. pneumoniae*. Nor did the presence of methicillin-resistance or ESBL production impact the magnitude of %T>MIC necessary for efficacy.
- Simulations based on a target %T>MIC of at least 35% support the use of a 500 mg x 1-hour infusion every 8 hours (q8h) in subjects with normal renal function for target pathogens with doripenem MICs ≤ 2 μg/mL.
- Plasma concentration sampling was not performed in any of the Phase 3 clinical trials of cUTI or cIAI. As such, a dose/concentration-response relationship could not be determined for clinical and microbiological outcomes in the clinical trials.
- Pathogen susceptibility data from the Phase 3 cIAI and cUTI trials were used in the final population PK model to assess PK/PD target attainment in all patients with varying degrees of renal impairment. The results indicate a high level of target attainment (≥95.5% for cUTI subjects and ≥91.7% for cIAI subjects) for the %T>MIC target of 35% when doripenem was dosed according to the recommended dosing regimen based on renal function.
- Doripenem MIC distributions from the cIAI trials indicate that most pathogens (93.4%) had MIC values of ≤ 2 μg/mL. Enterococcus spp. demonstrated the greatest resistance, with 35%, 16% and 19% of strains exhibiting MIC values of 4, 8 and ≥ 16 μg/mL, respectively. Similarly, 96.8% of pathogens from the cUTI trials had MIC values of ≤ 2 μg/mL. UTI pathogens with higher MIC values (≥4) included *P. aeruginosa*, Enterococcus spp. and Staphylcoccus spp.
- No dose-limiting adverse events have been identified for doripenem. A small study conducted in Japan attempted to examine the relationship between drug exposure and abnormal hepatobilliary laboratory results. No relationship was identified, though limitations in study design and a small number of subjects with elevated enzymes limits the interpretation of these results. In an ascending, multiple-dose PK study conducted in Western healthy volunteers, there was an apparent dose-response trend for an increase in hepatic enzymes following repeated doripenem administration. The trend was most pronounced at the highest dose – 1000 mg q8h. However, evaluation of doripenem PK parameters in the 5 subjects with elevated liver enzymes reveals no apparent relationship between elevated enzymes and increased drug exposure within the ascending dosage cohorts.
- Administration of doripenem at doses of 500 mg over 1 hour q8h (x 4 doses) and 1000 mg over 1 hour q8h (x 4 doses) demonstrated no signal of any effect on cardiac repolarization. There was no signal of any relationship between the plasma concentration of doripenem and change in QTc from baseline.

Pharmacokinetics Summary:

- A summary of PK parameters in healthy Western subjects on Day 1 and Day 7 following multiple ascending dosing of doripenem 500 mg and 1000 mg, q12h and q8h are listed in Table 1.3-1 below.

Table 1.3-1 Summary of Doripenem Pharmacokinetic Parameters (Geometric Mean [%CV])

Parameter	Cohort A (500 mg Q12h[a])		Cohort B (500 mg Q8h[a])		Cohort C (1000 mg Q12h[a])		Cohort D (1000 mg Q8h[a])	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
n	6	6	6	5[b]	6	6	6	6
C_{max} (ng/ml)	32982 (6.81)	30250 (14.7)	31770 (18.8)	31204 (11.5)	49335 (22.5)	45934 (11.5)	47999 (8.75)	42867 (9.20)
t_{max} (h)[c]	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0.5-0.58)	0.5 (0.5-0.5)	1.00 (1.0-1.0)	1.00 (1.0-1.0)	1.00 (1.0-1.0)	1.00 (1.0-1.0)
$AUC_{0-\tau}$ (ng·h/ml)	35869 (6.37)	33687 (8.36)	36140 (16.7)	35292 (12.5)	79300 (21.8)	71016 (17.5)	75513 (10.6)	65408 (9.48)
$AUC_{0-\infty}$ (ng·h/ml)	35746 (6.34)	--	36144 (16.6)	--	79122 (21.9)	--	76484 (9.99)	--
t1/2 (h)	0.868 (8.06)	0.824 (4.33)	1.00 (22.6)	0.869 (8.29)	1.03 (11.7)	1.13 (8.24)	1.03 (24.2)	0.932 (11.0)
CL (ml/min)	233 (7.00)	--	231 (17.9)	--	211 (22.6)	--	218 (9.49)	--
CL_R (ml/min)	--	156 (13.6)	--	164 (11.5)	--	156 (21.7)	--	179 (17.5)
Vss (ml)	13711 (10.4)	--	14773 (16.3)	--	14533 (20.7)	--	16404 (14.0)	--
R_O	--	0.939 (6.10)	--	0.923 (8.73)	--	0.896 (9.74)	--	0.866 (8.27)

[a] 500 mg doses were infused over 30 minutes; 1000 mg doses were infused over 1 hour
[b] Subject 12 withdrew prior to Day 7 dosing
[c] Median (min-max) data

Source: Clinical Study Report DORI-01

- No evidence of accumulation of doripenem was observed at any of the dose levels studied upon repeat dosing. Clearance of doripenem appears to remain constant at the range of doses studied.
- Doripenem has demonstrated linear pharmacokinetics over a dosage range of 125 mg to 1000 mg. Dose proportionality was confirmed for 1-hour and 4-hour infusions of 500 mg and 1000 mg doses of doripenem.
- The population PK analysis determined cUTI / pyelonephritis disease state was not an independent predictor of doripenem clearance.

Absorption:

Not applicable; drug is administered intravenously.

Distribution:

- The median (range) doripenem volume of distribution at steady-state in healthy Western subjects was 16.6 L (8.09 – 55.5L), similar to the extracellular fluid volume in humans. No relationship between Vd_{ss} and doripenem dose was observed.
- *In vitro* protein binding of doripenem in human plasma was 8.1% at a concentration of 100 µg/mL. *Ex vivo* binding to serum proteins was 5.4 to 15.2% across a dosage range of 125 mg to 1000 mg in single- and multiple-dose studies conducted in Japanese subjects.

- Doripenem exposure in various body tissues and fluids was evaluated in Phase 2 and 3 Japanese studies. Peritoneal exudate concentration at t_{max} was a mean of 3.2 μg/mL (20% of plasma concentrations) in a study of 5 surgical patients. Peritoneal exposure persisted at 2.5 hours post-dose, lowering to 1.1 μg/mL (160% of plasma concentrations) at 4.5 hours post-dose.

Metabolism:

- The results of *in vitro* studies conducted with pooled human liver microsomes (HLM) in the presence and absence of NADPH indicate that doripenem undergoes no metabolism, CYP450-mediated or otherwise. Further, doripenem had no effect on the modulation of CYP enzymes or UDP-glucuronosyltransferase (UGT) enzymes in HLM and human hepatocytes.
- In 2 Japanese studies the application of TLC-bioautography found no active metabolites of doripenem in plasma or urine following single doses of 25 mg to 1000 mg.
- *In vitro* studies have confirmed the role of dehydropeptidase-1 (DHP-1) in the metabolism of doripenem to doripenem-M1 (doripenem dicarboxylic acid), the inactive ring-opened metabolite. After incubating doripenem, meropenem and imipenem in purified murine DHP-1 for 90 min., residual concentrations of the respective agents were 82.4%, 78.1% and 23.2%, indicating that doripenem has a similar rate of hydrolysis as meropenem. Like meropenem, doripenem should be administered without the addition of a DHP-1 inhibitor.
- The mean ratio of doripenem-M1 to doripenem AUC was 18.3% across single-dose healthy volunteer studies conducted in Western populations.

Excretion:

- As a consequence of its primarily renal route of elimination, doripenem concentrates well in the urine, exceeding plasma concentrations by an average of 600-fold for 4 hours post-infusion.
- Doripenem is excreted mainly unchanged. Across pooled studies conducted in Western populations, approximately 70% and 15% of doripenem doses (500 mg and 1000 mg) were excreted as the parent drug and doripenem-M1, respectively.
- The mean renal clearance of doripenem across healthy Western populations administered 500 mg and 1000 mg single- and multiple-doses is 170 mL/min. This value exceeds normal rates of glomerular filtration in healthy adults, indicating a contribution from active tubular secretion (ATS) to renal excretion. Results of a drug interaction study conducted with probenecid confirm the role of ATS in doripenem renal elimination.

Intrinsic Factors:

- Renal impairment has a significant effect on doripenem exposure. In a study conducted in a Western population of subjects with mild, moderate, severe and end-stage renal impairment (post-hemodialysis infusion), doripenem AUC was 1.6-, 2.8-, 5.1- and 7.3-times that of healthy control subjects.
- Based on the knowledge that patients with renal impairment have significantly higher exposure of doripenem, Monte Carlo simulations were performed to determine doses necessary for achieving the PK/PD target in individuals with mild, moderate and severe degrees of renal impairment. Table 1.3-2 lists the recommended doses proposed by the Sponsor for varying degrees of renal impairment based on these simulations.
- A study was conducted in which subjects with end-stage renal disease (ESRD) were administered 500 mg doripenem pre- and post-hemodialysis (HD). A standard 4-hour HD session started 1 hour after the end of doripenem infusion decreased doripenem and doripenem-M1 concentrations by approximately 90% and 82%, respectively. Concentrations rebounded slightly thereafter, likely due to redistribution.

- In ESRD subjects administered a 500 mg dose of doripenem immediately prior to HD, the mean extraction ratio of a 4-hr HD session was 0.56 for doripenem and 0.49 for doripenem-M1, resulting in the removal of approximately half of the original doripenem dose (259 mg).

Table 1.3-2 Target Attainment Rates and Relative Exposure Ratios for Varying Degrees of Renal Impairment

Dose	Renal Category	MIC (μg/mL)	% Subjects with % T>MIC 35%	MIC (μg/mL)	% Subjects with % T>MIC 35%	C_{max} Ratio[a]	AUC_{24} Ratio[a]
500 mg q8h	Normal	1	98.5	2	76.5	1	1
500 mg q8h	Mild	1	100	2	97.6	1.12	1.39
250 mg q8h	Moderate	1	99.7	2	88.3	0.6	0.99
250 mg q12h	Severe	1	99.3	2	84.6	0.65	1.03

[a] Ratio of predicted exposure at steady state relative to "normal" category

Source: Module 2.7 Clinical Summary, Section 2.7.2

- In a study evaluating the effects of age on doripenem PK, elderly subjects had a 33% lower total body clearance than non-elderly subjects. Doripenem exposure in elderly subjects was approximately 1.5 times that of younger subjects. Renal clearance was 30% lower in the elderly, roughly equivalent to the difference in creatinine clearance, which was 32% lower. The observed increase in doripenem exposure in the elderly is primarily due to reduced renal function, as opposed to age.
- No significant gender-related differences in doripenem pharmacokinetics were observed.
- The effect of race on doripenem PK was examined in the population PK analysis, which determined there is no clinically relevant difference in doripenem PK between Caucasians, Hispanic/Latino, African American and Asian subjects. Comparison of doripenem exposure across Western and Japanese studies did not reveal any marked differences between the two populations.

Extrinsic Factors:

- In vitro data from human liver microsomes suggest a low probability of drug-drug interactions between doripenem and drugs that are metabolized by cytochrome P450 enzymes.
- Concomitant administration of probenecid, an inhibitor of renal organic anionic transporters (OATs), resulted in a 75% increase in doripenem AUC_{0-12}, a 15% increase in C_{max} and a 53% increase in half-life. The increase in doripenem exposure observed in this study is less than what has been observed with the 1000 mg dose of doripenem administered alone. However, experience with the 1000 mg dose in humans is extremely limited, particularly multiple dosing. Based on the lack of safety data at the higher anticipated doripenem exposure, the Sponsor's recommendation to avoid probenecid co-administration with doripenem is appropriate.
- A clinically significant reduction in serum valproic acid (VPA) concentrations has been reported for other carbapenem antibiotics. *In vitro* studies evaluating the effect of doripenem on VPA metabolism demonstrated doripenem's inhibition of VPA-glucuronide hydrolysis. Studies conducted in rats and monkeys confirmed that doripenem inhibits VPA-glucuronide hydrolysis *in vivo*. However, in these animal studies VPA serum concentrations were not significantly lowered. A study evaluating the effect of doripenem on VPA exposure has not

been conducted in humans. Serum concentrations of VPA should be monitored during co-administration with doripenem therapy.

LIST OF ABBREVIATIONS

CE	Clinically evaluable
EOT	End of therapy
TOC	Test-of-cure
ME	Microbiologically evaluable
mMITT	Microbiological modified intent-to-treat

2. QUESTION BASED REVIEW

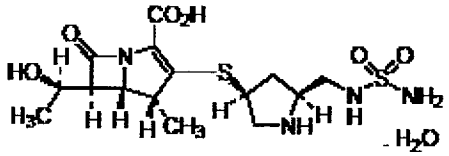
2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Doripenem is a synthetic broad-spectrum antibacterial agent, a member of the penem class of β-lactam antibiotics. The chemical structure and physical-chemical properties of doripenem monohydrate are described below:

Structural Formula: $C_{15}H_{24}N_4O_6S_2 \cdot H_2O$

Chemical Structure:



Chemical Name: (4R,5S,6S)-3-[((3S,5S)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl)thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1- azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Molecular Weight: 420.50 g/mol

Solubility Profile:
Doripenem monohydrate is soluble in *N,N*-dimethylformamide, sparingly soluble in water and pH slightly soluble in and practically insoluble in at 20 °C. The solubility in aqueous solvents relevant to clinical performance is as follows:

Solvent	Solubility (mg/mL)	pH	USP Definition
Purified Water	23.5	5.19	Sparingly soluble
Sodium Chloride Injection	23.6	5.15	Sparingly soluble
Dextrose Injection	23.3	5.02	Sparingly soluble

Partition Coefficient:
The distribution ratio in 1-octanol/water is 0.002 at 20 °C.

Drug Product:
The drug product is a white to slightly yellowish, off-white crystalline powder. Single-use 20 mL glass vials contain 500 mg (anhydrous) of sterile doripenem powder for consititution (no excipients).

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Doripenem is an injectable, sterile, synthetic broad-spectrum carbapenem (β-lactam) with *in vitro* activity against aerobic and anaerobic gram-positive and gram-negative bacteria. Doripenem shares the bactericidal mode of action of other β-lactams by targeting penicillin-binding proteins (PBPs) to inhibit the biosynthesis of the bacterial cell wall, and has a high affinity for multiple major PBPs of susceptible species. Its *in vitro* antibacterial spectrum includes methicillin-susceptible staphylococci, streptococci (including PRSP), Enterobacteriaceae, *Haemophilus influenzae, Pseudomonas aeruginosa,* ceftazidime-susceptible *Acinetobacter* spp., *Bacteroides* spp., *Prevotella* spp., *Clostridium* spp., and other gram-positive anaerobes. Minimum concentrations that inhibit 90% of strains (MIC_{90}) for these species are usually <1 μg/ml.

Like the other carbapenems, doripenem is resistant to hydrolysis by a variety of β-lactamases, including penicillinases, cephalosporinases, and extended spectrum β-lactamases; thus doripenem retains activity against most cephalosporin-resistant gram-negative bacilli.

Doripenem is proposed for the treatment of adults with the following infections caused by susceptible bacteria:

- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (cUTI), including [redacted] pyelonephritis

2.1.3. What is the proposed dosage and route of administration?

The proposed dose of doripenem for injection is 500 mg every 8 hours (q8h) administered by intravenous infusion over 1 hour. The recommended duration by infection is described below:

Infection	Dose	Duration
Complicated intra-abdominal infections (cIAI)	500 mg q8h	5 – 14 Days[†]
Complicated urinary tract infections (cUTI), including [redacted] pyelonephritis	500 mg q8h	10 Days[†‡]

[†] Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy.
[‡] Duration may be extended up to 14 days for patients with concurrent bacteremia.

The Applicant has proposed the following changes in dose based on renal function status:

Renal Status	CrCl (mL/min)[†]	Dose
Moderate renal impairment	30 – 50	250 mg q8h
Severe renal impairment	> 10 to < 30	250 mg q12h

[†] Based on Cockroft-Gault formula, using actual body weight

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Based on a target %T>MIC of 27 – 43% of the dosing interval derived from animal studies, the Sponsor determined doses of doripenem that would result in concentrations remaining above expected MICs for at least 35% of the dosing interval for evaluation in Phase 1 and 2. Phase 1 studies, including Western studies DORI-01, DORI-04 and DORI-NOS-1004, assessed the safety, tolerability and PK of doripenem following single- and multiple-dose administration of 500 mg and 1000 mg doses. Multiple-dose administration included 500 mg and 1000 mg every 8 hours and every 12 hours for 7 to 10 days. Phase 2 study DORI-03 was a randomized, double-blind, dose-finding study, in which two dosing regimens of doripenem were evaluated – 250 mg q8h and 500 mg q8h – for 7 to 14 days in the treatment of cUTI in 120 adults. Both doses were administered over 1 hour. No switch to oral therapy was permitted in this study. All subjects returned to the study center at 5 to 9 days and 28 to 35 days for the test of cure (TOC) and late follow-up visits, respectively. The primary outcome was microbiological response at the TOC visit in the microbiologically-evaluable population. Both doses evaluated had similar efficacy results (microbiological outcome) as compared to other cUTI studies in which parenteral antibiotics are used solely. Per subject microbiological response at TOC was not statistically different for the two doses.

Doses were selected for Phase 3 study using the preliminary population PK model, clinically relevant pathogen MIC data and PK/PD targets from the animal infection model. Monte Carlo simulations were performed to estimate the probability of target attainment. Simulations based on a target %T>MIC of at least 35% support the use of a 500 mg x 1-hour infusion every 8 hours (q8h) in subjects with normal renal function for target pathogens with doripenem MICs ≤ 2 μg/mL.

The renal impairment study (DORI-02) determined that doripenem AUCs in subjects with mild, moderate, severe and end-stage renal impairment were 1.6-, 2.8-, 5.1- and 7.7-fold that of healthy subjects with normal renal function. Simulations using a preliminary population PK model determined the following doses in order to achieve target attainement rates in renally impaired subjects similar to those respective values in subjects with normal renal function administered 500 mg q8h: mild (500 mg q8h), moderate (250 mg q8h), and severe (250 mg q12h).

The design features of the clinical studies proposed to support the efficacy of doripenem in cIAI and cUTI include the following:

Complicated UTI and Pyelonephritis: The efficacy of doripenem in subjects with cUTI or pyelonephritis was evaluated in two Phase 3 studies. The dose of doripenem evaluated was 500 mg x 1 hour infusion administered q8h, with dosing adjustments made for subjects with moderate and severe renal impairment, as described above.

- DORI-05 was a multi-center, prospective, randomized, double-blind study of doripenem versus levofloxacin (250 mg q24h) in the treatment of cUTI or pyelonephritis in adults conducted in North America, South America and Europe. After ≥ 9 doses of IV drug therapy had been given, patients were allowed to be switched to oral levofloxacin (250 mg q24h) based on clinical and microbiological status. The total treatment duration was 10 days.

- DORI-06 was a multi-center, prospective, open-label, single arm study of doripenem in the treatment of cUTI or pyelonephritis in adults conducted in North America, South America

and Europe. After ≥ 9 doses of IV drug therapy had been given, patients were allowed to be switched to oral levofloxacin (250 mg q24h) based on clinical and microbiological status. The total treatment duration was 10 days.

Complicated Intra-abdominal Infection: The efficacy of doripenem in subjects with cIAI was evaluated in two Phase 3 studies. The dose of doripenem evaluated was 500 mg x 1 hour infusion administered q8h, with dosing adjustments made for subjects with moderate and severe renal impairment, as described above.

- DORI-07, conducted in North America, South America and Europe, was a multicenter, prospective, randomized, double-blind, double-dummy study of doripenem versus meropenem (1 g IV bolus q8h) in the treatment of adults with cIAI. After ≥ 9 doses of IV study drug therapy, patients could have been switched to oral amoxicillin/clavulanate therapy (875/125 mg twice daily) if clinical and laboratory criteria were met. Study duration was a minimum of 5 and a maximum of 14 days.

- DORI-08, conducted in North America, South America and Europe, was a multicenter, prospective, randomized, double-blind, double-dummy study of doripenem versus meropenem (1 g IV bolus q8h) in the treatment of adults with cIAI. After ≥ 9 doses of IV study drug therapy, patients could have been switched to oral amoxicillin/clavulanate therapy (875/125 mg twice daily) if clinical and laboratory criteria were met. Study duration was a minimum of 5 and a maximum of 14 days.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

For the cIAI clinical studies the primary efficacy endpoint was the clinical cure rate at test-of-cure (TOC) visit in the microbiologically evaluable (ME) population and the clinical cure rate at any time up to 60 days after the last dose of study drug therapy in the microbiological modified intent-to-treat (mMITT) analysis set. Secondary measures of efficacy included clinical cure or improvement at the end-of-therapy (EOT) visit, clinical cure at the end of follow-up (EFU) visit, and microbiological cure rates at the EFU and TOC visits.

For the cUTI clinical studies the primary efficacy endpoint was the microbiological cure rate (eradication of all baseline pathogens) at the test-of-cure (TOC) visit in the microbiologically evaluable (ME) and modified microbiological intent-to-treat (mMITT) analysis sets. Secondary measures of efficacy included clinical cure rates at the TOC visit and per uropathogen microbiological cure rate at the TOC visit.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Doripenem, the active parent compound, is metabolized to one ring-opened inactive metabolite, doripenem-M1. Shionogi initially developed a microbioassay for determination of doripenem in plasma and urine for early studies. An HPLC assay was subsequently developed and validated by Shionogi for the analysis of doripenem-M1 in plasma and urine. Later in the development program, Peninsula Pharmaceuticals developed LC-MS/MS validated assays for the quantification of

doripenem and doripenem-M1 in plasma and urine, which were then used for most of the Western clinical studies. Please see section 2.6 for a full description of the analytical methods.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy?

The exposure-response relationship for doripenem has been evaluated using *in vitro* time-kill studies, *in vivo* animal models of infection, Monte Carlo simulations, efficacy results from Phase 3 studies, and exploratory PK/PD analyses.

2.2.4.1.1. Time-Kill Studies

Time-kill experiments performed with doripenem demonstrated bactericidal activity over time. A summary of doripenem bactericidal activity, as well as that of comparators meropenem, imipenem and ceftazidime against 20 strains each of *S. aureus*, *E. coli* and *P. aeruginosa*, is displayed in Table 2.2.4.1.1-1. Doripenem maintained consistent bactericidal activity against the *S. aureus* and *E. coli* strains tested, with MBC_{90} and MIC_{90} values of 0.12 and 0.06, respectively, against both pathogens. Against *P. aeruginosa*, doripenem MBC_{90} and MIC_{90} values were half those of either imipenem or meropenem. The MBC_{90} / MIC_{90} ratios were 2 for all 3 pathogens tested, indicating potent bactericidal activity for these organisms. In a second study measuring MBC and MIC values of doripenem against 10 strains of gram-positive and gram-negative organisms, an MBC/MIC ratio of 8 was observed for strains of *A. baumannii*, *E. cloacae*, *E. coli* and *P. aeruginosa*, while the remaining 6 strains exhibited MBC/MIC ratios of 2 to 4 (Table 2.2.4.1.1-2).

Table 2.2.4.1.1-1 Activity of Doripenem and Comparators Against *S. aureus*, *E. coli* and *P. aeruginosa* Clinical Isolates

Isolate	**N**	**Compound**	**MIC_{90} (µg/ml)**	**MBC_{90} (µg/ml)**	**MBC_{90}/MIC_{90}**
S. aureus	20	Doripenem	0.06	0.12	2
S. aureus	20	Meropenem	0.12	0.25	2
S. aureus	20	Imipenem	0.03	0.06	2
S. aureus	20	Ceftazidime	16	16	1
E. coli	20	Doripenem	0.06	0.12	2
E. coli	20	Meropenem	0.03	0.06	2
E. coli	20	Imipenem	0.5	1	2
E. coli	20	Ceftazidime	0.25	0.25	1
P. aeruginosa	20	Doripenem	1	2	2
P. aeruginosa	20	Meropenem	2	4	2
P. aeruginosa	20	Imipenem	2	4	2
P. aeruginosa	20	Ceftazidime	8	32	4

Source: Module 2, Section 2.7.2.4 Special Studies – Summary of Microbiology

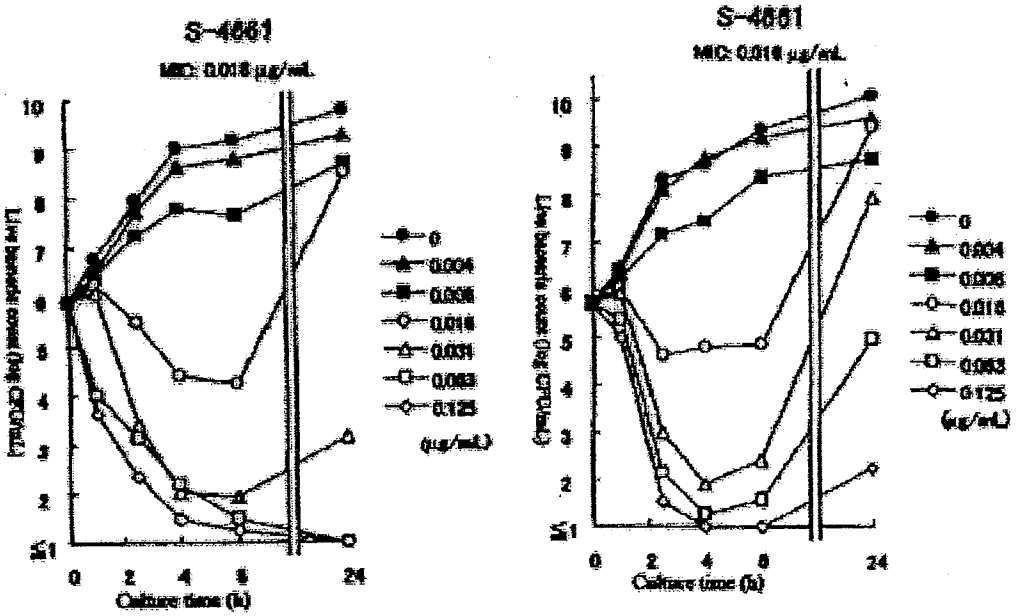
Table 2.2.4.1.1-2 Bacterial Activities of Doripenem Against 10 Individual Gram-Positive and Gram-Negative Isolates

Isolate	MIC (µg/ml)	MBC (µg/ml)	MBC/MIC
A. baumannii	0.5	4	8
E. cloacae	0.25	2	8
E. coli	0.015	0.12	8
E. coli	0.03	0.06	2
K. pneumoniae	0.06	0.25	4
P. aeruginosa	0.25	2	8
E. faecalis	2	8	4
S. aureus	0.03	0.12	4
S. aureus	0.03	0.12	4
S. pneumoniae	0.03	0.12	4

Source: Module 2, Section 2.7.2.4 Special Studies – Summary of Microbiology

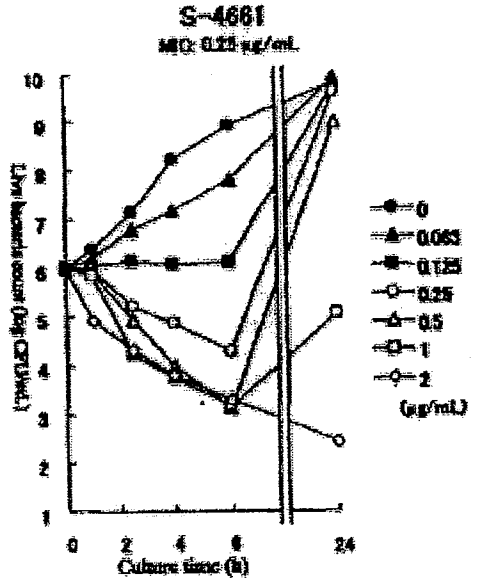
Figure 2.2.4.1.1-1 demonstrates the activity of doripenem against 3 isolates – *S. aureus* Smith (MIC 0.016 µg/mL), *E. coli* NIHJ JC-2 (MIC 0.016 µg/mL), and *P. aeruginosa* ATCC 27853 (MIC 0.25 µg/mL) – at increasing drug concentrations. Doripenem exhibited similar rates of bactericidal activity against the *S. aureus* and *E. coli* strains, with CFU values decreasing approximately 3-$\log_{10}$ magnitudes within the first 2 hours post-exposure at concentrations 2-, 4- and 8-times the MIC. For the *S. aureus* strain, some re-growth occurred by 24 hours, although bacterial counts remained low. For the *E. coli* strain, re-growth had occurred by 24 hours at all concentrations. Results for the two strains were similar for meropenem and imipenem, with the exception of meropenem activity against the *E. coli* strain. Meropenem was more rapidly bactericidal, and no re-growth was noted at 2-, 4- or 8-times the MIC at 24 hours.
When evaluated against *P. aeruginosa* ATCC 27853, doripenem was bactericidal after 6 hours, with CFU values decreasing by approximately 3-$\log_{10}$ values at 2-, 4- and 8-times the MIC. By 24 hours re-growth had occurred for concentrations 2- and 4-times the MIC. At 8-times the MIC, doripenem was bactericidal over 24 hours, reducing the CFU value by approximately 3.5-$\log_{10}$. Results were similar for meropenem and imipenem. In general, the rate of bactericidal activity of the 3 carbapenems tested was similar for the 3 strains of *S. aureus, E. coli* and *P. aeruginosa* tested at 2-, 4- and 8-times the MIC.

Figure 2.2.4.1.1-1 Bactericidal Activity of Doripenem Against *S. aureus* Smith, *E. coli* NIHJ JC-2 and *P. aeruginosa* ATCC 27853



S. aureus Smith

E. coli NIHJ JC-2

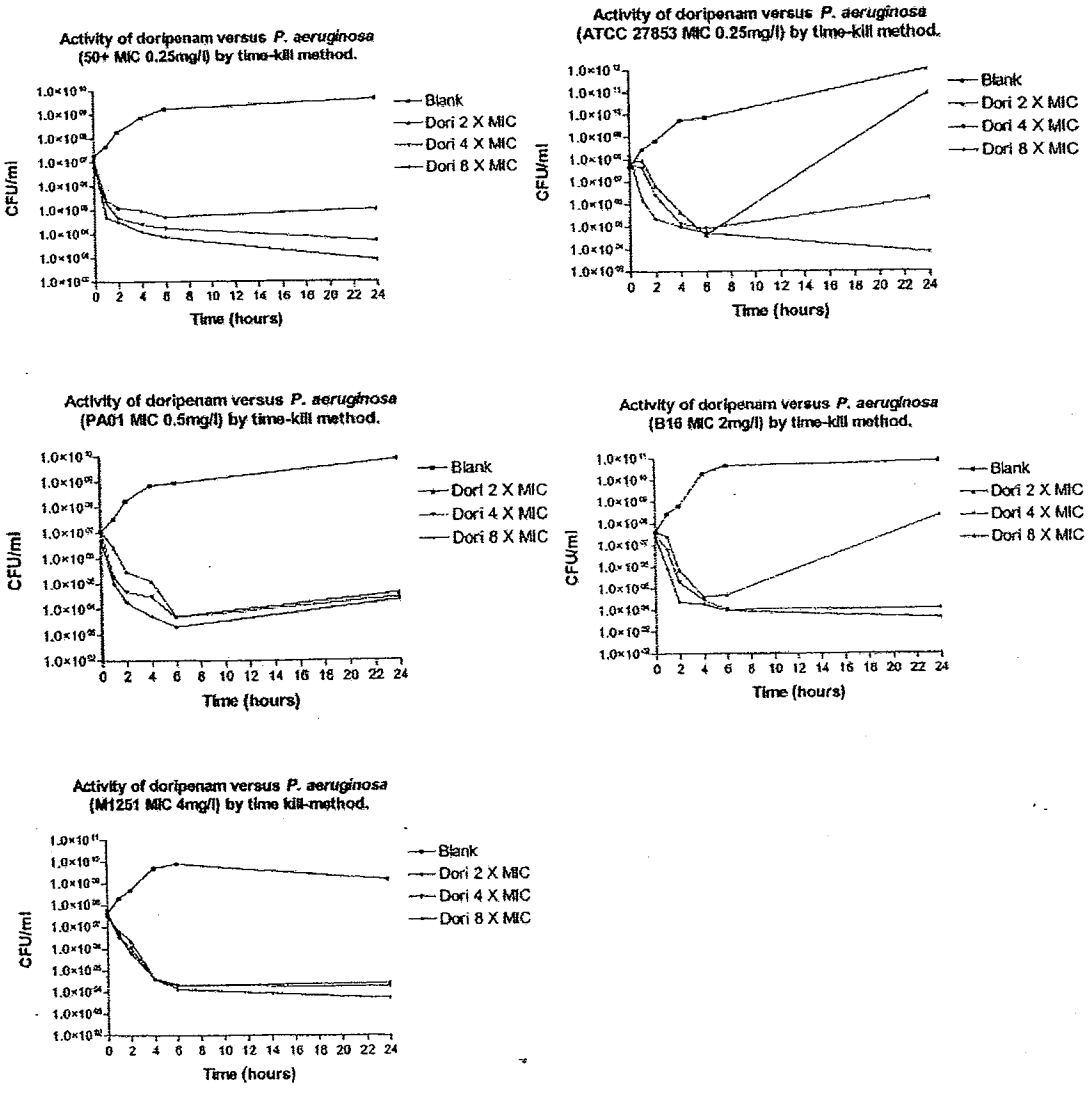


P. aeruginosa ATCC 27853

Source: Module 2, Section 2.7.2.4 Special Studies – Summary of Microbiology

In a separate time-kill study, doripenem was evaluated against five *P. aeruginosa* strains at 2-, 4- and 8-times the MIC (Figure 2.2.4.1.1-2). Killing began immediately for all strains, with a 2-log reduction during the first 2 hours of exposure. At 2x the MIC, doripenem was bactericidal (>3 log decrease in CFU/mL) at 6 hours in 3 of the 5 strains, and at 24 hours in 1 of the 5 strains. At 4x the MIC, doripenem was bactericidal at 6 hours and 24 hours in 3 of the 5 strains. At 8x the MIC, doripenem was bactericidal at 6 hours and 24 hours in 4 of the 5 strains tested. Killing was more extensive at 8x the MIC than at lower concentrations for all strains except the least susceptible (M1251) organism.

Figure 2.2.4.1.1-2 Activity of Doripenem Against 5 Strains of *P. aeruginosa* at 2-, 4- and 8-Times the MIC



Source: Study Report DORI-M-009

The postantibiotic effect (PAE) of doripenem was assessed *in vitro*, and found to be species dependent (Table 2.2.4.1.1-3). Doripenem exhibited a moderate PAE of 1.8 to 1.9 hours against *S. aureus* and *P. aeruginosa*, and a short PAE of less than 1 hour against *E. coli* and *K. pneumoniae*. However, a second *in vitro* study conducted with *P. aeruginosa* demonstrated a relatively short PAE of only 0.8 hours for doripenem. In this study the PAE for meropenem and imipenem was 1.1 and 1.5 hours, respectively.

Table 2.2.4.1.1-3 *In vitro* Postantibiotic Effect of Doripenem

Strains[a]	Doripenem	Imipenem	Panipenem	Ceftazidime
S. aureus Smith	1.9	1.6	1.8	1.8
K. pneumoniae BK	0.3	0.5	0.4	0.1
E. coli ATCC 25922	0.5	0.6	0.6	0.4
P. aeruginosa ATCC 27853	1.8	1.0	1.0	-0.3

[a] Tested at 4 x MIC for 2 hours

2.2.4.1.2. Animal Models of Infection

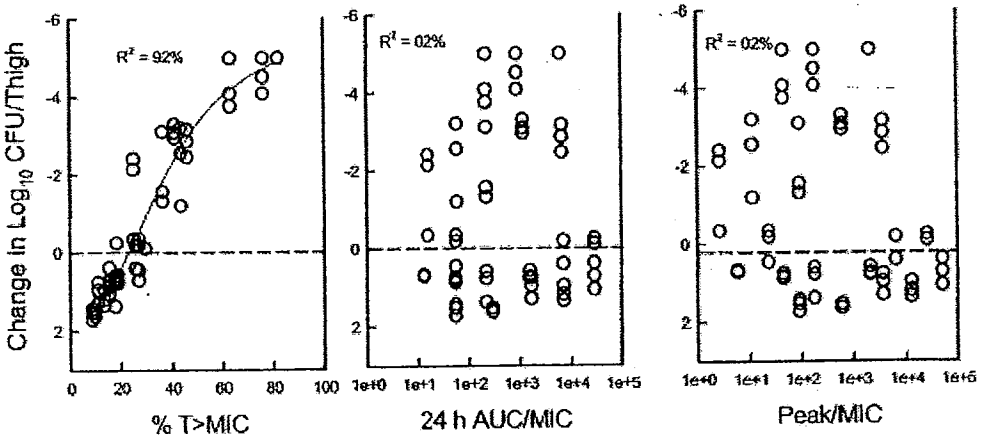
The therapeutic efficacy of doripenem was evaluated in a neutropenic mouse thigh infection model using female Swiss ICR mice (DORI-M-002). The study evaluated 7 strains of *S. pneumoniae*, including PSSP, PRSP, and quinolone resistant strains, 3 strains of *S. aureus*, including methicillin-susceptible and methicillin-resistant strains, and 10 strains of Gram-negative bacilli (*E. coli, K. pneumoniae, E. cloacae, and P. aeruginosa*), including cephalosporin-susceptible and cephalosporin-resistant strains due to ESBL production. The MICs ranged from 0.004 to 4.0 µg/mL. Multiple dosing regimens were evaluated, with varying doses and dosage intervals administered to groups of mice for 24 hours. The dosing intervals studied were every 3, 6, 12 and 24 hours. Five total doses of four-fold increases were studied for each dosing regimen, enabling characterization of each dosing interval. Each dose-response curve was characterized using a maximal effect model (Emax).

The PK/PD parameter that best correlated with efficacy was the percentage of the dosing interval that plasma concentrations exceed the MIC (%T>MIC). The coefficients of determination (R^2) observed for %T>MIC were 75% for *K. pneumoniae*, 80% for *S. pneumoniae* and 92% for *S. aureus*, versus R^2 values of 2 – 15% for C_{max}/MIC and 2 – 37% for AUC/MIC (Figure 2.2.4.1.2-1). Figure 2.2.4.1.2-2 illustrates the dose response curves at the different dosing intervals studied for the three pathogens. As the dosing interval increases, the dose-response curve is shifted to the right, indicating decreased efficacy with larger, less frequent dosing, consistent with time-dependent activity.

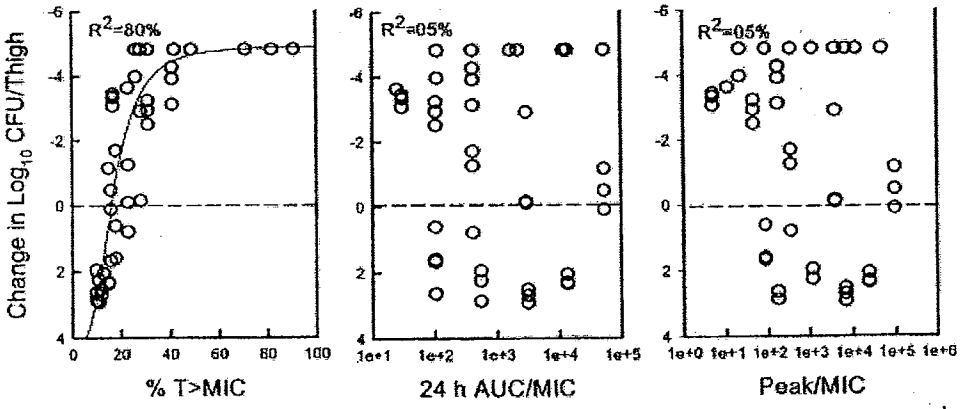
To evaluate whether the %T>MIC requirements were similar for different pathogens, the activity of q6h dosing regimens were determined for various strains of pathogens with a range of MICs (Table 2.2.4.1.2-1). The %T>MIC required to produce a static effect for the multiple pathogens studied ranged from 2.3 to 38%. The static doripenem doses varied from 0.01 mg/kg to 55.6 mg/kg every 6 hours (> 5000-fold difference in dose). There was no major difference in %T>MIC for the different strains of *S. pneumoniae*, regardless of penicillin or quinolone resistance, with a mean value of 12.4% for a static effect. Gram-negative bacilli and *S. aureus* both required mean %T>MIC values of 29% for a static effect. The presence of methicillin resistance or ESBL production did not significantly impact the magnitude of the PK/PD parameter required for efficacy. The %T>MIC required to produce a 2-log kill ranged from a mean of 27% for *S. pneumonia* to a mean of 43% for GNB.

Figure 2.2.4.1.2-1 Relationship Between Doripenem PK/PD Parameters and *In Vivo* Efficacy Against *S. aureus* (A), *S. pneumoniae* (B) and *K. pneumoniae* (C).

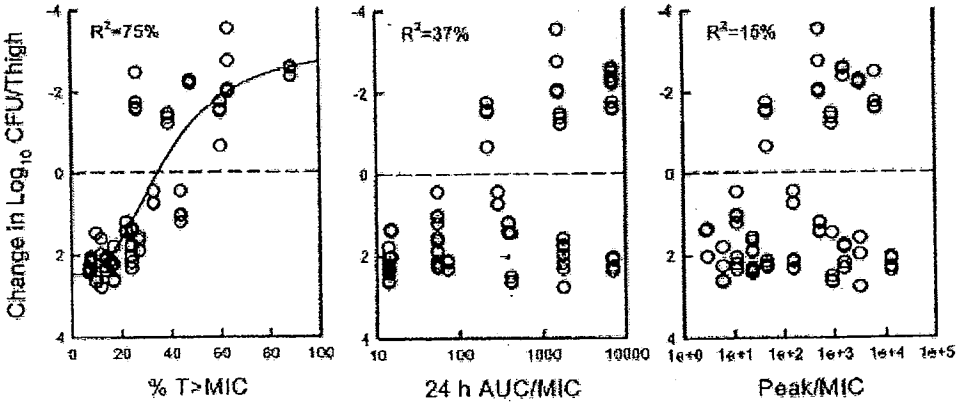
(A) *S. aureus*



(B) *S. pneumoniae*

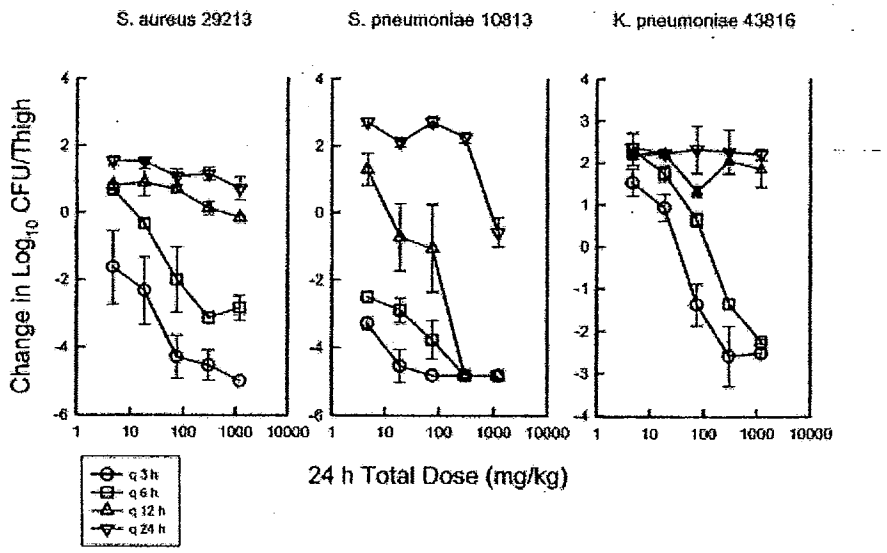


(C) *K. pneumoniae*



Source: Study Report DORI-M-002

Figure 2.2.4.1.2-2 Dose-Response Relationship for Doripenem for Varying Total 24-hour Doses and Dosing Intervals in the Neutropenic Thigh Infection Model



Source: Study Report DORI-M-002

Table 2.2.4.1.2-1 Doripenem *In Vivo* Activity in the Murine Thigh Infection Model[a]

Organism	MIC (mg/L)	SD (mg/kg)	%T>MIC	1 Log Kill (mg/kg)	%T>MIC	2 Log Kill (mg/kg)	%T>MIC
S. pneumoniae 6301	0.004	0.01	23	0.06	15	0.59	31
S. pneumoniae MNO418	0.004	0.21	15	0.89	34	5.42	47
S. pneumoniae 10813	0.004	0.08	17	0.21	24	0.49	30
S. pneumoniae 1396	0.12	1.22	12	2.45	17	6.86	24
S. pneumoniae 1293	0.25	11.0	21	93	31.3	na	na
S. pneumoniae 143	0.50	2.40	7.3	3.19	10	4.54	12
S. pneumoniae 146	0.50	4.97	12.2	10.5	16.7	25.2	20
mean ± SD			12.4 ± 6.2		21.1 ± 8.9		27.3 ± 11.9
S. aureus 25923	0.015	4.09	35	12.9	40	57.9	41
S. aureus smith	0.015	1.05	25	1.82	29	3.18	34
S. aureus 307192	4.0	362	27	494	28	882	31.3
mean ± SD			29 ± 5.3		32.3 ± 6.7		35.4 ± 5.0
E. coli 25922	0.015	22.1	38	113	47	na	na
E. coli 145	0.03	6.15	33	12.4	35	253	51
E. coli 154	0.06	7.32	28	24.7	30	97.4	38
K. pneumoniae 43816	0.06	29	29	75.3	35	210	46
K. pneumoniae 51504	0.06	55.6	34	216	49	na	na
K. pneumoniae 149	0.06	26.3	28	56.4	34	116	40
K. pneumoniae 152	0.06	12.6	31	98	39	1111	54
E. cloacae 31-59a	0.25	38.3	26	158	37	1074	47
E. cloacae 31-54a	0.50	23.7	20	78.4	27	276	36
P. aeruginosa 27853	0.50	46	23	100	28	245	35
mean ± SD			29 ± 5.3		36.1 ± 7.4		43.3 ± 7.1

[a] Based on q6h dosing interval

Source: Study Report DORI-M-002

The PAE of doripenem was also assessed in several animal models. In the neutropenic mouse thigh infection model doripenem was found to exhibit a bacterial species dependent PAE. Doripenem, imipenem-cilastatin, or panipenem-betamipron (50 mg/kg or 100 mg/kg), were injected subcutaneously into both thighs. The PAE for doripenem ranged from 5 hours for *K. pneumoniae* to 8 hours for *S. aureus* and *P. aeruginosa* (Table 2.2.4.1.2-2)

Table 2.2.4.1.2-2 *In vivo* Postantibiotic Effect of Doripenem in the Neutropenic Mouse Thigh Infection Model

Strains	Doripenem	Imipenem	Panipenem	Ceftazidime
S. aureus Smith	7.8	12.3	10.8	ND
K. pneumoniae BK	5.0	5.5	4.3	6.0
P. aeruginosa ATCC 27853	8.0	9.8	8.3	2.7

Doripenem's PAE was also examined in a mouse respiratory infection model in which mice were inoculated intranasally with ceftazidime-resistant *P. aeruginosa* E2 following induction of neutropenia. Mice were given 3 mg/kg of subcutaneous doripenem, meropenem or imipenem, or 10 mg/kg of ceftazidime 2.5 hours after infection. The PAE was calculated by determining the time difference between the control and the treated animals for the bacteria in the lungs to grow 10-fold compared to the time at which the serum concentration of drug fell below its MIC for *P. aeruginosa* E-2. The PAE effect of doripenem was 6.1 hours, similar to meropenem-cilastatin (5.9 hours) (Table 2.2.4.1.2-3).

Table 2.2.4.1.2-3 *In vivo* Postantibiotic Effect of Doripenem in the Neutropenic Respiratory Infection Model

Organism (CFU/mouse)	Compound[a]	MIC (µg/ml)	PAE (reliability limit, h)
P. aeruginosa E-2, CAZ-R (1.1 x 107)	Doripenem	1	6.12 (3.15-9.08)
	Meropenem	1	5.90 (3.12-8.67)
	Imipenem	0.5	3.49 (1.40-5.58)
	Ceftazidime	4	0.35[b]

[a] Single dose, 2.5 hours after infection
[b] No limits obtained due to nearly absent PAE

The antimicrobial efficacy and lipopolysaccharide (LPS) release following treatment with doripenem, meropenem-cilastatin, imipenem-cilastatin, and ceftazidime was evaluated in a neutropenic rat model of bloodstream infection. Doripenem produced the lowest serum LPS concentration of any of the carbapenems tested at 1 and 3 hours.

2.2.4.1.3. Monte-Carlo Simulations

Using a preliminary population PK model based on pooled Phase 1 and 2 data, clinically relevant pathogen MIC data and PK/PD targets from the animal infection models, Monte Carlo simulations were performed to estimate the probability of achieving a target %T>MIC of at least 25%, 30% or 35% for subjects with normal and impaired renal function. A target of 30% is appropriate based on the results of the murine thigh infection model in which mean %T>MIC values were 29% for GNB (including *E. coli, K. pneumoniae, E. cloacae* and *P. aeruginosa*) and 29% for *S. aureus*. The population PK simulation of the pooled clinical data was performed using NONMEM. Assessment of %T>MIC was determined for MIC values of 0.06 to 16 µg/mL based on actual MICs observed in Phase 3 trials of cIAI and cUTI (DORI-05, -06, -07 and -08).

Since doripenem has a much shorter half-life than the dose interval for any given CrCl value and the PK accumulation ratio is close to one, %T>MIC was calculated from single dose PK profiles. At each MIC and for each dosing regimen, %T>MIC was determined for 5000 simulated subjects.

Tables 2.2.4.1.3-1 and -2 contain the target attainment rates for doripenem 500 mg q8h infused over 1 and 4 hours based on actual MIC values of cIAI and cUTI pathogens from Phase 3studies. A target attainment rate of 35% was achieved by ≥ 80% of simulated subjects following a 1-hour infusion for most species of pathogens found in the clinical trials. The pathogens with target attainment rates of <80% were *S. maltophilia* (all with MIC ≥ 16 μg/mL), Entercoccus spp. (69% of strains with MIC ≥ 4 μg/mL), Staphylococcus spp. in UTI (26% of strains with MIC ≥ 4 μg/mL), *Burkholderia cepacia* (MIC = 2), and *P. aeruginosa* in UTI (22% of strains with MIC ≥ 4 μg/mL).

Fractional target attainment rates for the 500 mg q8h (1-hour infusion) scenario are shown in Figure 2.2.4.1.3-1 and in Table 2.2.4.1.3-3. The target attainment rate is > 90% for pathogens with an MIC ≤ 1 μg/mL for all targets (25%, 30% and 35% T>MIC). The rate continues to remain above 90% for pathogens with an MIC ≤ 2 μg/mL for %T>MIC targets of 25% and 30%. As the MIC increases from 2 to 4 μg/mL there is a substantial drop in target attainment rates for all three targets.

Table 2.2.4.1.3-1 Target Attainment Rates for cIAI Pathogens[a]

Species specific target attainment (n)	500 mg, q8h, 1-hour infusion			500 mg, q8h, 4-hour infusion		
	25% T>MIC	30% T>MIC	35% T>MIC	25% T>MIC	30% T>MIC	35% T>MIC
Enterobacteriaceae (659)	100	100	99.98	100	100	100
Non-Enterobacteriaceae (95)	98.06	97.62	96.74	98.22	98.15	98.07
Acinetobacter spp. (7)	85.6	84.24	81.53	85.82	85.79	85.76
Stenotrophomonas maltophilia (2)	1.26	0.7	0.34	0.7	0.5	0.3
Haemophilus spp. (6)	100	100	100	100	100	100
Enterococcus spp. (133)	60.52	49.18	39.41	69.61	68.34	66.61
Staphylococcus spp. (80)	90.53	90.06	89.57	90.81	90.64	90.46
Streptococcus pneumoniae (3)	100	100	100	100	100	100
Streptococcus spp. (- *S. pneumoniae*) (282)	100	99.99	99.97	100	100	100
Other Gram-Positive (5)	80.25	80.11	79.91	80.14	80.1	80.06
All Anaerobes (664)	97.78	97.35	96.86	98.12	98.03	97.92
Enterococcus faecalis (56)	78	62.65	48.89	90.23	89.12	87.34
Pseudomonas aeruginosa (76)	97.57	97.04	95.94	97.78	97.69	97.60

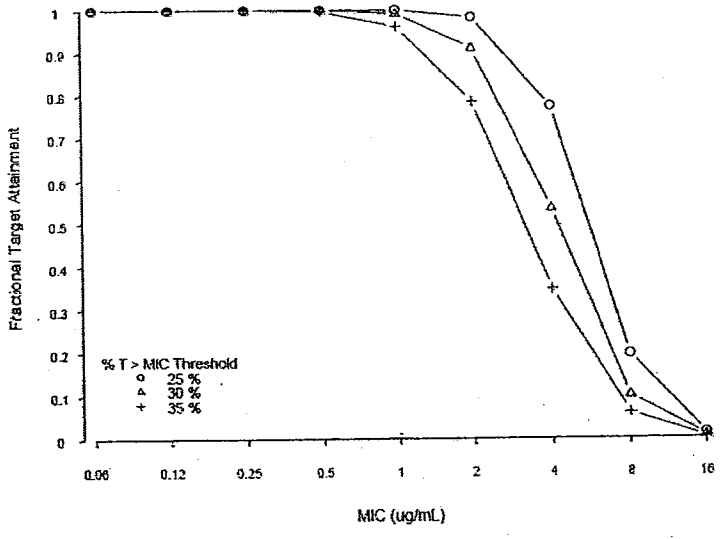
[a] Pathogens and MICs from Phase III studies DORI-07 and DORI-08

Table 2.2.4.1.3-2 Target Attainment Rates for cUTI Pathogens[a]

Species specific target attainment	500 mg, q8h, 1-hour infusion			500 mg, q8h, 4-hour infusion		
	25% T>MIC	30% T>MIC	35% T>MIC	25% T>MIC	30% T>MIC	35% T>MIC
Enterobacteriaceae (862)	99.77	99.7	99.63	99.81	99.8	99.79
Non-Enterobacteriaceae (all *P. aeruginosa*) (36)	83.61	80.69	77.68	85.8	85.21	84.54
Acinetobacter spp. (11)	99.76	98.52	95.44	100	100	100
Burkholderia cepacia (1)	98.14	90.9	78.32	100	100	100
Enterococcus spp. (23)	74.93	61.09	48.94	85.94	85.58	84.54
Staphylococcus spp. (19)	81.82	78.46	75.07	84.1	84	83.77
Streptococcus spp. (- *S. pneumoniae*) (1)	100	100	100	100	100	100
All Anaerobes (1)	100	100	100	100	100	100
Enterococcus faecalis (20)	82.18	67.52	54.52	93.86	93.49	92.42

[a] Pathogens and MICs from Phase III studies DORI-05 and DORI-06

Figure 2.2.4.1.3-1 Fractional PK-PD Target attainment by MIC for 500 mg q8h, 1-hour Infusion



Source: Target Attainment Report

Tablet 2.2.4.1.3-3 Target Attainment in cIAI or cUTI for Doripenem 500 mg q8h, 1-hour Infusion

MIC (μg/ml)	T>MIC 25%	T>MIC 30%	T>MIC 35%
0.06	100	100	100
0.12	100	100	100
0.25	100	100	100
0.5	100	99.9	99.6
1	99.9	99.0	96.0
2	98.1	90.9	78.3
4	77.3	53.4	34.6
8	19.5	10.0	6.0
16	1.3	0.7	0.3

The final target attainment rates for actual MIC values observed in cIAI and cUTI Phase III studies (range 0.06 to 16 μg/mL) were also determined for various levels of renal function after dosage adjustment (Tables 2.2.4.1.3-4 and -5). Target attainment rates are >90% for all degrees of renal impairment, suggesting the proposed dosage adjustments are appropriate.

Table 2.2.4.1.3-4 Final Target Attainment Rates for Doripenem in cIAI Based on Renal Function Status

Dose in cIAI (mg)	Dosing Interval (hr)	Infusion time (hr)	Renal Function Status	CrCl (mL/min)	Final TAR 25% T>MIC	30% T>MIC	35% T>MIC
500	8	1	Superior Renal Function	150	94.19	92.83	91.72
500	8	1	Normal Renal Function	98[a]	95.81	94.75	93.73
250	8	1	Moderate Impairment	50	95.38	94.50	93.74
250	8	1	Moderate Impairment	30	96.29	95.92	95.41
250	12	1	Severe Impairment	29	95.26	94.36	93.59
250	12	1	Severe Impairment	10	97.06	96.68	96.35
500	8	1	Mixed Population	16 – 216[b]	95.84	94.85	93.93
500	8	4	Mixed Population	16 – 216[b]	96.59	96.47	96.30

[a] Median CrCl observed in Phase I and II studies

[b] CrCl values were randomly sampled (for 5000 simulated subjects) from the distribution observed in Phase I and II trials.

Table 2.2.4.1.3-5 Final Target Attainment Rates for Doripenem in cUTI Based on Renal Function Status

Dose in cUTI (mg)	Dosing Interval (hr)	Infusion time (hr)	Renal Function Status	CrCl (mL/min)	Final TAR 25% T>MIC	30% T>MIC	35% T>MIC
500	8	1	Superior Renal Function	150	97.25	96.32	95.54
500	8	1	Normal Renal Function	98[a]	98.25	97.56	96.89
250	8	1	Moderate Impairment	50	98.02	97.44	96.94
250	8	1	Moderate Impairment	30	98.53	98.36	98.04
250	12	1	Severe Impairment	29	97.95	97.36	96.83
250	12	1	Severe Impairment	10	98.76	98.66	98.55
500	8	1	Mixed Population	16 – 216[b]	98.20	97.60	97.01
500	8	4	Mixed Population	16 – 216[b]	98.61	98.58	98.52

[a] Median CrCl observed in Phase I and II studies
[b] CrCl values were randomly sampled (for 5000 simulated subjects) from the distribution observed in Phase I and II trials.

The Sponsor has proposed a breakpoint c

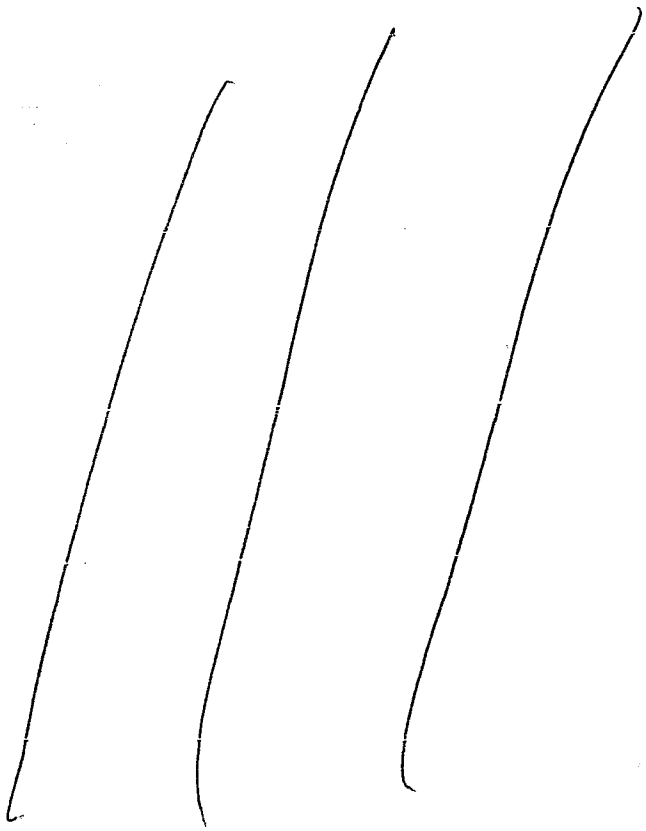


Table 2.2.4.1.3-7 Baseline MIC Values Per Pathogen for Doripenem-Treated Subjects in cUTI and cIAI Phase III Trials (n)[a]

Oranism	Minimum Inhibitory Concentrations (µg/ml) at Baseline									
	All	≤ 0.25	0.5	1	2	4	8	16	32	≥ 64
Gram positive Aerobes										
Enterococcus spp.	48	3	0	1	14	15	2	3	4	6
E. faecalis	30	3	0	1	11	12	2	1	0	0
Staphylcoccal spp.	18	14	0	0	1	1	0	0	2	0
S. aureus	14	10	0	0	1	1	0	0	2	0
Streptococci (not *S. pneumoniae*)	119	118	1	0	0	0	0	0	0	0
S. anginosus group	54	54	0	0	0	0	0	0	0	0
S. anginosus	8	8	0	0	0	0	0	0	0	0
S. constellatus	10	10	0	0	0	0	0	0	0	0
S. intermedius	36	36	0	0	0	0	0	0	0	0
Gram negative Aerobes										
Enterobacteriaceae	746	715	29	3	0	0	0	0	0	0
E. coli	549	549	0	0	0	0	0	0	0	0
K. pneumoniae	57	56	1	0	0	0	0	0	0	0
P. mirabilis	37	26	11	0	0	0	0	0	0	0
Gram negative Non-fermenters										
Acinetobacter spp.	14	5	1	7	1	0	0	0	0	0
P. aeruginosa	62	28	12	11	5	1	3	2	0	0
Anaerobes	274	222	31	12	3	2	3	0	1	0
B. fragilis	63	56	4	2	0	1	0	0	0	0

[a] From cUTI trials (DORI-05 and DORI-06) and cIAI trials (DORI-07 and DORI-08)

2.2.4.1.4. Summary of Efficacy

Dose-Response Studies

DORI-03 was a randomized Phase II dose-finding study comparing doripenem 250 mg q8h or 500 mg q8h (both 1-hour infusions) in 107 patients with cUTI or pyelonephritis. The primary objective was to compare the microbiologic response of the two dosing regimens. The microbiological success rate at TOC in the microbiologically evaluable population was 64% in the 250 mg q8h group and 68% in the 500 mg q8h group. The eradication rate of the most frequently isolated organisms (*E. coli, P. mirabilis, K. pneumoniae, S. saprophyticus, E. faecalis*, and *P. aeruginosa*) was 82% in the high-dose group versus 69% in the low-dose group at TOC. The percentage of successes was greater in the 500 mg q8h group than in the 250 mg q8h group in per subject microbiological responses and per pathogen microbiological outcomes at TOC.

Plasma concentrations of doripenem were obtained in DORI-03 in order to correlate PK parameters with clinical and microbiological outcomes. Sparse sampling of blood was performed on Day 1 (end of infusion and 2 hrs after the end of infusion), Day 2 (pre-dose, end of infusion, and 4 hrs after end of infusion), and Day 3 (pre-dose, end of infusion, and 6 hrs after end of infusion). Plasma concentrations of doripenem were also included in a population PK analysis using nonlinear mixed effects modeling (NONMEM). The relationship between the percentage of the dosing interval in which doripenem concentrations exceeded the MIC and efficacy at the TOC visit are shown in Table 2.2.4.1.4-1. There is no apparent relationship between %T>MIC and clinical or microbiological response with increasing %T >MIC. The lack of a PK-PD relationship in this study is likely due to

the fact that doripenem is concentrated in urine, where concentrations exceed the MICs of most uropathogens, including organisms with elevated MICs. In other words, the %T>MIC in plasma predicted by modeling is likely lower than that attained in urine, at the site of infection. In addition, there was a limited number of patients with %T >MIC less than 80% of the dosing interval, which makes interpretation of exposure-response data difficult.

Table 2.2.4.1.4-1 PK/PD analysis of DORI-03 Based on %T>MIC and Efficacy at the TOC Visit

	Time above the MIC (T >MIC)				
Outcome	**≤20**	**>20-40**	**>40-60**	**>60-80**	**>80**
250 mg dose					
Microbiological					
Eradicated	60 % (3/5)	100% (1/1)	100% (3/3)	100% (2/2)	68% (27/40)
Persistent	40% (2/5)	0% (0/1)	0% (0/3)	0% (0/2)	33% (13/40)
Clinical					
Success	100% (5/5)	100% (2/2)	100% (3/3)	50% (1/2)	92% (35/38)
Failure	0% (0/5)	0% (0/2)	0% (0/3)	50% (1/2)	8% (3/38)
500 mg dose					
Microbiological					
Eradicated	0% (0/1)	100% (2/2)	0% (0/1)	0% (0/1)	79% (27/34)
Persistent	100% (1/1)	0% (0/2)	100% (1/1)	100% (1/1)	21% (7/34)
Clinical					
Success	100% (1/1)	100% (2/2)	100% (1/1)	0% (0/1)	89% (31/35)
Failure	0% (0/1)	0% (0/2)	0% (0/1)	100% (1/1)	11% (4/35)

Study 9634**R142D** was an early Phase 2 non-randomized, non-controlled dose-finding study conducted in Japanese patients with one of the following infections: complicated cystitis, pyelonephritis (acute uncomplicated or complicated), acute bacterial prostatitis, and bacterial epididymitis. Subjects were administered one of the following doripenem doses as chosen by the investigator based on clinical severity: 250 mg twice daily, 250 mg three times daily, 125 mg twice daily, and 500 mg twice daily. A total of 32 subjects were included in the efficacy evaluation. The primary endpoint was clinical efficacy rates, with clinical efficacy judged by the investigators. Over two-thirds of subjects (24 of 32) were treated with the 250 mg twice daily dose, particularly subjects with complicated cystitis and pyelonephritis (19 of 20 subjects), while over half of subjects with acute bacterial prostatitis and epididymitis received a dose of 250 3x/day or 500 mg twice daily. The clinical efficacy rate in R142D was 100.0% (1/1 subject) for acute uncomplicated pyelonephritis, 100.0% (9/9) for complicated pyelonephritis, 81.8% (9/11) for complicated cystitis, 50.0% (3/6) for acute bacterial prostatitis, and 100.0% (5/5) for bacterial epididymitis, resulting in an overall efficacy rate of 84.4% (27/32). Because dose selection of doripenem was made by the investigator based on clinical severity, and due to the limited number of subjects treated for each infection, no conclusions about dose-response can be made based on the results of this study. However, the results do show that a 250 mg twice daily dose of doripenem (one-third of the proposed daily dose) achieved a 90% clinical efficacy rate in the 20 subjects with complicated cystitis and pyelonephritis.

Study 9633**R142U** was a Japanese multicenter, parallel-group double-bind study of two i.v. doses of doripenem for cUTI. The two doses studied were 250 mg twice daily and 500 mg twice daily (over 30 to 60 min.) for 5 days. A total of 83 patients received the investigational product and 70 were evaluated in the primary efficacy analysis. In the primary efficacy analysis, the clinical cure

rates were 97.4% (37/38) in the 250 mg dose group and 96.9% (31/32) in the 500 mg dose group. There were no significant differences between the doses in any of the secondary efficacy parameters, including eradication of bacteriuria. The investigators concluded that a dose of 250 mg twice daily is an appropriate standard dose for the treatment of cUTI.

U.S.Clinical Trials

Four Phase III studies were submitted in support of the cIAI and cUTI indications. Three of the 4 studies investigated a single dosage regimen of doripenem administered in a blinded fashion with an active comparator. The fourth study, DORI-06, was a single-arm study of doripenem for cUTI. All four studies evaluated a doripenem dose of 500 mg q8h administered over 1 hour.

cIAI

The primary efficacy endpoint in the cIAI trials (DORI-7 and DORI-8) was the clinical cure rate at the TOC visit (21 to 60 days after the last dose of study drug therapy). This endpoint was analyzed in the ME at TOC and the mMITT analysis sets. The primary comparison was based on the difference between i.v. doripenem and i.v. meropenem in the proportion of subjects assessed as clinically cured in the ME at TOC analysis set. Results are shown in Table 2.2.4.1.4-2 below. Both studies independently met the Sponsor's pre-specified non-inferiority margin of -15%, indicating non-inferiority of doripenem to meropenem for cIAI. As expected, the overall clinical cure rates were lower in the mMITT analysis set because the assessment of outcome in this group was more conservative; subjects with missing or indeterminate responses were counted as failures. In contrast, subjects with missing information were excluded from the ME at TOC (and also the clinically evaluable [CE] at TOC) analysis sets.

Microbiological cure rates were similar to clinical response rates in both cIAI studies. Microbiological cure (eradication) at TOC for doripenem treated subjects in DORI-7 and DORI-8 was lowest for *K. pneumoniae* (78.1%) and highest for *B. vulgatus* (100.0%). Eradication rates ranged from 80% (*E. faecalis*) to 90% (*Streptococcus constellatus*) for Gram positive organisms, and from 78.1% (*K. pneumoniae*) to 85.0% (*P. aeruginosa*) for Gram negative organisms. Eradication rates were 87.9% for Bacteroides fragilis group. The per pathogen eradication rates are shown in Table 2.2.4.1.4-3. There was no significant difference in eradication rates between the test and control arms for any of the pathogens.

Of 634 subjects in the pooled ME at TOC analysis set, 75% were switched to oral study drug therapy. These subjects received a mean duration of 5.7 days of i.v. therapy prior to the switch to oral study drug therapy, and a mean total duration of 11 days of drug therapy. The clinical cure/improvement rates at the EOT (i.v.) were 93.8% versus 92.9% in the doripenem and meropenem treatment arms, respectively. The high clinical cure rates at EOT (i.v.) suggest that clinical efficacy can be attributed to the i.v. study drug therapy portion of the treatment, as opposed to oral amoxicillin/clavulanate therapy. Efficacy analyses were conducted in the subgroup of subjects who received only i.v. therapy in an attempt to further evaluate the contribution of i.v. therapy. However, interpretation was confounded by different proportions of subjects who were switched to oral therapy in each treatment arm.

Table 2.2.4.1.4-2 Summary of Clinical and Microbiological Cure Rates for cIAI Studies

	Doripenem 500 infusion q8h			Meropenem 1 g bolus q8h				
	N	n	(%)	N	n	(%)	% Diff	95% CI
Study DORI-07								
Clinical Cure at TOC/ME at TOC	163	140	(85.9)	156	133	(85.3)	(0.6)	(-7.7; 9.0)
Clinical Cure/mMITT	195	152	(77.9)	190	150	(78.9)	(-1.0)	(-9.7; 7.7)
Clinical Cure/CE at TOC	188	163	(86.7)	186	161	(86.6)	(0.1)	(-7.3; 7.6)
Microbiological Cure at TOC/ME at TOC	163	139	(85.3)	156	132	(84.6)	(0.7)	(-7.8; 9.1)
Study DORI-08								
Clinical Cure at TOC/ME at TOC	162	135	(83.3)	153	127	(83.0)	(0.3)	(-8.6; 9.2)
Clinical Cure/mMITT	200	149	(74.5)	185	140	(75.7)	(-1.2)	(-10.3; 8.0)
Clinical Cure/CE at TOC	192	161	(83.9)	192	165	(85.9)	(-2.1)	(-9.8; 5.6)
Microbiological Cure at TOC/ME at TOC	162	135	(83.3)	153	129	(84.3)	(-1.0)	(-9.7; 7.8)
Pooled Data From Studies DORI-07 and DORI-08								
Clinical Cure at TOC/ME at TOC	325	275	(84.6)	309	260	(84.1)	(0.5)	(-5.5; 6.4)
Clinical Cure/mMITT	395	301	(76.2)	375	290	(77.3)	(-1.1)	(-7.4; 5.1)
Clinical Cure/CE at TOC	380	324	(85.3)	378	326	(86.2)	(-1.0)	(-6.2; 4.3)
Microbiological Cure at TOC/ME at TOC	325	274	(84.3)	309	261	(84.5)	(-0.2)	(-6.1; 5.8)

CE=Clinically evaluable; ME=Microbiologically evaluable; mMITT=Microbiological modified intent-to-treat; N was the number of subjects in each treatment arm; n was the number of subjects who were clinically cured; TOC=Test-of-Cure

Table 2.2.4.1.4-3 Per Baseline Pathogen Eradication Rates for cIAI Studies

	Doripenem 500 mg 1-hour infusion q8h			Meropenem 1 g bolus injection q8h				
	N	n	(%)	N	n	(%)	Diff[a] (%)	95% CI[b]
Gram positive, Aerobic	176	150	(85.2)	168	131	(78.0)	(7.3)	(-1.5; 16.0)
Viridans group streptococci	109	93	(85.3)	90	71	(78.9)	(6.4)	(-5.3; 18.2)
Streptococcus constellatus	10	9	(90.0)	7	5	(71.4)	(18.6)	
Streptococcus intermedius	36	30	(83.3)	29	21	(72.4)	(10.9)	(-12.5; 34.4)
Enterococcus faecalis	20	16	(80.0)	17	13	(76.5)	(3.5)	
Gram positive, Anaerobic	73	61	(83.6)	82	62	(75.6)	(8.0)	(-5.9; 21.8)
Peptostreptococcus micros	13	11	(84.6)	14	11	(78.6)	(6.0)	
Other Gram positive anaerobes	73	61	(83.6)	82	62	(75.6)	(8.0)	(-5.9; 21.8)
Gram negative, Aerobic								
Enterobacteriaceae	315	271	(86.0)	274	234	(85.4)	(0.6)	(-5.4; 6.6)
Escherichia coli	216	189	(87.5)	199	168	(84.4)	(3.1)	(-4.1; 10.3)
Klebsiella pneumoniae	32	25	(78.1)	20	19	(95.0)	(-16.9)	
Non-fermenters	51	44	(86.3)	39	28	(71.8)	(14.5)	(-4.8; 33.7)
Pseudomonas aeruginosa	40	34	(85.0)	32	24	(75.0)	(10.0)	(-11.5; 31.5)
Gram negative, Anaerobic	245	209	(85.3)	251	210	(83.7)	(1.6)	(-5.1; 8.4)
Bacteroides fragilis group	173	152	(87.9)	181	152	(84.0)	(3.9)	(-3.9; 11.7)
Bacteroides caccae	25	23	(92.0)	19	18	(94.7)	(-2.7)	
Bacteroides fragilis	67	56	(83.6)	68	54	(79.4)	(4.2)	(-10.4; 18.7)
Bacteroides thetaiotaomicron	34	30	(88.2)	36	32	(88.9)	(-0.7)	(-18.4; 17.1)
Bacteroides uniformis	22	19	(86.4)	18	15	(83.3)	(3.0)	
Non-fragilis Bacteroides	14	13	(92.9)	13	9	(69.2)	(23.6)	
Bacteroides vulgatus	11	11	(100.0)	8	6	(75.0)	(25.0)	

[a] Doripenem – meropenem

[b] 2-sided 95% CI based on normal approximation to the binomial distribution with continuity correction.

ME=Microbiologically Evaluable; N was the number of unique baseline isolates; n was the number of pathogens with a favorable microbiological outcome; TOC=Test-of-Cure. Major pathogens were baseline bacterial pathogens isolated in 10 or more subjects in the doripenem arm.

cUTI

The primary efficacy endpoint for the cUTI studies, DORI-5 and DORI-6 was microbiological cure rate at the TOC visit, 5 to 11 days after the last dose of study drug therapy in the ME at TOC analysis set. In DORI-05, microbiological cure rates of 82.1% and 83.4% were shown in the doripenem and levofloxacin arms, respectively. Microbiological efficacy at the TOC visit was also demonstrated in the open-label study (DORI-06), where the microbiological cure rate in doripenem-treated subjects was 83.5% compared with 83.4% in the levofloxacin arm of DORI-05. Clinical cure rates were slightly higher than the microbiological cure rates (95.1% and 93.0% in DORI-05 and DORI-06, respectively). Results are shown in Tables 2.2.4.1.4-4 and -5 below.

Table 2.2.4.1.4-4 Summary of Clinical and Microbiological Cure Rates for cUTI Studies

	Doripenem 500 infusion q8h			Levofloxacin 250 mg infusion q24h				
	N	n	(%)	N	n	(%)	% Diff	95% CI
Study DORI-05								
Microbiological Cure at TOC/ME	280	230	(82.1)	265	221	(83.4)	(-1.3)	(-8.0; 5.5)
Microbiological Cure/mMITT	327	259	(79.2)	321	251	(78.2)	(1.0)	(-5.6; 7.6)
Clinical Cure at TOC/CE	286	272	(95.1)	266	240	(90.2)	(4.9)	(0.2; 9.6)
Study DORI-06								
Microbiological Cure at TOC/ME	250	209	(83.6)	265	221	(83.4)	(0.2)	(-6.6; 7.0)
Microbiological Cure/mMITT	337	278	(82.5)	321	251	(78.2)	(4.3)	(-2.1; 10.7)
Clinical Cure at TOC/CE	257	239	(93.0)	266	240	(90.2)	(2.8)	(-2.4; 7.9)
Pooled Data From Studies DORI-05 and DORI-06								
Microbiological Cure at TOC/ME	530	439	(82.8)	265	221	(83.4)	(-0.6)	(-6.4; 5.2)
Microbiological Cure/mMITT	664	537	(80.9)	321	251	(78.2)	(2.7)	(-3.0; 8.3)
Clinical Cure at TOC/CE	543	511	(94.1)	266	240	(90.2)	(3.9)	(-0.5; 8.2)

CE=Clinically evaluable; ME=Microbiologically evaluable; mMITT=Microbiological modified intent-to-treat; N was the number of subjects in each treatment arm; n was the number of subjects who were cured (microbiologically or clinically); q24h=Every 24 hours; q8h=Every 8 hours; TOC=Test-of-Cure

Table 2.2.4.1.4-5 Per Baseline Pathogen Eradication Rates for cUTI Studies

	Doripenem 500 mg 1-hour infusion q8h			Levofloxacin 250 mg 1-hour infusion q24h			Difference[a]	
	N	n	(%)	N	n	%	(%)	95% CI[b]
Gram positive, Aerobic								
Enterococcus faecalis	12	8	(66.7)	3	1	(33.3)	(33.3)	
Gram negative, Aerobic								
Enterobacteriaceae	476	401	(84.2)	254	217	(85.4)	(-1.2)	(-6.9; 4.5)
Enterobacter cloacae	28	18	(64.3)	7	3	(42.9)	(21.4)	
Escherichia coli	357	313	(87.7)	211	184	(87.2)	(0.5)	(-5.6; 6.5)
Escherichia coli (levofloxacin-resistant)	43	26	(60.5)	21	6	(28.6)	(31.9)	
Klebsiella pneumoniae	33	26	(78.8)	8	5	(62.5)	(16.3)	
Proteus mirabilis	30	22	(73.3)	15	13	(86.7)	(-13.3)	
Non-fermenters	38	27	(71.1)	8	5	(62.5)	(8.6)	
Acinetobacter baumannii	10	8	(80.0)	1	0	(0.0)	(80.0)	
Pseudomonas aeruginosa	27	19	(70.4)	7	5	(71.4)	(-1.1)	

[a] Doripenem – levofloxacin (from DORI-05)

[b] 2-sided 95% CI for difference in cure rates using normal approximation to the difference of 2 binomial proportions with continuity correction.

Note: Major baseline pathogens were bacterial pathogens isolated in 10 or more subjects in the doripenem arm. ME at TOC=Microbiologically evaluable at Test-of-Cure; N was the number of baseline isolates; n was the number of isolates eradicated at TOC

A detailed listing of clinical and microbiologic outcome by pathogen MIC for cUTI, cIAI and pooled cUTI/cIAI studies for doripenem-treated patients is presented below in Table 2.2.4.1.4-6. Based on these data, the Applicant proposes a susceptibility breakpoint of [redacted]

Table 2.2.4.1.4-6 Per Pathogen Favorable Outcome (Clinical Cure or Microbiological Eradication) at TOC by Baseline MIC Value [n (%)]

		Clinical Outcome			Microbiologic Outcome		
Organism	MIC in µg/ml	cUTI[a]	cIAI[b]	cUTI & cIAI	cUTI	cIAI	cUTI & cIAI
Gram-positive Aerobes							
Enterococcus spp.	All tested	12/14 (86)	23/34 (68)	35/48 (73)	9/14 (64)	24/34 (71)	33/48 (69)
	≤0.25	3/3 (100)	0	3/3 (100)	3/3 (100)	0	3/3 (100)
	0.5	0	0	0	0	0	0
	1	1/1 (100)	0	1/1 (100)	0/1 (0)	0	0/1 (0)
	2	2/3 (67)	9/11 (82)	11/14 (79)	3/3 (100)	10/11 (91)	13/14 (93)
	4	5/5 (100)	7/10 (70)	12/15 (80)	3/5 (60)	7/10 (70)	10/15 (67)
	8	0	1/2 (50)	1/2 (50)	0	1/2 (50)	1/2 (50)
	16	0/1 (0)	1/2 (50)	1/3 (33)	0/1 (0)	1/2 (50)	1/3 (33)
	32	1/1 (100)	1/3 (33)	2/4 (50)	0/1 (0)	1/3 (33)	1/4 (25)
	≥64	0	4/6 (67)	4/6 (67)	0	4/6 (67)	4/6 (67)
E. faecalis	All tested	10/12 (83)	13/18 (72)	23/30 (77)	8/12 (67)	14/18 (78)	22/30 (73)
	≤0.25	3/3 (100)	0	3/3 (100)	3/3 (100)	0	3/3 (100)
	0.5	0	0	0	0	0	0
	1	1/1 (100)	0	1/1 (100)	0/1 (0)	0	0/1 (0)
	2	2/3 (67)	6/8 (75)	8/11 (73)	3/3 (100)	7/8 (80)	10/11 (91)
	4	4/4 (100)	6/8 (75)	10/12 (83)	2/4 (50)	6/8 (75)	8/12 (67)
	8	0	1/2 (50)	1/2 (50)	0	1/2 (50)	1/2 (50)
	16	0/1 (0)	0	0/1 (0)	0/1 (0)	0	0/1 (0)
	32	0	0	0	0	0	0
	≥64	0	0	0	0	0	0
Staphylococcal spp.	All tested	6/6 (100)	12/12 (100)	18/18 (100)	6/6 (100)	12/12 (100)	18/18 (100)
	≤0.25	2/2 (100)	12/12 (100)	14/14 (100)	2/2 (100)	12/12 (100)	14/14 (100)
	0.5	0	0	0	0	0	0
	1	0	0	0	0	0	0
	2	1/1 (100)	0	1/1 (100)	1/1 (100)	0	1/1 (100)
	4	1/1 (100)	0	1/1 (100)	1/1 (100)	0	1/1 (100)
	8	0	0	0	0	0	0
	16	0	0	0	0	0	
	32	2/2 (100)	0	2/2 (100)	2/2 (100)	0	2/2 (100)
	≥64	0	0	0	0	0	0
S. aureus	All tested	6/6 (100)	8/8 (100)	14/14 (100)	6/6 (100)	8/8 (100)	14/14 (100)
	≤ 0.25	2/2 (100)	8/8 (100)	10/10 (100)	2/2 (100)	8/8 (100)	10/10 (100)
	0.5	0	0	0	0	0	0
	1	0	0	0	1/1 (100)	0	1/1 (100)
	2	1/1 (100)	0	1/1 (100)	0	0	0
	4	1/1 (100)	0	1/1 (100)	1/1 (100)	0	1/1 (100)
	8	0	0	0	0	0	0
	16	0	0	0	0	0	0
	32	2/2 (100)	0	2/2 (100)	2/2 (100)	0	2/2 (100)
	≥64	0	0	0	0	0	0
Streptococci other than *S. pneumoniae*	All tested	0	97/119 (82)	97/119 (82)	0	101/119 (85)	101/119 (85)
	≤0.25	0	96/118 (81)	96/118 (81)	0	100/118 (85)	100/118 (85)
	0.5	0	1/1 (100)	1/1 (100)	0	1/1 (100)	1/1 (100)
	≥1	0	0	0	0	0	0
S. anginosus group	All tested	0	43/54 (80)	43/54 (80)	0	45/54 (83)	45/54 (83)
	≤0.25	0	43/54 (80)	43/54 (80)	0	45/54 (83)	45/54 (83)
	0.5	0	0	0	0	0	0
	≥1	0	0	0	0	0	0

(Continued)

Organism	MIC in µg/ml	Clinical Outcome			Microbiologic Outcome		
		cUTI[a]	cIAI[b]	cUTI & cIAI	cUTI	cIAI	cUTI & cIAI
S. aureus	All tested	0	5/8 (63)	5/8 (63)	0	6/8 (75)	6/8 (75)
	≤0.25	0	5/8 (63)	5/8 (63)	0	6/8 (75)	6/8 (75)
	0.5	0	0	0	0	0	0
	≥1	0	0	0	0	0	0
S. constellatus	All tested	0	9/10 (90)	9/10 (90)	0	9/10 (90)	9/10 (90)
	≤0.25	0	9/10 (90)	9/10 (90)	0	9/10 (90)	9/10 (90)
	0.5	0	0	0	0	0	0
	≥1	0	0	0	0	0	0
S. intermedius	All tested	0	29/36 (81)	29/36 (81)	0	30/36 (83)	30/36 (83)
	≤0.25	0	29/36 (81)	29/36 (81)	0	30/36 (83)	30/36 (83)
	0.5	0	0	0	0	0	0
	≥1	0	0	0	0	0	0
Gram-negative Aerobes							
Enterobacteriaceae	All tested	421/445 (95)	253/294 (86)	674/738 (91)	382/454 (84)	256/294 (87)	638/746 (86)
	≤0.25	398/419 (95)	246/287 (86)	645/706 (91)	366/428 (86)	250/287 (87)	616/715 (86)
	0.5	19/23 (86)	7/7 (100)	26/29 (90)	15/23 (65)	6/7 (86)	21/29 (72)
	1	3/3 (100)	0	3/3 (100)	1/3 (33)	0	1/3 (33)
	2	0	0	0	0	0	0
	4	0	0	0	0	0	0
	8	0/1 (0)	0	0	0/1 (0)	0	0
	16	0	0	0	0	0	0
	32	0	0	0	0	0	0
	≥64	0	0	0	0	0	0
E. coli	All tested	326/335 (97)	180/207 (87)	506/542 (93)	298/342 (87)	182/207 (88)	480/540 (87)
	≤0.25	326/335 (97)	180/207 (87)	506/542 (93)	298/342 (87)	182/207 (88)	480/540 (87)
	0.5	0	0	0	0	0	0
	≥1	0	0	0	0	0	0
K. pneumoniae	All tested	23/26 (88)	22/30 (73)	45/56 (80	22/27 (81)	24/30 (80)	46/57 (81)
	≤0.25	22/25 (88)	22/30 (73)	44/55 (80)	22/26 (85)	24/30 (80)	46/56 (82)
	0.5	1/1 (100)	0	1/1 (100)	0/1 (0)	0	0/1 (0)
	≥1	0	0	0	0	0	0
P. mirabilis	All tested	29/30 (97)	7/7 (100)	36/37 (97)	22/30 (73)	6/7 (86)	28/37 (76)
	≤0.25	22/22 (100)	4/4 (100)	26/26 (100)	16/22 (73)	4/4 (100)	20/26 (77)
	0.5	7/8 (91)	3/3 (100)	10/11 (91)	6/8 (75)	2/3 (67)	8/11 (73)
	>1	0	0	0	0	0	0
Gram-negative Non							
Acinetobacter spp.	All tested	10/10 (100)	4/4 (100)	14/14 (100)	8/10 (80)	4/4 (100)	12/14 (86)
	≤0.25	2/2 (100)	3/3 (100)	5/5 (100)	2/2 (100)	3/3 (100)	5/5 (100)
	0.5	1/1 (100)	0	1/1 (100)	1/1 (100)	0	1/1 (100)
	1	6/6(100)	1/1 (100)	7/7 (100)	5/6 (83)	1/1 (100)	6/7 (86)
	2	1/1 (100)	0	1/1 (100)	0/1 (0)	0	0/1 (0)
	≥4	0	0	0	0	0	0

(Continued)

Organism	MIC in ug/ml	Clinical Outcome cUTI[a]	cIAI[b]	cUTI & cIAI	Microbiologic Outcome cUTI	cIAI	cUTI & cIAI
P. aeruginosa	All tested	33/24 (96)	32/38 (84)	55/62 (89)	17/24 (71)	33/38 (87)	50/62 (81)
	≤0.25	7/7 (100)	19/21 (90)	26/28 (93)	6/7 (86)	20/21 (95) 2	26/28 (93))
	0.5	4/4 (100)	7/8 (88)	11/12 (92)	2/4 (50)	7/8 (100)	9/12 (75)
	1	4/4 (100)	4/7 (57)	8/11 (73)	3 /4 (75)	4/7 (57)	7/11 (64))
	2	3/3 (100)	2/2 (100)	5/5 (100)	2/3 (67)0	2/2 (100)	4/5 (80)
	4	1/1 (100)	0	1/1 (100)	1/1 (100)	0	1/1 (100)
	8	2/3 (67)	0	2/3 (67)	2/3 (67)(0)	0	2/3 (67))
	16	2/2 (100)	0	2/2 (100)	1 /2 (50)	0	1 /2 (50)
	32	0	0	0	0	0	0)
	≥64	0	0	0	0	0	0
Anaerobes	All tested	0	225/274 (82)	225/274 982)	0	234/274 (85)	234/274 (85)
	≤0.25	0	181/222 (82)	181/222 (82)	0	190/222 (86)	190/222 (86)
	0.5	0	26/31 (84)	26/31 (84)	0	26/31 984)	26/31 984)
	1	0	10/12 (83)	10/12 (83)	0	10/12 (83)	10/12 (83)
	2	0	3/3 (100)	3/3 (100)	0	3/3 (100)	3/3 (100)
	4	0	2/2 (100)	2/2 (100)	0	2/2 (100	2/2 (100
	8	0	2/3 (67)	2/3 (67)	0	2/3 (67)	2/3 (67)
	16	0	0	0	0	0	0
	32	0	1/1 (100)	1/1 (100)	0	1/1 (100)	1/1 (100)
	≥64	0	0	0	0	0	0
B. fragilis	All tested	0	53/63 (84)	53/63 (84)	0	53/63 (84)	53/63 (84)
	≤0.25	0	47/56 (84)	47/56 (84)	0	47/56 (84)	47/56 (84)
	0.5	0	4/4 (100)	4/4 (100)	0	4/4 (100)	4/4 (100)
	1	0	2/2 (100)	2/2 (100)	0	2/2 (100)	2/2 (100)
	2	0	0	0	0	0	0
	4	0	1/1 (100)	1/1 (100)	0	1/1 (100)	1/1 (100)
	≥8	0	0	0	0	0	0

[a]cUTI trials were DORI-05 and DORI-06
[b]cIAI trials were DORI-07 and DORI-008

Source: Module 2.7 Microbiology Summary, Section 2.7.2.4

2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety?

Adverse Events

In the pooled Phase 1 studies, of the 164 subjects with normal renal function, 40% of all doripenem-treated subjects experienced at least one adverse event (AE) compared with 25% of placebo-treated subjects. Adverse events reported at higher rates in pooled doripenem-treated subjects (i.e., 500 mg and 1,000 mg) than in placebo-treated subjects included diarrhea (6% versus 0%), nausea (6% versus 1%), injection site erythema (5% versus 0%), and injection site swelling (4% versus 1%, respectively). Among renally impaired subjects in the Phase 1 studies, the incidence of AEs did not appear to have any correlation with the degree of renal impairment. In study DORI-NOS-1005, 1 of 6 subjects with end-stage renal disease (ESRD) who were receiving hemodialysis experienced 3 AEs, compared with 2 of 6 healthy subjects who experienced 1 AE each.

Safety data for all Phase 2 and 3 studies (i.e., DORI-03, DORI-05, DORI-06, DORI-07, and DORI-08) were pooled for analysis. In addition, safety data were analyzed by indication (i.e., cUTI or cIAI). A total of 2,238 subjects, aged 18 years or older, were included in the pooled safety analysis set, including 1,292 subjects in the cUTI studies and 946 subjects in the cIAI studies. Overall, in the pooled Phase 2 and 3 safety analysis set, headache was the most commonly reported AE. Diarrhea was reported in 7.9%, 10.2%, and 11.1% of subjects in the doripenem, levofloxacin, and meropenem treatment arms, respectively. Nausea was reported in 6% to 9% of subjects across the 3 treatment arms. Phlebitis was reported in 6.9%, 4.0%, and 5.5% of subjects in the doripenem, levofloxacin, and meropenem arms, respectively. Anemia

was reported at similar rates in the doripenem and meropenem arms (5.3% and 5.5%, respectively) and was more common in the cIAI studies than in the cUTI studies. No seizures were reported in any doripenem-treated or meropenem-treated subjects in the Phase 1, 2 and 3 studies.

The 164 doripenem-treated subjects with normal renal function in the pooled Phase 1 analysis set included 107 subjects (doripenem 1,000 mg), 138 subjects (doripenem 500 mg), and 72 subjects (placebo). Eighty-one subjects received both doripenem 500 mg and 1,000 mg doses. The overall incidence of AEs for subjects who received i.v. doripenem 1,000 mg (33%) was slightly higher than for subjects who received doripenem 500 mg (26%) or placebo (25%). AEs were diverse and the numbers of subjects with each event were too small to draw definitive conclusions. The most commonly reported AE across all 3 treatment arms was headache, experienced by 10%, 9%, and 7% of subjects in the placebo, doripenem 500 mg, and doripenem 1,000 mg arms, respectively. Infusion site pain (5% and 1%) and injection site swelling (4% and 1%) were experienced at higher rates by subjects who received doripenem 1,000 mg than those who received 500 mg, respectively. The higher rates of these AEs in subjects receiving 1,000 mg doses of doripenem may be related to the dose infused. However, since the volume, concentration and infusion rates of the 500-mg and 1,000-mg doses of doripenem were not the same across all Phase 1 studies, an association between administration site events and doripenem dose cannot be concluded. In summary, a clear dose-response relationship with respect to safety was not observed in the Phase 1 studies. All subjects in the Phase 3 studies received a doripenem dose of 500 mg; therefore, a dose-response assessment could not be conducted.

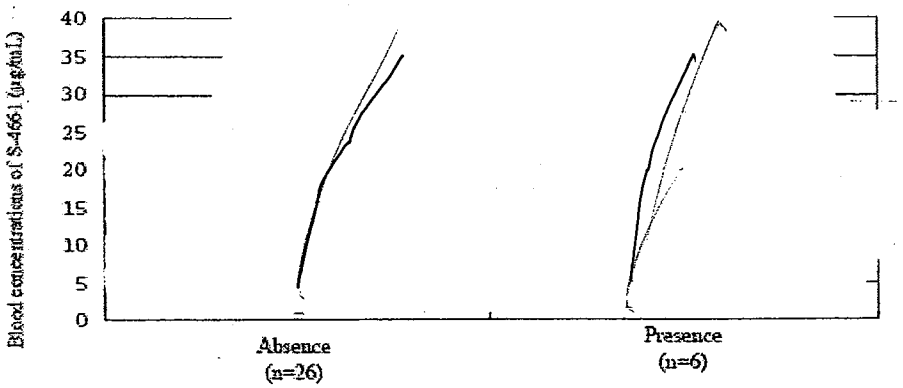
Laboratory Abnormalities

In general, few notable chemistry or hematology laboratory abnormalities were detected in doripenem-treated subjects and the rates and degrees of abnormalities were similar compared with comparator-treated subjects. In the Phase 1 studies, no dose-related trends in clinical laboratory values were demonstrated. In the Phase 1 PK study DORI-01 minor (< 3 x upper limit of normal [ULN]), reversible elevations in serum concentrations of ALT and aspartate aminotransferase (AST) were observed in 3 of 6 subjects who received doripenem 1,000 mg q8h, and 1 of 6 subjects in each of the doripenem 500 mg q8h and q12h cohorts. The 1 subject with the highest ALT elevation in the 1,000 mg q8h arm had an elevated total bilirubin at screening, suggesting a pre-existing hepatobiliary disorder. None of the 6 subjects in the 1,000 mg q12h cohorts had ALT and AST elevations during study drug therapy. Observed abnormalities were reversible in all cases in which follow-up labs were performed. Evaluation of doripenem PK parameters in the 5 subjects with elevated liver enzymes reveals no apparent relationship between increased drug exposure and elevated enzymes. In fact, AUC and Cmax values for each of the 5 subjects with elevated liver enzymes were consistently lower than the cohort average. In subsequent studies in which subjects received 1,000 mg doses of doripenem there were no trends towards an increased incidence of liver enzyme abnormalities. In addition, there were no clinically relevant changes in liver function or other laboratory parameters in subjects with impaired renal function receiving single 500-mg doses of doripenem.

A Phase 2 Japanese study conducted to evaluate the safety and efficacy of doripenem in urology patients also examined the relationship between doripenem concentration at the end of infusion (C_{max}) and laboratory parameters of hepatic function. Of the 39 subjects included in the safety analysis, 32 subjects had blood sampling performed according to protocol. The number of evaluable subjects with and without abnormal hepatobilliary laboratory values (SGOT, SGPT, alkaline phosphatase, total bilirubin, or γ-GTP) was 6 and 26, respectively. Sixteen adverse laboratory values were reported in 8 subjects and included SGOT increases (6 events), SGPT increases (6), γ-GTP increases (2), an alkaline phosphatase increase (1), and eosinophilia (1). The mean plasma concentrations of doripenem in subjects with and without abnormal hepatic

laboratory results were 9.1 ± 4.1 μg/mL and 12.1 ± 7.4 μg/mL, respectively (*t* test, $p = 0.3498$) (Figure 2.2.4.2.1).

Figure 2.2.4.2-1 Individual plasma doripenem concentrations in the presence or absence of abnormal hepatobilliary l[illegible]



Adverse drug reactions (laboratory values) in the hepatic function

Unfortunately, the results of this study are not particularly useful given the large number of problems with the study design and analysis. First of all, the number of assessable subjects with plasma concentration data is limited (32 total; 6 with abnormal hepatobilliary laboratory results). Further, there is no information regarding the day on which blood collection for PK determination took place. In addition, a relationship between concentration and adverse events is difficult to ascertain as most patients in the study received the same dose of 250 mg twice daily, with only a limited number of subjects receiving the higher doses of 250 mg 3x/day or 500 mg twice daily. The limited range of doses included in the study restricts the utility of the analysis, as most subjects had relatively similar exposures. Also, since Cmax was the only PK value determined, the exposure-response relationship could not be evaluated for other measures of exposure (C_{min}, AUC, etc.).

Changes in ALT and total bilirubin were evaluated in the Phase 3 studies using the Hy's High Risk (HHR) classification. A total 4 (0.3%) of 1,234 doripenem-treated (500 mg) subjects with paired values were evaluated and were classified as HHR (i.e., ALT > 3 times ULN and total bilirubin > 1.5 times ULN at the same time point). One subject was classified as HHR during i.v. doripenem therapy (in DORI-06), while the other 3 subjects were classified as HHR only after discontinuation of study drug therapy. All subjects had confounding medical events that were plausibly related to the recorded abnormalities.

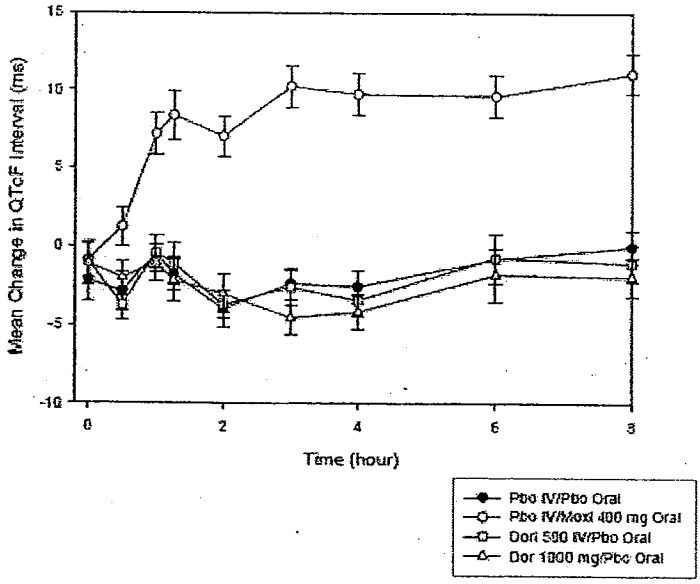
2.2.4.3. Does doripenem prolong QT or QTc interval?

A randomized, double-blind, placebo- and positive-controlled, double-dummy crossover QT study was conducted in healthy subjects administered multiple doses of doripenem at therapeutic (500 mg) and supratherapeutic (1000 mg) doses (DORI-NOS-1001). A total of 4 doses of doripenem were administered every 8 hours as 1 hour infusions on Days 1 and 2. The supratherapeutic dose (1000 mg Q8h) produces levels of exposure greater than those expected in all clinical scenarios at the standard dose (elderly, mild renal impairment, etc.). A single 400 mg oral dose of moxifloxacin was administered on Day 2 for the positive control. Serial ECGs and serial blood sampling for PK assessments were taken at specified time points after dose administration on Day 2 in each treatment period. Serial ECGs were also performed on Day -1

to be used as baseline measurements. The Fridericia correction (QTcF) was used as the primary correction method for QT intervals. A PK/PD evaluation was performed using doripenem plasma concentrations and change from baseline in QTcF data. The change from baseline in QTc (ΔQTc) at each time point was the primary PD parameter. A non-inferiority criterion of 10 msec was used to test the difference in ΔQTc between doripenem and placebo. The incidence of subjects with out of range values in QTc intervals, ΔQTc, QRS interval, PR interval and abnormal T-wave and U-wave morphology were also tabulated.

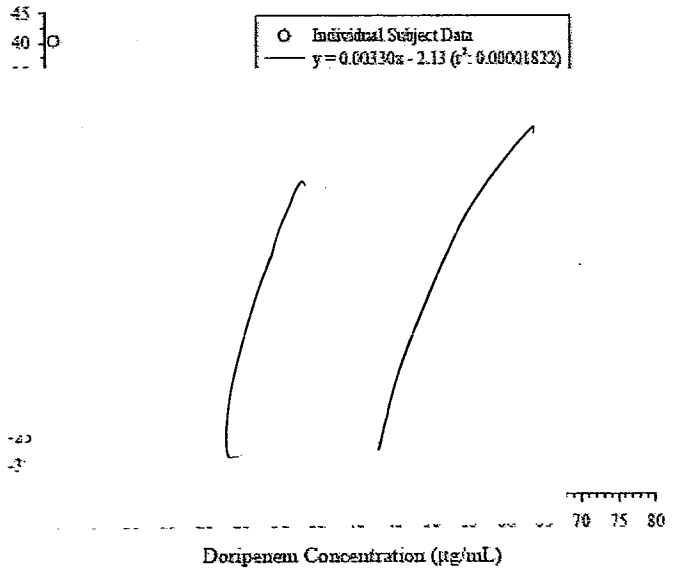
A total of 60 subjects were enrolled in the study and contributed to the analysis of ECG data; the number of subjects analyzed for each of the four treatments ranged from 57 to 59. The upper limit of the two-sided 90% CI for the difference in ΔQTc between doripenem and placebo was below the pre-defined 10 ms limit at all time points for both doripenem doses. Thus, the effect of doripenem on QT/QTc prolongation was no worse than that of placebo (Figure 2.2.4.3-1). Results obtained from the mixed effects model-based pairwise comparison of mean ΔQT corrected with Bazett's formula (ΔQTcB), ΔQT corrected with the population correction method (ΔQTlcP) and ΔQT corrected with the individual correction method (ΔQTcI) were consistent with results obtained for ΔQTcF. No subject had a QTcF value greater than 480 ms during any treatment at any time point. No subject had a postdose QTcF greater than 450 ms after receiving either doses of doripenem or placebo treatment at any time point. No subject had a time-matched ΔQTcF exceeding 60 ms in any treatment at any time point. There was no relationship between ΔQTcF and doripenem concentration for either the 500 mg or 1000 mg treatment groups (Figure 2.2.4.3-2).

Figure 2.2.4.3-1. Mean (SE) Change in QTcF From Baseline Over Time



Source: Clinical Study Report DORI-NOS-1001, Section 4.4.2.1.

Figure 2.2.4.3-1 Individual ΔQTcF vs. Individual Doripenem Concentrations for Placebo, 500 mg and 1000 mg Doripenem Treatments



Source: Study Report DORI-NOS-1001, Section 4.5

Preclinical studies indicate little to no potential for adverse cardiac events as a result of elecrophysiologic effects. ECGs were not collected systematically in any of the Phase 3 studies. Adverse events of severe atrial flutter and severe atrial fibrillation with renal impairment were reported in two doripenem-treated subjects (500 mg) with cUTI in clinical studies. The cases were thoroughly reviewed and because of other plausible causative factors, the events were not considered ADRs.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Animal models of infection demonstrated that the PK/PD parameter best correlated with efficacy for doripenem is %T>MIC. The %T>MIC required to produce a static effect for the multiple pathogens studied in animal models ranged from 2.3 to 38%. The mean %T>MIC for a static effect was 29% for both GNB and *S. aureus* organisms, and 12.4% for *S. pneumoniae*. The presence of methicillin resistance or ESBL production did not significantly impact the magnitude of the PK/PD parameter required for efficacy. In addition, there was no major difference in %T>MIC for the different strains of *S. pneumoniae*, regardless of penicillin or quinolone resistance.

The Applicant's PK/PD target attainment analysis supports the proposed dose of 500 mg q8h infused over 1 hour for patients with normal renal function or mild renal impairment, and the reduced doses of 250 mg q8h and 250 mg q12h for patients with moderate and severe renal impairment, respectively. The Monte Carlo simulation demonstrated target attainment rates > 80% for %T>MIC of 25-35% for most pathogens found in the cIAI and cUTI clinical trials (Enterobacteriaceae, non-Enterobacteriaceae, *Staphylococcus* spp., *S. pneumoniae,* and other

Streptococcus spp.). Target attainment rates for *Enterococcus* spp. were more modest (40 – 75%). The animal model data support a %T>MIC target of 30% for GNB and *S. aureus*. Target attainment is >90% for a %T>MIC of 30% up to an MIC of 2 μg/mL. As the MIC increases from 2 to 4 μg/mL, the target attainment drops from 90.9% to 53.4% for a %T>MIC of 30%.

Exploratory PK/PD analyses were not conducted, as there was no PK sampling performed in any of the Phase 3 or Phase 2 clinical studies, with the exception of DORI-03. In DORI-03 sparse blood sampling was performed in cUTI patients to evaluate the PK/PD relationship of doripenem. However, as outlined above, there was no apparent relationship between %T>MIC and clinical or microbiological response with increasing T >MIC. The lack of an evident PK/PD relationship was likely due to doripenem's high concentration in the urine relative to the MIC values of typical uropathogens, as well as a limited number of patients with T >MIC less than 80% of the dosing interval.

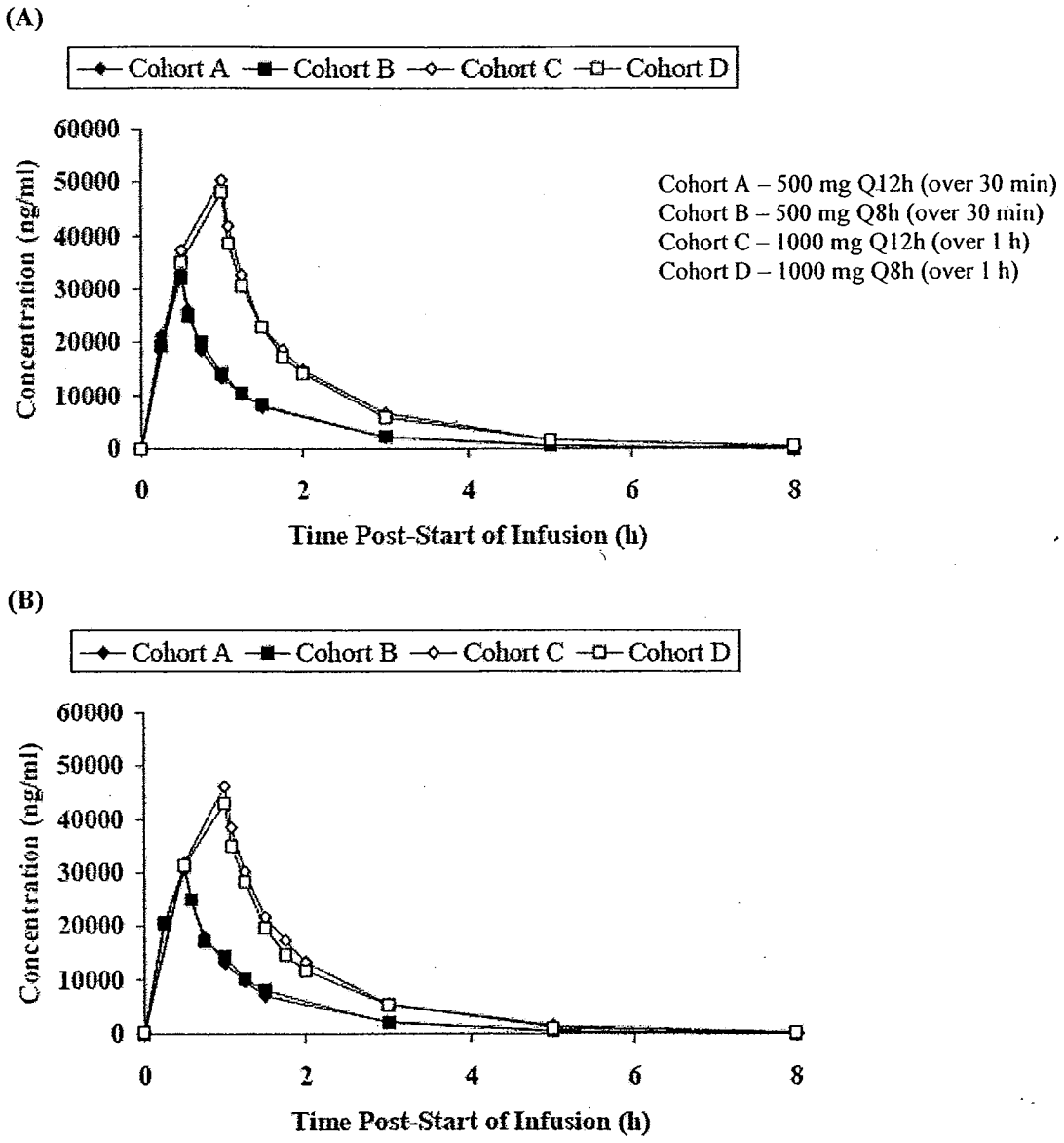
The results of the four Phase 3 clinical trials also support the proposed dose of 500 mg q8h for cIAI and cUTI indications. Clinical cure rates for doripenem in the two randomized cIAI trials were 83.3% and 85.9% -- demonstrating non-inferiority to the control (meropenem) arms. Microbiological cure rates were similar to the clinical response rates. Eradication rates at TOC for doripenem treated subjects ranged from 78.1% for *K. pneumoniae* to 100.0% for *B. vulgatus*. Microbiological cure ranged from 80% (*E. faecalis*) to 90% (*Streptococcus constellatus*) for Gram positive organisms, from 78.1% (*K. pneumoniae*) to 85.0% (*P. aeruginosa*) for Gram negative organisms, and were 87.9% for Bacteroides fragilis group. The microbiological cure rates in DORI-05, the randomized controlled trial of doripenem for cUTI, were 82.1% and 83.4% in the doripenem and levofloxacin arms, respectively. Microbiological efficacy at the TOC visit was also demonstrated in the non-controlled study DORI-06, where the microbiological cure rate in doripenem-treated subjects was 83.5%. Clinical cure rates were slightly higher than the microbiological cure rates in the cUTI trials (95.1 and 93.0%).

2.2.5. What are the PK characteristics of doripenem?

2.2.5.1. What are the single and multiple dose PK parameters?

A total of 26 clinical pharmacology studies have been conducted – 8 Phase 1 studies in Western populations, 8 phase I studies in Japanese subjects and an additional 10 Phase 2 and 3 studies in which concentrations in various tissues and fluids were collected. In DORI-01 a comparison of 4 dosing regimens of doripenem demonstrated that systemic exposure was approximately dose proportional for 500 mg (over 30 minutes) vs. 1000 mg (over 1 hour) following single and multiple dosing (7 days) in healthy adult subjects (Figure 2.2.5.1-1 and Table 2.2.5.1-1 below). C_{max} was less than dose proportional, likely due to differences in infusion duration. Thereafter, plasma doripenem concentrations declined in a bi-phasic manner with a mean apparent terminal half-life ($t_{1/2}$) ranging from 0.8 to 1 hour.

Figure 2.2.5.1-1. Mean Doripenem Plasma Concentration Time Curves Following Single (A) and Multiple Dose (B) Administration of Various Dosing Regimens



Source: Clinical Study Report DORI-01, Section 9.4.2.1

Table 2.2.5.1-1. Summary of Doripenem Pharmacokinetic Parameters Following (A) Single and (B) Multiple Dose Administration of 4 Dosing Regimens in Healthy Subjects (Geometric mean [CV%])

(A)

Parameter	Cohort A 500 mg Q12h	Cohort B 500 mg Q8h	Cohort C 1000 mg Q12h	Cohort D 1000 mg Q8h
n	6	6	6	6
Cmax (ng/ml)	32982 (6.81)	31770 (18.8)	49335 (22.5)	47999 (8.75)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.5-0.58)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
AUC0-τ (ng·h/ml)	35869 (6.37)	36140 (16.7)	79300 (21.8)	75513 (10.6)
AUC0-∞ (ng·h/ml)	35746 (6.34)	36144 (16.6)	79122 (21.9)	76484 (9.99)
t1/2 (h)	0.868 (8.06)	1.00 (22.6)	1.03 (11.7)	1.03 (24.2)
CL (ml/min)	233 (7.00)	231 (17.9)	211 (22.6)	218 (9.49)
Vss (ml)	13711 (10.4)	14773 (16.3)	14533 (20.7)	16404 (14.0)

(B)

Parameter	Cohort A 500 mg Q12h	Cohort B 500 mg Q8h	Cohort C 1000 mg Q12h	Cohort D 1000 mg Q8h
n	6	5	6	6
Cmax (ng/ml)	30250 (14.7)	31204 (11.5)	45934 (11.5)	42867 (9.20)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.5-0.5)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
AUC0-τ (ng·h/ml)	33687 (8.36)	35292 (12.5)	71016 (17.5)	65408 (9.48)
t1/2 (h)	0.824 (4.33)	0.869 (8.29)	1.13 (8.24)	0.932 (11.0)
Ro	0.939 (6.10)	0.923 (8.73)	0.896 (9.74)	0.866 (8.27)
CL_R (ml/min)	156 (13.6)	164 (11.5)	156 (21.7)	179 (17.5)

[a] Median (min-max) data

Doripenem exhibits linear and time-independent pharmacokinetics. Dose proportionality has been demonstrated across a range of 125 mg to 1000 mg in Japanese and Western studies. Steady-state concentrations are attained on the first day of dosing, with no appreciable accumulation following multiple (7 days) of dosing. Pooling of results from all PK studies conducted in Western populations (Table 2.2.5.1-2) indicates a mean (SD) doripenem $t_{1/2}$ of 1.15 (0.51) hours. Mean total systemic clearance is 15.9 L/hr (range 13.0 to 28.7 L/hr). Approximately 70% of the dose is excreted as unchanged parent drug, while 15% is excreted as the M1 ring-opened metabolite.

Table 2.2.5.1-2 Across-Study Comparison of Doripenem and Doripenem-M1 Pharmacokinetic Parameters Following Doripenem Administration in Western Populations (Mean [SD])

				Doripenem				M-1
Study	Dose (mg)	Infusion Duration	N	$t_{1/2}$ (hr)	CL (L/hr)	CL_R (L/hr)	Ae (%, Dose)	Ae (%, Dose)
Single Dose								
DORI-01	500	0.5 hr	12	0.945 (0.180)	14.0 (1.81)	ND	ND	ND
DORI-02[a]	500	0.5 hr	8	1.11 (0.192)	13.7 (1.98)	11.3 (2.12)	83.1 (5.16)	ND
DORI-NOS-1004	500	1 hr	23	1.20 (0.104)	14.6 (3.61)	10.3 (4.19)	69.8 (22.3)	16.3 (6.21)
DORI-NOS-1005[a]	500	1 hr	6	1.30 (0.238)	13.2 (1.98)	9.66 (4.19)	72.4 (29.0)	10.0 (3.22)
DORI-NOS-1006[b]	500	1 hr	12	0.997 (0.130)	13.9 (2.62)	9.56 (2.02)	68.6 (7.44)	16.7 (4.53)
DORI-04	500	4 hr[d]	6	1.05 (0.254)	18.0 (3.55)	ND	63.8 (12.4)	10.4 (2.81)
DORI-NOS-1004	500	4 hr	23	1.23 (0.214)	14.6 (3.17)	10.3 (3.94)	69.8 (17.5)	16.2 (4.68)
DORI-01	1000	1 hr	12	1.05 (0.191)	13.0 (2.14)	ND	ND	ND
DORI-04	1000	4 hr[d]	6	0.940 (0.148)	25.1 (3.67)	ND	72.4 (15.1)	13.9 (6.02)
DORI-NOS-1004	1000	4 hr	24	1.53 (1.58)	13.8 (2.88)	10.3 (4.82)	73.5 (26.4)	16.9 (6.90)
DORI-04	1000	6 hr[e]	6	0.992 (0.136)	24.2 (4.11)	ND	50.7 (13.9)	6.70 (2.55)
Single Dose Studies Pooled			138	1.18 (0.693)	15.1 (4.26)	10.2 (3.90)[c]	70.3 (20.1)[f]	15.1 (6.04)[g]
Multiple Dose								
DORI-01	500	0.5 hr[c]	6	0.825 (0.0357)	ND	9.43 (1.28)	64.0 (11.3)	ND
DORI-01	500	0.5 hr[d]	5	0.872 (0.0723)	ND	9.91 (1.13)	70.0 (8.40)	ND
DORI-NOS-1001	500	1 hr	58	1.15 (0.287)	15.3 (3.54)	ND	ND	ND
DORI-04	500	4 hr[d]	5	1.04 (0.255)	19.5 (4.51)	ND	ND	ND
DORI-01	1000	1 hr[e]	6	1.14 (0.0937)	ND	9.55 (2.09)	67.0 (8.24)	ND
DORI-01	1000	1 hr[d]	6	0.936 (0.103)	ND	10.9 (1.91)	71.3 (9.56)	ND
DORI-NOS-1001	1000	1 hr	58	1.19 (0.169)	15.0 (3.66)	ND	ND	ND
DORI-04	1000	4 hr[d]	6	1.04 (0.229)	28.7 (5.06)	ND	ND	ND
DORI-04	1000	6 hr[e]	6	1.09 (0.296)	25.8 (5.33)	ND	ND	ND
Multiple Dose Studies Pooled			156	1.12 (0.239)	16.7 (6.27)[h]	9.95 (1.67)[i]	68.0 (9.30)[i]	ND
All Studies Pooled			294	1.15 (0.505)	15.9 (5.37)[j]	10.2 (3.57)[k]	69.9 (18.8)[l]	15.1 (6.04)[g]

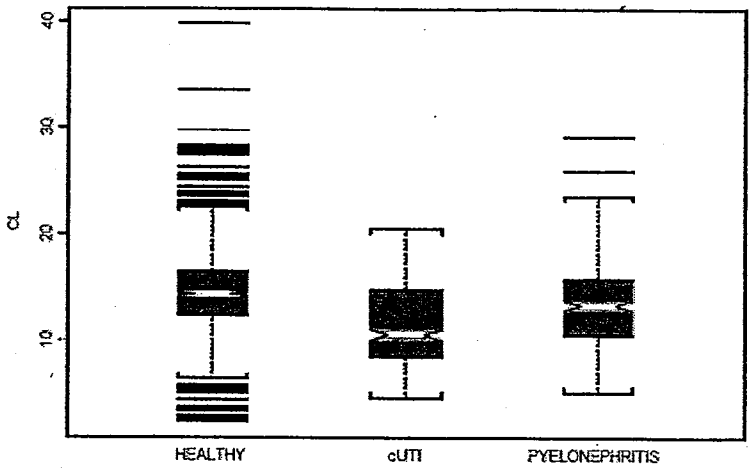
ND - Not Determined; [a] Subjects with normal renal function.; [b] Non-Elderly subjects.
[c] q12h; [d] q8h; [e] n=96; [f] n=116; [g] n=108; [h] n=133; [i] n=23; [j] n=271; [k] n=119; [l] n=139

Source: Module 2.7 Clinical Pharmacology Summery, Section 3.3

2.2.5.2. *How does the PK of doripenem in healthy volunteers compare to that in patients?*

There was no PK sampling performed in any of the Phase 2 or Phase 3 clinical studies, with the exception of DORI-03, in which sparse blood sampling was performed in patients with cUTI to evaluate the PK/PD relationship of doripenem. Plasma concentrations from DORI-03 were also included in the population PK analysis of pooled data from healthy subjects with varying degrees of renal impairment to assess disease state as a covariate. Despite a 20% lower clearance rate in patients with cUTI versus healthy volunteers (see figure below), disease state was not identified as a significant independent predictor of doripenem clearance in the model due to confounding by other covariates.

Figure 2.2.5.2-1 Doripenem Clearance in Healthy vs. cUTI Patient Populations



Note: White notch indicates median; bar indicates inter-quartile range (25^{th} and 75^{th}); whiskers indicate data range

Source: Module 2.7 Clinical Pharmacology Summary, Section 3.6

2.2.5.3. What are the characteristics of drug absorption?

Not applicable; drug is administered intravenously.

2.2.5.4. What are the characteristics of drug distribution?

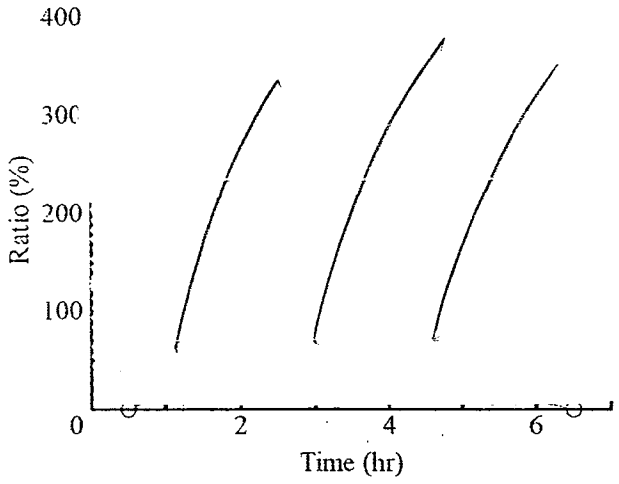
The median (range) doripenem volume of distribution at steady state (Vd_{ss}) in healthy Western subjects was 16.6 L (8.09 – 55.5L), similar to the extracellular fluid volume in humans. *In vitro* protein binding of doripenem in human plasma was 8.1% at a concentration of 100 µg/mL. *Ex vivo* binding to serum proteins was 5.4 to 15.2% across a dosage range of 125 mg to 1000 mg in single- and multiple-dose studies conducted in Japanese subjects.

The concentration of doripenem in peritoneal exudate was evaluated in 5 male and female Japanese patients undergoing abdominal surgery following a single 250 mg dose of doripenem (Study R143W). Mean peritoneal exudate concentrations were approximately 4 µg/mL at 0.5 hours (end of infusion) and 3.2 µg/mL at 2.5 hours, decreasing gradually to 0.50 µg/mL at 6.5 hours (Table 2.2.5.4-1). The half-life of doripenem in peritoneal fluid was just slightly longer than that observed in plasma (1.5 hrs vs. 1.2 hrs, respectively). There was a delay in distribution to the peritoneum, with peritoneal exudate / plasma concentration ratios increasing gradually from 0.2 at the end of infusion to 1.6 at four hours post-infusion (Figure 2.2.5.4-1). Overall drug exposure in the peritoneum was approximately half that of the plasma; the mean (SD) ratio of peritoneal fluid $AUC_{0\text{-}6.5}$ / plasma $AUC_{0\text{-}6.5}$ was 0.46 (±0.27).

Table 2.2.5.4-1 Concentrations of Doripenem in Peritoneal Exudate Following a 250 mg Dose

Subject ID	Concentration in peritoneal exudate (μg/mL)			
	0.5 hr	2.5 hr	4.5 hr	6.5 hr
1				
2				
3				
4				
6				
Mean	**3.97**	**3.18**	**1.11**	**0.50**
S.D.	**1.05**	**1.39**	**0.46**	**0.24**

Figure 2.2.5.4-1 Individual Subject Time Profiles of Peritoneal Exudate/Plasma Concentration Ratio of Doripenem (Following 250 mg Single Dose Over 30 Min.)



Source: Study Report 0106R143W

Assuming linear pharmacokinetics of doripenem in peritoneal exudate, and based on the results of the limited number of subjects included in this study, concentrations of unbound doripenem in peritoneal exudate could be estimated to be approximately 6 μg/mL and 2 μg/mL at 2.5 hours and 4.5 hours, respectively, following a 500 mg intravenous dose. Nearly 95% of the 1,936 strains reported in the Phase III cIAI studies had doripenem MIC values ≤ 1 μg/mL. Taken together, this would suggest that doripenem exposure in the peritoneum exceeds the MIC of most cIAI pathogens, up to an MIC of 2 μg/mL, for over half of the dosing interval. However, peritoneal concentrations are below the Sponsor's proposed susceptibility breakpoint of

A second Japanese study evaluated doripenem distribution in a range of fluids and tissues in various patient populations, including patients with chronic respiratory infections, cUTI and pre-operative surgical patients (Study R142A). Doripenem exposure was assessed in the bile and

gallbladder tissue of 10 pre-operative patients and in the retroperitoneal fluid of 10 pre-operative patients. Gallbladder tissue samples were limited, and the sampling times highly variable, making conclusions about distribution to the gallbladder difficult. Sampling times of bile were also variable, as were the respective concentrations. Doripenem concentrations ranged from <0.16 μg/mL at 60 minutes in one subject to 15.4 μg/mL at 215 minutes in another. Based on this limited data set (n=10), it appears that doripenem exposure in bile peaks later than in plasma, with concentrations ≥1 μg/mL at 2.5 to 3.5 hours in some individuals (Table 2.2.5.4-2).

Table 2.2.5.4-2 Gallbladder and Plasma Concentrations of Doripenem in Pre-Operative Patients Administered a 250 mg Dose (Over 30 Min.)

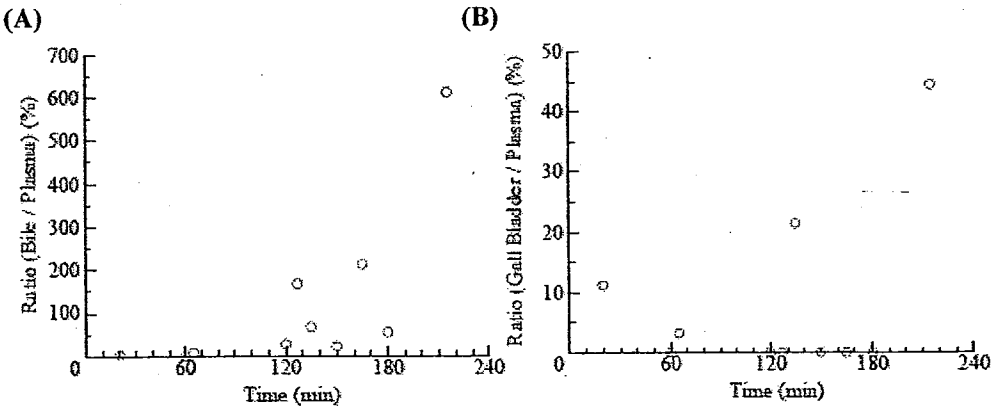
	Plasma						
Subject No.	**Time[1] (min)**	**Conc. (μg/mL)**	**Tissue Time[1] (min)**	**Bile Conc. (μg/mL)**	**Gall Bladder Conc. (μg/g)**	**Bile Ratio (%)**	**Gall Bladder Ratio[2] (%)**
30001A	180		180			54.9	0.0
30002A	215		215			611.1	44.4
30003A	165		165			212.6	0.0
30004A	60		60			0.0	0.0
30005A	65		70			7.6	3.2
30006A	20		20			3.1	11.2
30007A	60		----			----	----
	135		180			67.1	21.4
	240		----			----	----
30008A	127		145			166.7	0.0
30009A	120		135			26.2	0.0
30010A	150		210			21.8	0.0
	Mean					**117.1**	**8.0**
	S.D.					**188.0**	**14.6**
	Minimum					**0.0**	**0.0**
	Maximum					**611.1**	**44.4**

[1] Sampling time – from start of infusion

[2] Ratio of tissue conc./ plasma conc. x 100%

N.D. – Not determined (fluid conc < 0.16 μg/mL or tissue conc < 0.10 or <0.20 μg/g)

Figure 2.2.5.4-2 Doripenem Concentration Ratios for Individual Subjects for (A) Bile/plasma or (B) Gallbladder tissue/plasma



Source: Study Report 9502R1412

Retroperitoneal and plasma concentrations of doripenem were assessed in 10 patients administered either 250 mg or 500 mg doripenem (over 30 min.) pre-operatively. Retroperitoneal exposure peaked at approximately 1 to 1.5 hours, with mean peak concentrations of 5.76 µg/mL and 12.0 µg/mL following 250 mg and 500 mg infusions, respectively (Table 2.2.5.4-3). Retroperitoneal exposure appears to be approximately dose-proportional, and was similar to the peritoneal exposure reported in Study R143W, relative to dose. The mean retroperitoneal concentration at 4.5 hours was 3.67 µg/mL (range — µg/mL) following a 500 mg infusion. This data would suggest that doripenem exposure exceeds MICs of ≤ 2 in the retroperitoneum for over half of the dosing interval. Relative to plasma concentrations, retroperitoneal exposure was at least 100% greater 2 to 6 hours post-dose (Figure 2.2.5.4-3). Mean plasma and retroperitoneal concentration-time profiles are shown together in Figure 2.2.5.4.4.

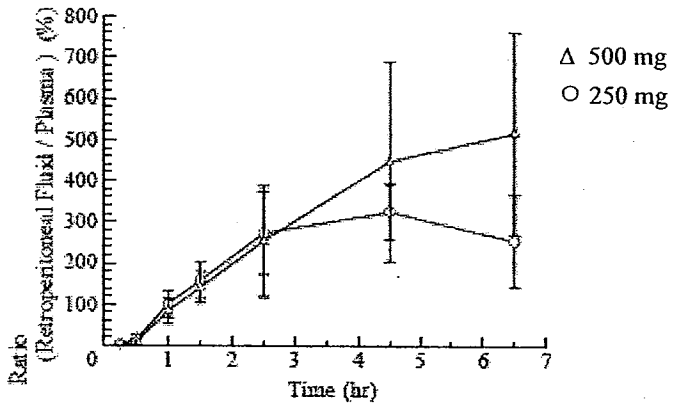
Table 2.2.5.4-3 Retroperitoneal Concentrations of Doripenem following a 250 mg or 500 mg Dose Administered Pre-Operatively (Over 30 Min.)

	Conc. in Retroperitoneal Fluid (µg/mL)								
Subject No.	**pre-dose**	**0.25hr**	**0.5 hr**	**1 hr**	**1.5 hr**	**2.5 hr**	**4.5 hr**	**6.5 hr**	**8.5 hr**
250mg / 30min infusion									
40001A									
40002A									
40003A									
40004A									
40016A									
40017A									
Mean	**0.04**	**0.63**	**3.38**	**6.69**	**5.76**	**3.71**	**1.12**	**0.27**	--
S.D.	--	**0.56**	**1.97**	**2.78**	**2.42**	**1.45**	**0.37**	**0.15**	--

Subject No.	pre-dose	Conc. in Retroperitoneal Fluid (µg/mL) 0.25hr	0.5 hr	1 hr	1.5 hr	2.5 hr	4.5 hr	6.5 hr	8.5 hr
500mg / 30min infusion									
40010A	NS								
40012A	NS								
40014A	NS								
40015A	NS								
Mean	--	**1.08**	**4.27**	**10.6**	**12.0**	**9.51**	**3.67**	**1.27**	--
S.D.	--	**1.44**	**3.88**	**2.1**	**1.9**	**1.74**	**1.18**	**0.62**	--

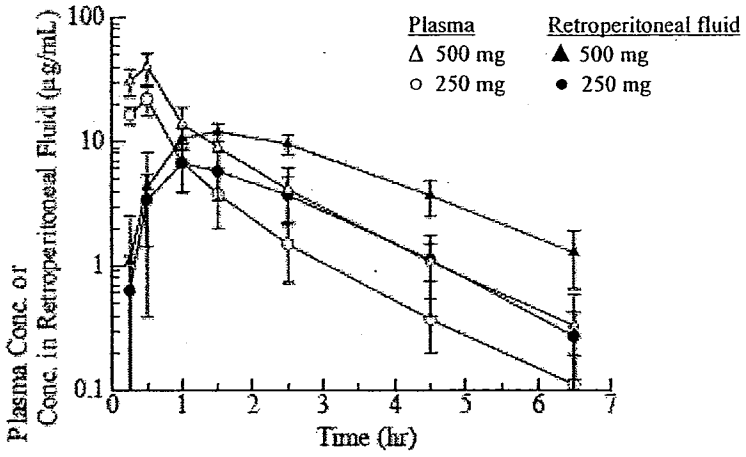
[1] NS – No sample
[2] < 0.03 µg/mL
[3] < 0.016 µg/mL

Figure 2.2.5.4-3 Ratio of Retroperitoneal Fluid/Plasma Doripenem Concentrations Following a Pre-Operative 250 mg or 500 mg Infusion (Over 30 Min.)



Source: Study Report 9502R142A

Figure 2.2.5.4-4 Mean Plasma and Retroperitoneal Fluid Doripenem Concentrations Following Single Pre-Operative Infusions of 250 mg or 500 mg (Over 30 Min.)



Source: Study Report 9502R142A

Samples of retroperitoneal fluid were also collected in female Japanese subjects undergoing total hysterectomy (Study R142H). Subjects were administered a single 250 mg dose over 30 min. pre-operatively. In general, retroperitoneal concentrations were significantly greater than the retroperitoneal concentrations reported in R142A or the peritoneal concentrations reported in R143W, particularly between 1 and 4.5 hours post-dose (Table 2.2.4.5-4). In this study fluid exposure was nearly 10-fold the exposure in plasma at 2.5 hours. However, the analysis included samples from only 3 subjects. In addition, there was large variability in retroperitoneal concentrations between the 3 subjects -- up to a 13-fold difference in concentrations for the same time point. The reason for the large range in fluid concentrations is not clear.

Table 2.2.5.4-4 Retroperitoneal Concentrations of Doripenem in Patients Administered a 250 mg Dose (Over 30 Min) Pre-Operatively

Time	N	Retroperitoneal Fluid (μg/mL) (Range)	Plasma (μg/mL) (Range)	Fluid / Plasma Concentration Ratio (%) Mean (Range)
0.25 hr	3			5.5 (2.80-8.80)
0.5 hr	3			46.7 (23.7-63.7)
1 hr	3			274 (90.0-590)
1.5 hr	3			642 (126-1622)
2.5 hr	3			990 (173-2609)
4.5 hr	3			836 (170-2015)
6.5 hr	3			234 (190-279)

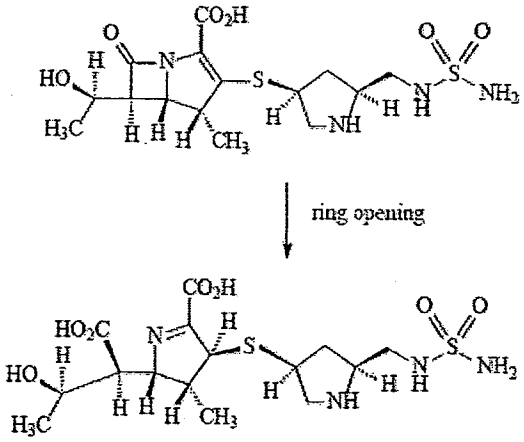
2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

The metabolism and excretion of 500 mg of ^{14}C-doripenem was evaluated in 8 healthy young men. The results confirmed that doripenem is eliminated almost exclusively through urinary excretion. Approximately 93% of the dose was excreted in the urine by 12 hours post-dose. Doripenem and doripenem-M1 accounted for an average of 80.7% and 12.7% of plasma radioactivity AUC_{∞}, respectively. Fecal excretion accounted for less than 1% of the radioactive dose.

2.2.5.6. What are the characteristics of drug metabolism?

The β-lactam ring of doripenem is cleaved by dehydropeptidase-I to the inactive ring-opened metabolite, doripenem dicarboxylate, designated as doripenem-M1 (Figure 2.2.5.6-1). In pooled studies of Western populations, the mean (SD) plasma doripenem-M1/doripenem AUC ratio following single 500 mg and 1000 mg doses was 0.183 (0.0718) (Studies DORI-04, DORI-NOS-1004, DORI-NOS-1005, and DORI-NOS-1006). Mean urinary recovery of doripenem-M1, expressed as a percentage of the administered doripenem dose, averaged 15.1% across studies and appears to be independent of dose.

Figure 2.2.5.6-1 Ring Cleavage of Doripenem by Dehydropeptidase-I



Source: Module 3.2.S.1.2

In 2 Japanese studies, thin layer chromatography (TLC)-bioautography was performed to assess antibiotic activity in plasma and urine. The results revealed no active metabolites of doripenem in plasma or urine after administration of single doses ranging from 25 mg to 1000 mg. *In vitro* studies using human liver microsomes and human hepatocytes have demonstrated that doripenem is neither a substrate for, nor inhibits or induces metabolizing enzymes, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, CYP4A11 and UGT1A1.

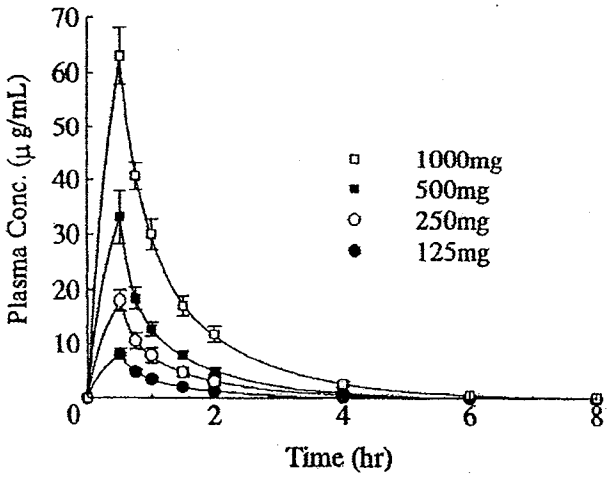
2.2.5.7. What are the characteristics of drug excretion?

The primary route of elimination of doripenem and doripenem-M1 is via renal excretion, with approximately 70% of the dose excreted unchanged and 15% of the dose excreted as the M1 metabolite. Doripenem renal clearance (mean 170 mL/min) exceeds the glomerular filtration rate in humans (approx. 125 mL/min), indicating a contribution from active tubular secretion. Results from the probenecid drug interaction study demonstrated reduced renal clearance following probenecid administration, confirming that doripenem undergoes active tubular secretion.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

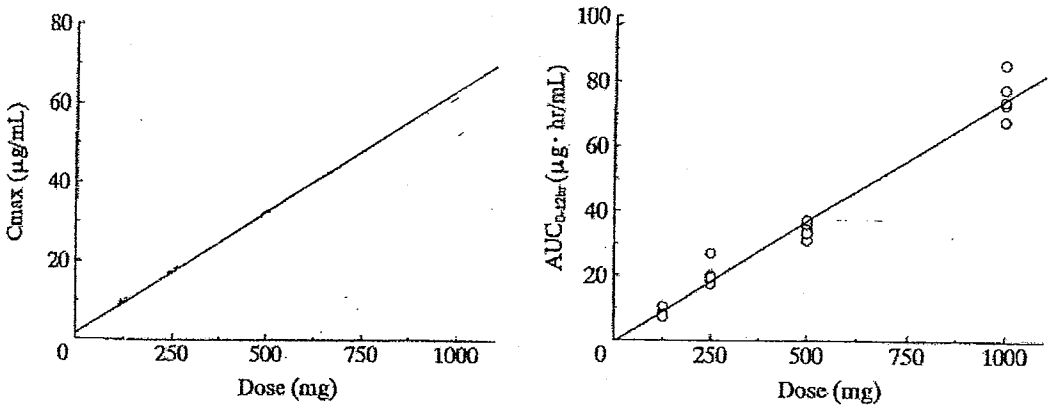
In a study of 24 Japanese males (Study R1412), linearity of doripenem was demonstrated over a dosage range of 125 mg to 1000 mg (single doses) (Figure 2.2.5.8-1). The elimination half-life was about 1 hour, regardless of dose. Dose proportionality of C_{max} and AUC are shown below in Figure 2.2.5.8-2.

Figure 2.2.5.8-1 Mean Plasma Concentration Time Curves for Increasing Doses of Doripenem



Source: Study Report 940R1412

Figure 2.2.5.8-2 Effect of Increasing Dose of Doripenem C_{max} and AUC_{0-12}



Source: Study Report 940R1412

Dose proportionality was also demonstrated for 500 mg and 1000 mg single and multiple doses in a Western population (Study DORI-01). Doripenem exposure, as assessed by AUC, was approximately dose-proportional on both Days 1 and 7 of dosing, as shown in Tables 2.2.5.8-1 and -2 below. C_{max} was less than dose proportional, likely due to differences in infusion duration (1-hour for 1000 mg vs. 0.5-hour for 500 mg). There was no accumulation of doripenem with repeat dosing, consistent with its short half-life.

Table 2.2.5.8-1 Pharmacokinetic Parameters of Doripenem on Day 1 (geometric mean [%CV])

Parameter	Cohort A 500 mg Q12h (over 30 min)	Cohort B 500 mg Q8h (over 30 min)	Cohort C 1000 mg Q12h (over 1 hr)	Cohort D 1000 mg Q8h (over 1 hr)
n	6	6	6	6
Cmax (ng/ml)	32982 (6.81)	31770 (18.8)	49335 (22.5)	47999 (8.75)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.5-0.58)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
$AUC_{0-\tau}$ (ng·h/ml)	35869 (6.37)	36140 (16.7)	79300 (21.8)	75513 (10.6)
$AUC_{0-\infty}$ (ng·h/ml)	35746 (6.34)	36144 (16.6)	79122 (21.9)	76484 (9.99)
t1/2 (h)	0.868 (8.06)	1.00 (22.6)	1.03 (11.7)	1.03 (24.2)
CL (ml/min)	233 (7.00)	231 (17.9)	211 (22.6)	218 (9.49)
Vss (ml)	13711 (10.4)	14773 (16.3)	14533 (20.7)	16404 (14.0)

[a] Median (min-max) data

Table 2.2.5.8-2 Pharmacokinetic Parameters of Doripenem on Day 7 (geometric mean [%CV])

Parameter	Cohort A 500 mg Q12h (over 30 min)	Cohort B 500 mg Q8h (over 30 min)	Cohort C 1000 mg Q12h (over 1 hr)	Cohort D 1000 mg Q8h (over 1 hr)
n	6	5	6	6
Cmax (ng/ml)	30250 (14.7)	31204 (11.5)	45934 (11.5)	42867 (9.20)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.5-0.5)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
$AUC_{0-\tau}$ (ng·h/ml)	33687 (8.36)	35292 (12.5)	71016 (17.5)	65408 (9.48)
t1/2 (h)	0.824 (4.33)	0.869 (8.29)	1.13 (8.24)	0.932 (11.0)
Ro	0.939 (6.10)	0.923 (8.73)	0.896 (9.74)	0.866 (8.27)
CLR (ml/min)	156 (13.6)	164 (11.5)	156 (21.7)	179 (17.5)

[a] Median (min-max) data

In a study assessing doripenem exposure following prolonged infusions (4 and 6 hours), doripenem AUC and C_{max} were not dose proportional (Study DORI-04). When the dose was doubled from 500 mg q8h to 1000 mg q8h (both over 4 hours), doripenem AUC and Cmax increased about 40% on Day 1 and 30% on Day 7. However, this study did not utilize a crossover design. Further, doripenem clearance in each of the dose cohorts in this study was higher than what has been reported in other Western studies (mean range 18.0 – 28.7 L/hr versus 13.0 – 15.3 L/h). This variation in clearance cannot be explained by differences in study populations, as DORI-04 enrolled only non-elderly healthy volunteers with normal renal function, similar to previous studies.

In response to the findings of DORI-04, DORI-NOS-1004 was conducted to confirm dose proportionality for prolonged infusions (4 hours) of doripenem using a cross-over design and a larger number of subjects. The AUC and C_{max} for doripenem and doripenem-M1 were dose-proportional for single doses of 500 mg and 1000 mg administered over a 4-hour infusion (Table 2.2.5.8-3). Clearance values were the same for 500 mg over 1 hour, 500 mg over 4 hours, and 1000 mg over 4 hours, and were consistent with other healthy volunteer studies conducted with shorter infusion durations. There was no difference in doripenem AUC following 500 mg over 1-hour versus 500 mg over 4 hours.

2.2.5.8-3 Mean (SD) Doripenem Pharmacokinetic Parameters Following Single Dose Administration (Study DORI-NOS-1004)

PK Parameters	500 mg Doripenem x 1 hr N=24	500 mg Doripenem x 4 hr N=24	1000 mg Doripenem x 4 hr N=24
Cmax (µg/mL)	23.0 (6.61)	8.69 (1.73)	18.8 (4.95)
tmax[a] (hr)	0.92 (0.75-1.17)	3.92 (3.00-4.08)	3.92 (2.00-4.17)
AUC_{last} (µg.hr/mL)	37.4 (10.9)	35.7 (7.12)	74.9 (16.0)
AUC∞ (µg.hr/mL)	36.3 (8.77)[b]	35.6 (6.95)[b]	75.4 (16.0)
CL (L/hr)	14.6 (3.61)[b]	14.6 (3.17)[b]	13.8 (2.88)
Vss (L)	16.8 (5.50)[b]	18.0 (4.03)[b]	18.0 (5.44)
Half-life (hr)	1.20 (0.104)[b]	1.23 (0.214)[b]	1.53 (1.58)
λz (hr-1)	0.582 (0.0511)[b]	0.587 (0.146)[b]	0.556 (0.116)

PK Parameters	500 mg Doripenem x 1 hr N=24	500 mg Doripenem x 4 hr N=24	1000 mg Doripenem x 4 hr N=24
AE (μg)	349008 (111282)	349138 (87355)	735138 (264229)
AE, % Dose	69.8 (22.3)	69.8 (17.5)	73.5 (26.4)
CL_R (L/hr)	10.3 (4.19)[b]	10.3 (3.94)[b]	10.3 (4.82)

[a] Represented by median (range).
[b] n=23

2.2.5.9. How do PK parameters change with time following chronic dosing?

Several studies have evaluated the pharmacokinetics of doripenem following multiple dose administration, up to a total of 7 days. Doripenem clearance parameters were similar in single and multiple dose studies of 500 mg and 1000 mg conducted in Western populations, including dosing regimens of Q8h and Q12h. There was no accumulation of doripenem noted following 7-days of administration of various 500 mg and 1000 mg doses (Q8h and Q12h) in Studies DORI-01 and DORI-04. This finding is consistent with doripenem's short half-life (approximately 1 hour).

2.2.5.10. What is the inter- and intra-subject variability in volunteers and patients, and what are the major causes of variability?

Intersubject variability of doripenem in healthy volunteer studies conducted in Western populations was generally low and consistent between studies. Mean coefficient of variation (%CV) values ranged from 6.4% to 31% for doripenem AUC and C_{max} in subjects with normal renal function. Variability was unchanged in subjects with impaired renal function, with the exception of subjects with end-stage renal disease (ESRD) who received doripenem post-dialysis, in which case the %CV was as high as 66% for doripenem AUC. Intersubject variability of doripenem in patients was not assessed, as only sparse PK sampling was performed in one Phase II study.

There was no difference in intrasubject variability of doripenem following 1-hour and 4-hour infusions, nor between the first day of drug administration and Day 7.

Intersubject variability (%CV) of doripenem-M1 AUC and C_{max} were between 24 and 30%. The %CV for urinary excretion of drug was 6 to 40% for doripenem and 27 to 43% for doripenem-M1 in Western studies.

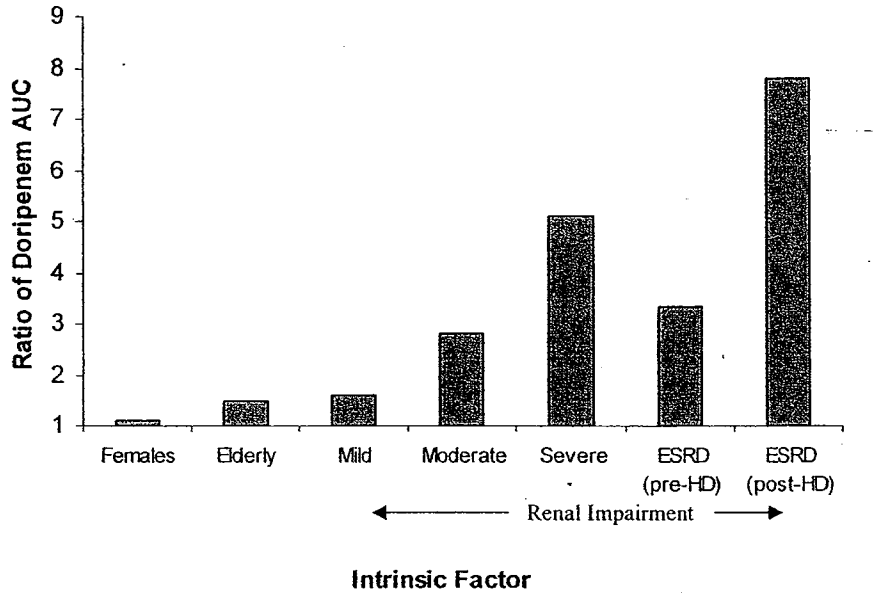
2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

An overview of the effects of various intrinsic factors on doripenem exposure, as assessed in Phase 1 healthy volunteer studies, is presented in Figure 2.3.1-1. Of the factors evaluated, renal impairment was the only factor independently related to drug exposure, consistent with the fact that doripenem is primarily excreted by renal elimination. Other covariates associated with drug exposure were not independent predictors after correcting for renal function. Dose adjustment is

warranted in patients with moderate and severe renal impairment, but not for other intrinsic covariates.

Figure 2.3.1-1 Overview of the Influence of Intrinsic Factors on Doripenem Exposure†



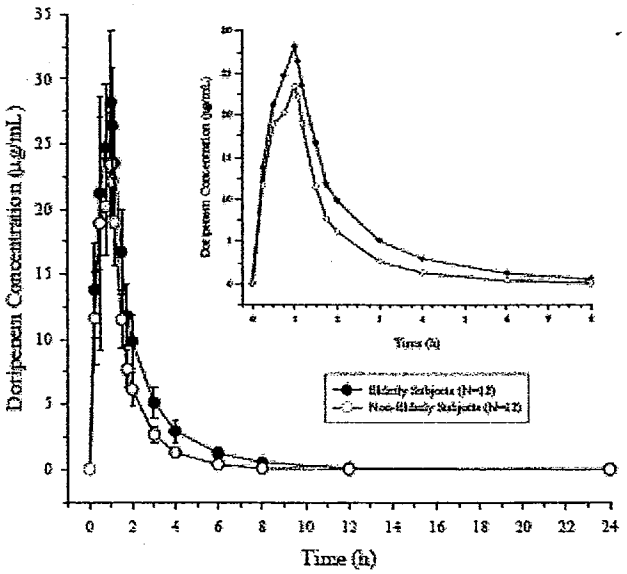
† Ratios of doripenem AUC for females vs. males, elderly vs. non-elderly, and renally impaired subjects vs. subjects with normal renal function.

2.3.2. *Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

2.3.2.1. Elderly

The effect of age ≥ 65 years on the pharmacokinetics of doripenem following a single dose of 500 mg was assessed in DORI-NOS-1006. Twelve healthy elderly subjects (mean age 74.1 years) were compared with 12 non-elderly subjects (mean age 19.8 years). Total body clearance of doripenem in the elderly group was approximately 33% lower compared to non-elderly subjects (9.31 L/hr and 13.9 L/hr, respectively), resulting in 1.5-times the exposure (Figure 2.3.2.1). Renal clearance (CL_R) of doripenem was approximately 30% lower in the elderly, consistent with a 32% lower baseline creatinine clearance. Non-renal clearance (CL_{NR}) of doripenem was 40% lower in elderly subjects. The renal clearance of doripenem-M1 was reduced by 70% in the elderly, though plasma exposure of the metabolite was increased by 133%. These findings suggest that other elimination pathway(s) of doripenem-M-1 (e.g. metabolic) are also somewhat reduced in the elderly.

Figure 2.3.2.1 Mean (SD) Doripenem Plasma Concentration vs. Time Curves for Elderly and Non-elderly Subjects



Source: Study Report DORI-NOS-1006

A subanalysis of elderly patients enrolled in the Phase 3 cIAI trials was performed for the pooled ME at TOC data set (age ≥ 65 years [106 subjects] and ≥ 75 years [37 subjects]). Clinical cure rates at the TOC visit were slightly lower in the elderly, but were similar in the 2 treatment arms. These differences are not unexpected based on the effects of age alone and are likely the result of more severe co-morbidities and later presentation in the elderly. Furthermore, the rate of microbiological cure for the elderly subgroup aged ≥ 65 years was slightly higher in the doripenem treatment arm (81.1% [43/53] for doripenem vs. 75.5% [40/53] for meropenem), although the number of patients in this subgroup is small. Slightly lower clinical cure rates were seen in both treatment arms for patients aged ≥ 75 years (72.2% [13/18] for doripenem; 73.7% [14/19] for meropenem) in the pooled ME at TOC analysis set.

In a pooled analysis of the ME at TOC data set from the cUTI trials, elderly patients ≥ 65 years (275 subjects) or ≥ 75 years (118 subjects) had slightly lower microbiological cure rates at the TOC visit. However, rates were similar in the 2 treatment arms – 76.1% (137/180) for doripenem and 77.0% (74/95) for levofloxacin for patients ≥ 65 years, and 71.4% (55/77) for doripenem and 73.2% (30/41) for levofloxacin for patients aged ≥ 75 years. As in the cIAI trials, a higher rate of co-morbidities in the elderly likely contributed to the lower cure rate.

Based on the results of DORI-NOS-1006, a change in dose is not indicated for elderly subjects in the absence of altered renal function.

2.3.2.2. Pediatric Patients

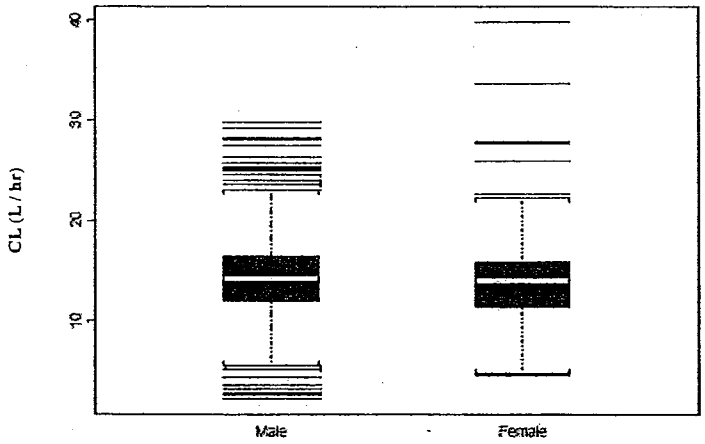
The Sponsor has proposed a pediatric development plan in order to satisfy the Pediatric Research Equity Act (PREA) requirement,. Tentative plans include

2.3.2.3. *Gender*

The effect of gender on the pharmacokinetics of doripenem was evaluated in DORI-NOS-1006, in which the pharmacokinetics of a single 500 mg dose of doripenem were compared between 12 males and 12 females. The study also entailed a comparison between elderly and non-elderly subjects; as such, there was wide variability with respect to age in the two gender groups (range 18 to 84 years). Doripenem clearance was 12% lower in females versus males, resulting in a statistically significant 12% greater AUC (90%CI 100.2 – 126.2). However, after normalizing for weight, doripenem clearance is approximately the same for males and females (0.15 vs. 0.16 L/h/kg, respectively). In addition, creatinine clearance was 26% lower in females than in males (79 mL/min vs 107 mL/min). The relatively small difference in exposure between females and males is likely a reflection of reduced renal clearance in this study.

The effect of gender was evaluated in the population PK analysis using pooled data of subjects and patients with varying degrees of renal function. As shown below, no difference in mean doripenem clearance was observed between males and females. No dosage adjustments are recommended based on gender.

Figure 2.3.2.3-1 Doripenem Clearance vs Gender in Population PK Analysis



Note: White notch indicates median; bar indicates inter-quartile range (25th and 75th); whiskers indicate data range

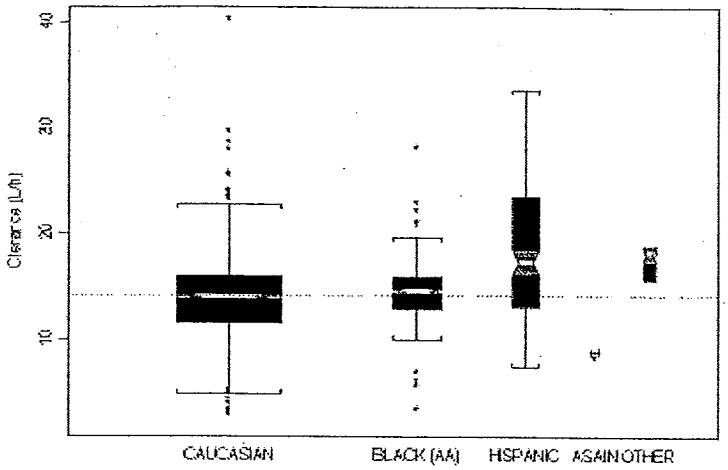
Source: Module 2.7 Clinical Summary, Section 2.7.2

2.3.2.4. *Race*

The effect of race was evaluated in the population PK analysis using pooled data from 230 (80.7%) Caucasians, 27 (9.47%) Blacks, 25 (8.77%) Hispanic or Latino subjects, 2 (0.7%) Asians and 1 subject of "other" origin. Compared to Caucasians, the model indicated a 14% increase in mean clearance in subjects of Hispanic or Latino ancestry, whereas no significant differences were observed for subjects of African American, Asian and Other Ancestry. The apparent

increase in clearance in Hispanic/Latino subjects is considered to be not clinically relevant. Hence, no dosage adjustments are recommended based on race.

Figure 2.3.2.3-1 Doripenem Clearance vs Race in Population PK Analysis



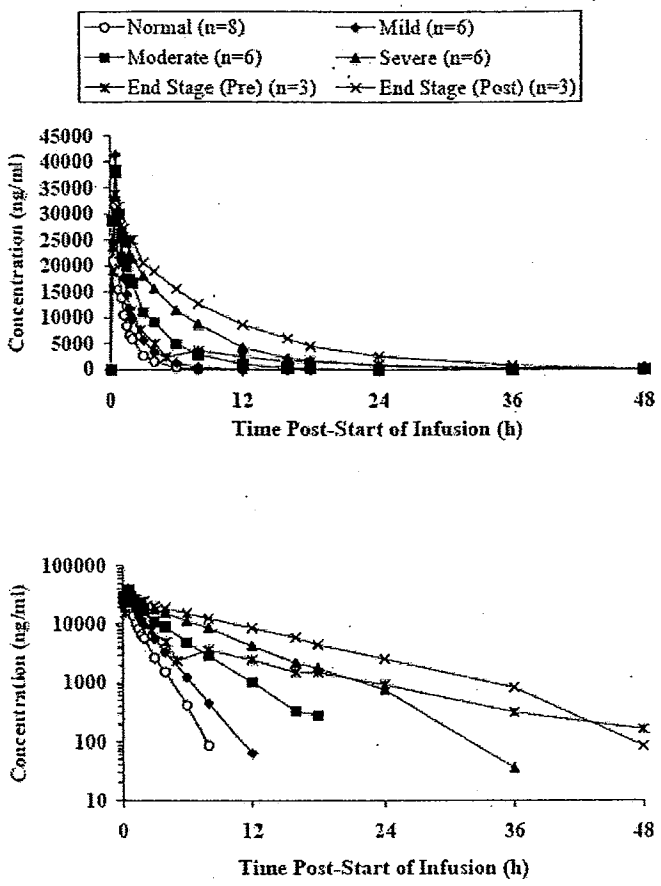
Note: White notch indicates median; bar indicates inter-quartile range (25th and 75th); whiskers indicate data range; box width is proportional to the number of subjects in each group

Source: Module 2.7 Clinical Summary, Section 2.7.2

2.3.2.5. Renal Impairment

The effect of renal impairment on the pharmacokinetics of doripenem following a single 500 mg dose was assessed in 32 subjects with varying degrees of renal impairment. Subjects were enrolled in 1 of 6 cohorts based on degree of renal impairment: normal (CrCl ≤ 80 ml/min), mild (51 – 79 ml/min), moderate (31 – 50 ml/min), severe (≤30 ml/min), ESRD (pre-dialysis infusion) and ESRD (post-dialysis infusion). Renally impaired subjects were matched for age, gender and weight to control subjects. As shown in Figure 2.3.2.5-1 below, mean apparent terminal elimination half-life increased with decreasing renal function, from 1 hour (normal) to 9 hours (post-dialysis ESRD). Mean doripenem clearance values ranged from 226 mL/min (normal) to 30.9 mL/min (ESRD). Total drug clearance correlated well with individual CrCl (R^2=0.901) (Figure 2.3.2.5-2). The apparent volume of distribution (Vd) did not change appreciably with renal impairment, with the exception of ESRD subjects that received a pre-dialysis infusion, in which case Vd was influenced by additional hemodialyser volume. Figure 2.3.2.5-3 demonstrates the relationship between CrCl and systemic exposure of doripenem for the 6 groups.

Figure 2.3.2.5-1. Mean Plasma Concentration-Time Profiles for Doripenem Following Single Dose Administration of 500 mg in Subjects with Varying Degrees of Renal Function



Source: Study Report DORI-02

Figure 2.3.2.5-2 Relationship Between Creatinine Clearance and Total Doripenem Clearance Following a Single 500 mg Dose

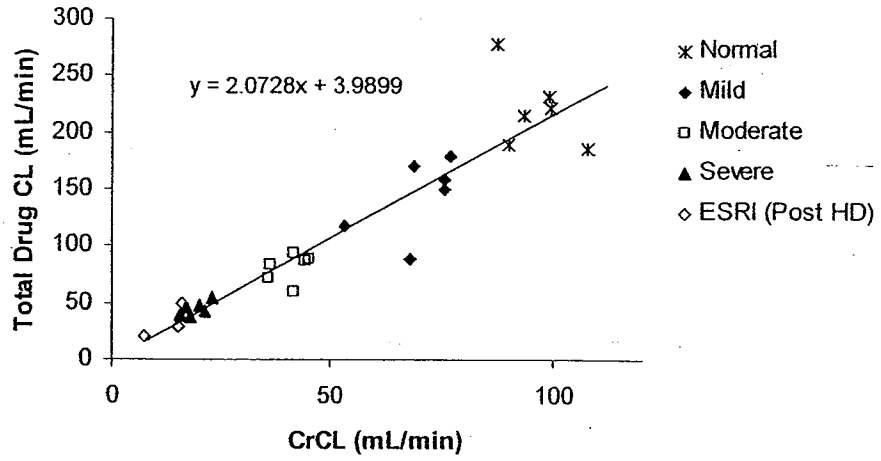
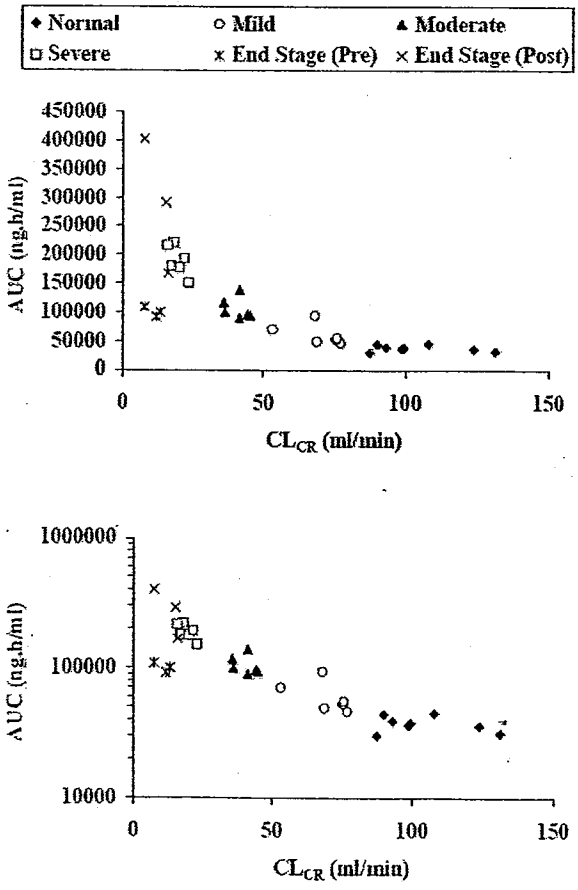


Figure 2.3.2.5-3 Relationship Between Creatinine Clearance and Doripenem AUC_{∞} Following Administration of a Single 500 mg Dose



Source: Study Report DORI-02

As shown in Table 2.3.2.5-1 below, doripenem concentrations at the end of infusion (C_{inf}) were not appreciably different in renally impaired subjects as compared to that of control subjects. Total drug exposure, as assessed by AUC_{∞}, in mild, moderate, severe and ESRD (post-dialysis infusion) impaired groups was 1.6-, 2.8-, 5.1- and 7.3-times that of normal controls, while clearance was 0.62, 0.35, 0.19 and 0.14-times that normal controls.

Table 2.3.2.5-1. Effect of Renal Impairment on Doripenem PK Following Single-Dose Administration of 500 mg

Geometric Means & Ratios	**Renal Function Group**					
	Normal (n=8)	Mild (n=6)	Moderate (n=6)	Severe (n=6)	ESRD (Pre) (n=3)	ESRD (Post) (n=3)
Cinf (ng/mL)	30774	40267	37671	32771	-	33458
Ratio (Impaired/Normal)	-	1.31	1.22	1.06	-	1.09
AUC (ng·h/ml)	36929	59455	104505	188409	99659	269541
Ratio (Impaired/Normal)	-	1.61	2.83	5.10	2.70	7.30
CL (mL/min)	226	140	79.7	44.2	83.6	30.9
Ratio (Impaired/Normal)	-	0.62	0.35	0.19	0.37	0.14

The Sponsor performed Monte Carlo simulations to assess target attainment rates for clinically relevant MICs for patients with mild, moderate and severe renal impairment. The results of the simulations support the following proposed doses:

Table 2.3.2.5-2 Effect of Renal Impairment on Systemic Exposure of Doripenem Following Single-Dose Administration of 500 mg

Dose	Renal Category	MIC (µg/mL)	% Subjects with % T>MIC 35%	MIC (µg/mL)	% Subjects with % T>MIC 35%	C_{max} Ratio[a]	AUC_{24} Ratio[a]
500 mg q8h	Normal	1	98.5	2	76.5	1	1
500 mg q8h	Mild	1	100	2	97.6	1.12	1.39
250 mg q8h	Moderate	1	99.7	2	88.3	0.6	0.99
250 mg q12h	Severe	1	99.3	2	84.6	0.65	1.03

Ratio of predicted exposure at steady state relative to "normal" category

Source: Module 2.7 Clinical Summary, Section 2.7.2

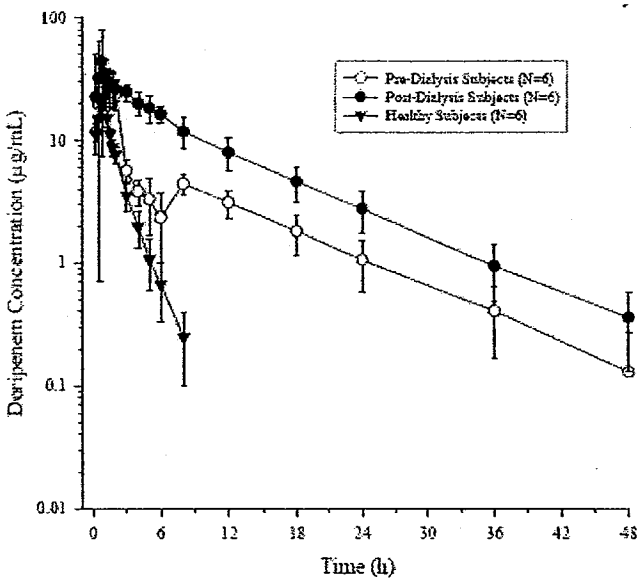
Upon completion of the pivotal clinical studies, the Sponsor repeated the Monte Carlo simulations using the final population PK model developed from Phase I and II studies and pathogen susceptibility data from the cUTI and cIAI Phase III trials to assess the proposed renal impairment doses. The findings indicate that target attainment rates were at least 91.7% for all patients in the cIAI studies and 95.5% for all patients in the cUTI studies based on the most conservative %T>MIC target of 35%. Target attainment rates were consistent across the various degrees of renal impairment using the proposed dosing recommendations.

Patients with renal impairment were evaluated for efficacy in a subanalysis of the Phase 3 clinical trial results. In the two cIAI trials, there were a total of 48 patients (7.6%) requiring a dose adjustment for renal impairment in the pooled ME at TOC analysis set. In this subgroup, clinical

cure rates were lower compared to those patients with normal or mild renal insufficiency (85.7% [257/300] versus 72.0% [18/25] in the doripenem treatment arm, and 86.7% [248/286] versus 52.2% [12/23] in the meropenem treatment arm, respectively). Overall, this subgroup had a greater prevalence of risk factors (e.g., greater number of patients aged > 65 years). Further, 46% of patients in this subgroup had APACHE II scores > 10, compared to 10% overall. Thus, the lower clinical cure rates associated with renal impairment appear to be related to concurrent risk factors in this population, and are not likely due to a reduced effect of the adjusted study drug dose. In the cUTI trials there were 98 patients (18.5%) with renal impairment requiring dose adjustments in the pooled ME at TOC analysis set. Similar to the cIAI study findings, microbiological cure rates were lower in these patients. Again, the finding is most likely due to the greater prevalence of high-risk factors (e.g., older age, more subjects with cLUTI and complicated pyelonephritis). In this subgroup, microbiological cure rates at the TOC visit were higher in doripenem-treated patients than in levofloxacin-treated patients, relative to patients with no renal dose adjustment (75.0% [54/72] versus 84.1% [385/458] for doripenem; 57.7% [15/26] versus 86.2% [206/239] for levofloxacin, respectively). Thus, the lower microbiological cure rates associated with renal impairment requiring study drug dose adjustment appear to be related to concurrent risk factors in this population, and not due to a reduced effect of the adjusted study drug dose. Unfortunately PK sampling was not performed in any of the clinical trials, so an evaluation of drug exposure in patients receiving renally-adjusted doses could not be conducted.

The pharmacokinetics of doripenem and doripenem-M1 have been assessed in ESRD subjects following a single 500 mg infusion administered prior to and after hemodialysis (HD) (Study DORI-NOS-1005). Linear plots of doripenem concentrations in normal controls (n=6) vs. post-HD and pre-HD infusions in ESRD subjects (n=6) are shown below in Figure 2.3.2.5-3. As evident from the figure, doripenem concentrations were highest in ESRD subjects following the post-HD infusion. Mean doripenem AUCs for post-HD infusions and pre-HD infusions in ESRD subjects were 7.8-fold and 3.3-fold the exposure in the normal group, respectively. Respective C_{max} values were 1.6-fold and 1.3-fold that of normal controls. Similar to doripenem, exposure of the M-1 metabolite was markedly higher in ESRD subjects following the post-HD infusion versus that of the healthy subjects.

Figure 2.3.2.5-3 Mean Doripenem Plasma Concentration vs. Time Profiles Following a Single 500 mg Dose in Normal (n=6) and ESRD (n=6) Subjects



Source: Study Report DORI-NOS-1005

Following termination of the 4-hour HD session (started 1 hour after the end of infusion) plasma concentrations of doripenem were reduced by about 90% (Range: 81% to 95%). However, mean plasma concentrations rose rapidly immediately after the dialysis session, suggesting redistribution into the plasma. The dialysis extraction ratios remained fairly constant throughout the 4-hour session, with an overall mean extraction ratio of 0.560. The mean HD clearance of doripenem was 7.15 L/hr, and the amount of doripenem removed by the 4-hour HD session was 231 mg (46% of the dose). Similarly, the mean overall extraction ratio for doripenem-M1 was 0.490 and the mean HD clearance was 6.25 L/hr. The mean recovery of doripenem-M-1 in the dialysate was 28 mg (5.6% of the dose).

The Sponsor has not proposed a dosing regimen for patients on HD. The reviewer performed dosing simulations using the PK data from DORI-NOS-1005 to estimate doripenem exposure at 24, 48 and 72 hours post-dose in subjects with ESRD following a single 500 mg or 250 mg dose administered post-HD (Table 2.3.2.5-3). The 500 mg dose results in a mean C_{48h} of 0.25 µg/mL in ESRD subjects, similar to C_{8h} in subjects with normal renal function (0.18 µg/mL). Mean C_{72h}, on the other hand, is only 0.03 µg/mL in ESRD subjects. The AUC_{0-48} in ESRD subjects administered 500 mg of doripenem was similar to six times the AUC_{0-8} observed in healthy subjects with normal renal function (283 versus 230 µg•h/mL, respectively).

Table 2.3.2.5-3 Mean (SD) PK Parameter Values for Simulated Doses of Doripenem in Subjects with ESRD (n=6)

PK Parameter	Dose simulation in ESRD patients (Single post-HD infusion over 1 hr)			
	500 mg x 1	Ratio (ESRD/Normal)[a]	250 mg x 1	Ratio (ESRD/Normal)[a]
CL (L/h)	1.83 (0.53)	0.14		
AUC_{0-48} (µg•h/mL)	282.8 (70.5)	1.2[b]	141.4 (35.3)	0.6[b]
C_{max} (µg/mL)	44.5 (26.6)	2.0	22.2 (13.3)	1
C_{24h} (µg/mL)	2.35 (1.1)	13[c]	1.17 (0.55)	6.4[c]
C_{48h} (µg/mL)	0.25 (0.22)	1.4[c]	0.13 (0.11)	0.71[c]
C_{72h} (µg/mL)	0.03 (0.04)	0.16[c]	0.01 (0.02)	0.05[c]
T > 2 µg/mL (h)	25.3 (5.2)		18.5 (3.9)	
T > 1 µg/mL (h)	31.8 (6.7)		25.3 (5.2)	

[a] Versus values from subjects with normal renal function (n=6) administered 500 mg x 1 in study DORI-NOS-1005
[b] Ratio versus AUC_{8h} x 6
[c] Ratio versus C_{8h}

2.3.2.6. Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of doripenem has not been assessed. However, as doripenem does not appear to undergo hepatic metabolism or biliary excretion, doripenem pharmacokinetics are not expected to be affected by changes in hepatic function. Further, as doripenem is only minimally protein bound (approximately 8%), the effect of varying serum albumin concentrations is not expected to have a significant impact on doripenem distribution.

2.3.2.7. Pregnancy and Lactation

The Sponsor has not provided any information regarding the use of doripenem in pregnant or lactating humans.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors influence dose-exposure and/or –response, and what is the impact of any differences in exposure on response?

The potential for drug-drug interactions with doripenem is discussed below in Section 2.4.2. The effect of other extrinsic factors (e.g. smoking, alcohol) has not been assessed.

2.4.2. Drug-Drug Interactions

2.4.2.1. Is there any in vitro basis to suspect in vivo drug-drug interactions?

Based on the results of *in vitro* microsome and hepatocyte studies, neither doripenem nor doripenem-M1 appears to induce or inhibit the cytochrome (CYP) P450 enzymes. Further, doripenem is not metabolized by CYP450 enzymes. These data suggest a low probability of interaction between doripenem and drugs that are cleared by these enzymes. The Sponsor has not provided any information regarding doripenem specificity for P-glycoprotein (P-gp) or other transport proteins.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

The substrate potential of doripenem was assessed in human liver microsomes (HLM) versus that of a positive control (testosterone 6β-hydroxylation) (Study DORI-PK-001). There was no evidence of doripenem metabolism following 0, 30 and 120 minute incubations at high (100 μM) and low (5 μM) substrate exposures.

2.4.2.3. Is the drug an inhibitor and/or inducer of CYP enzymes?

An *in vitro* study was conducted to evaluate the potential for doripenem to inhibit the following cytochrome P450 enzymes in human liver microsomes (Study XT025016): CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A11. Doripenem was incubated in duplicate HLM mixtures at 37°C at 8 different concentrations, ranging from 0 – 300 μM (0 – 126 μg/mL), to assess for both direct and metabolism-dependent inhibition. The results indicate that doripenem does not inhibit any of the enzymes studied up to a concentration of 300 μM.

The potential for doripenem and doripenem-M1 to induce CYP450 and UDP-glucuronosyltransferase (UGT) enzymes was assessed in primary cultures of human hepatocytes (Study FK5908). Three preparations of cultured human hepatocytes from 3 separate human livers were treated once daily for 3 consecutive days with 1 of 3 concentrations of doripenem and doripenem-M1 (1, 10 or 100 μg/mL), or one of five known human P450 inducers. Microsomal incubations were carried out at 37°C with probe substrates for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4/5 and UGT1A1. The results indicate that doripenem and doripenem-M1 do not cause an increase in the activity of any of the 6 enzymes evaluated.

2.4.2.4. *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

In vitro studies investigating doripenem as a substrate or inhibitor of P-glycoprotein (P-gp) were not conducted.

2.4.2.5. *Are there other metabolic/transporter pathways that may be important?*

The primary route of elimination of doripenem is by renal excretion. The influence of probenecid, an inhibitor of renal organic anionic transporters (OATs), on doripenem pharmacokinetics was assessed in healthy male subjects (Study R1416). Concomitant administration of doripenem and probenecid (1 g two hours prior to doripenem and 0.5 g after doripenem infusion) resulted in a 75% increase in doripenem $AUC_{0\text{-}12}$ and a 15% increase in C_{max}, consistent with the observed 54% decrease in renal clearance. The findings from this interaction study confirm that active renal tubular secretion contributes to the renal elimination of doripenem. See section 2.4.2.7 for further details.

The primary metabolite of doripenem is the inactive ring-opened dicarboxylic acid, doripenem-M1, which is converted in the renal tubules and is recovered in the urine as approximately 15% of the administered dose. It is not expected that drug interactions with doripenem will result from interference in the conversion to doripenem-M1 by dehydropeptidase-I.

2.4.2.6. *What other co-medications are likely to be administered to the target patient population?*

The target patient populations with cIAI and cUTI, including pyelonephritis, range from somewhat healthy patients to patients with significant co-morbidities. Thus, doripenem may be used with a wide variety of co-medications from different drug classes for many different indications, including other non-beta-lactam antibiotics. Probenecid, a known inhibitor of renal OATs, was studied *in vivo* with doripenem in order to evaluate the potential for interaction.

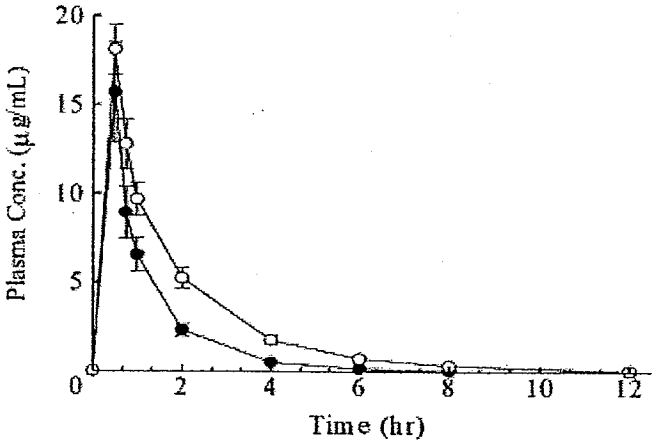
A clinically significant reduction in serum valproic acid (VPA) concentrations has been reported for other carbapenem antibiotics. *In vitro* studies evaluating the effect of doripenem on VPA metabolism indicate doripenem inhibits VPA-glucuronide hydrolysis. Studies conducted in rats and monkeys have also pointed toward this mechanism as a potential cause of decreased serum VPA levels in humans. However, in these animal studies VPA serum concentrations were not significantly lowered. A study evaluating the effect of doripenem on VPA exposure has not been conducted in humans.

2.4.2.7. *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

The effect of oral probenecid on the pharmacokinetics of a single 250 mg dose of doripenem (over 30 min.) was assessed in 8 healthy adult males in a two-way crossover study (Study R1415). Probenecid was administered in two doses – 1 gram two hours prior to doripenem and 0.5 g immediately after the end of the doripenem infusion. As demonstrated in Figures 2.4.2.7-1 and -2 below, mean doripenem plasma concentrations were increased, and the cumulative urinary excretion rate decreased following co-administration with probenecid. Doripenem C_{max} increased

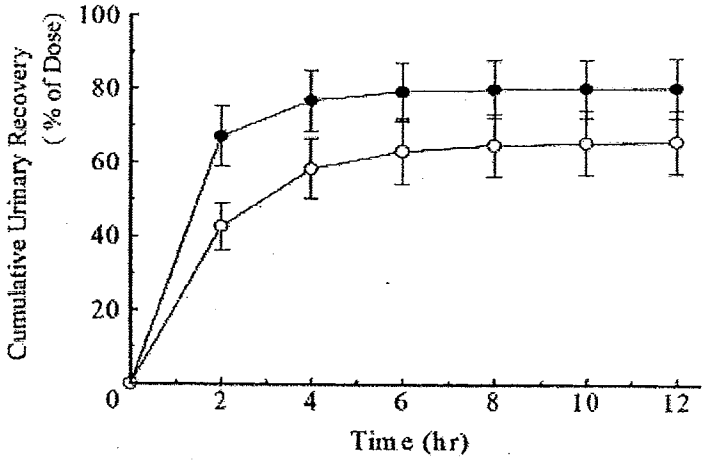
by 15%, AUC_{0-12} increased by 75%, CL_T decreased by 44%, CL_R decreased by 54% and Fe decreased by 18%. The half-life increased from 0.94 hours to 1.44 hours with probenecid.

Figure 2.4.2.7-1 Mean Plasma Concentration vs. Time Profile of Doripenem Following 250 mg Single-Dose Administration with Probenecid



(n=8, •: administration of S-4661 alone; ○: coadministration of S-4661 with probenecid; mean values ± standard deviations)

Figure 2.4.2.7-2 Mean Cumulative Urinary Excretion of Doripenem Alone and Following Co-Administration with Probenecid



(n=8, •: administration of S-4661 alone; ○: coadministration of S-4661 with probenecid; mean values ± standard deviations)

The Sponsor has recommended that probenecid not be co-administered with doripenem. Based on the 75% increase in AUC and 15% increase in C_{max} observed in this study, the exposure that is expected to result from co-administration of probenecid with 500 mg of doripenem is less than what is observed with 1000 mg doripenem alone. However, experience with the 1000 mg dose in

humans is limited, particularly multiple dosing. There is no clear relationship between any of the toxicities noted in the clinical studies and doripenem plasma exposure. However, in the Phase I study DORI-01, minor (< 3x ULN) reversible elevations in ALT and AST were observed in 3 of 6 subjects who received doripenem 1,000 mg q8h, versus 1 of 6 subjects each in the 500 mg q8h and 500 mg q12h dosing groups. Based on the lack of safety data at the higher anticipated doripenem exposure, the Sponsor's recommendation is appropriate.

2.4.2.8. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

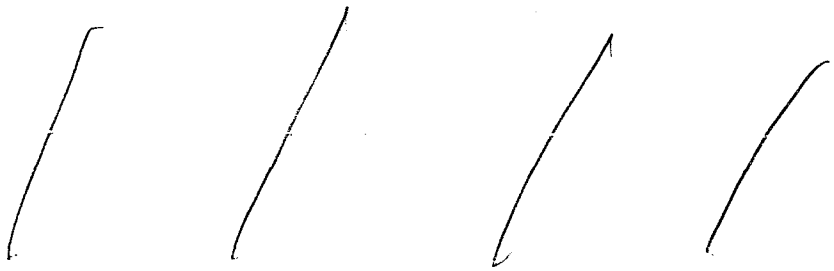
There is no known mechanistic basis for potential pharmacodynamic interactions with doripenem.

2.4.2.9. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no significant unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding for doripenem.

2.4.3. What issues related to dose, dosing regimens or administration are unresolved and represent significant omissions?

The only unresolved issue relating to dosing is the Sponsor's omission of a dosing recommendation for patients on hemodialysis. The PK characteristeics of doripenem in subjects with ESRD on HD, as well as the dialysis clearance rate of doripenem, were determined in DORI-NOS-1005.



2.5. General Biopharmaceutics

2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not applicable; doripenem is intended for administration by intravenous infusion only.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The composition of doripenem for injection (500 mg) is provided below in Table 2.5.2-1. The to-be-marketed formulation is the same formulation used throughout clinical development and in the Phase III clinical trials.

Table 2.5.2-1 Composition of Doripenem for Injection (500 mg)

Component	Function	Quantity per Unit
Doripenem monohydrate	Active ingredient	500 mg/vial[a]

[a] Anhydrous basis

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

2.5.4. When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5. How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

Not applicable.

2.5.6. If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable.

2.5.7. If the NDA is for a modified release formulation of an approved immediate release product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated?

Not applicable.

2.5.9. What other significant, unresolved issues related to in vitro dissolution or in vivo BA or BE need to be addressed?

Not applicable.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moiety, doripenem, was measured in plasma by microbioassay in early clinical development. Subsequent methods for determination of doripenem in plasma included validated HPLC assays and LC/MS/MS methods.

2.6.2. Which metabolites have been selected for analysis and why?

Doripenem-M1 is the primary (inactive) metabolite of doripenem and was appropriately selected for quantitation in plasma, urine and dialysate in the clinical pharmacology studies.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total doripenem concentrations were measured in all clinical pharmacology and biopharmaceutics studies. The protein binding of doripenem is relatively low at approximately 8%. The decision to measure total doripenem is appropriate.

2.6.4. What bioanalytical methods are used to assess concentrations?

Shionogi initially developed a microbioassay for the analytical evaluation of doripenem in human plasma, urine and bile in early development. The validated bioassay was used for the determination of doripenem in urine and plasma in studies R1415, R1416, R1418 and R1419. The bioassay method was also used for analysis of plasma, tissue samples and body fluids in R142A (gall bladder tissue, bile, uterine tissue, sputum, retroperitoneal fluid) and R142H (retroperitoneal fluid). Shionogi later complimented the bioassay with a validated HPLC assay with UV detection to verify and cross validate the bioassay results in study R1412 and others. The HPLC assay was also used to evaluate peritoneal exudate in R143W. Later in the program HPLC assays with UV detection were developed and validated by Shionogi for the analysis of doripenem-M1 in plasma and urine. Samples from R1412 were analyzed for doripenem-M1 using these assays.

An LC/MS/MS assay was eventually validated at for the quantification of doripenem in plasma and urine. This assay was used in several Phase 1 and 2 studies, including DORI-01, DORI-02, DORI-03 and DORI-04. Later in the program LC/MS/MS assays for the quantification of doripenem and doripenem-M1 in plasma, urine and dialysate were validated at These assays were used for the measurement of doripenem M1 in DORI-03 and DORI-04. The validated assays were also used for analysis of doripenem and doripenem-M1 in DORI-NOS-1001, DORI-NOS-1004, DORI-NOS-1005, DORI-NOS-1006. Most recently, an LC/MS/MS assay was developed and validated for the simultaneous measurement of doripenem and doripenem-M1 at .

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4.2.2. General Pharmacokinetics

Study DORI- 01
A Phase 1 Double-Blind Dose Escalation Study To Determine The Safety, Tolerability And Pharmacokinetics Of Intravenous Doripenem In Healthy Subjects

Dates: July – September 2002

Study Sites: [redacted]

Objective:
To assess the safety and tolerability of doripenem administered intravenously to healthy subjects, and investigate the pharmacokinetic profile of doripenem in a non-Asian population.

Methods:
Study Design
DORI-01 was a Phase 1, double-blind, dose escalation study of intravenous doripenem in healthy subjects. There were four cohorts of 8 subjects each, including both male and female subjects. Subjects in each cohort were randomized to receive either doripenem (6 subjects) or placebo (2 subjects). Subjects received study drug for Q8h or Q12h for 7 days (with a single dose on Day 7). Subjects returned on Day 11 for follow-up safety tests.

Test Product
Doripenem for Injection, lot number CF2032, administered by intravenous infusion at doses of 500 mg every 12 hours (Q12h), 500 mg every 8 hours (Q8h), 1000 mg Q12h and 1000 mg Q8h, depending on the cohort (Table 1). The 500 mg doses were infused over 30 minutes, and 1000 mg doses were infused over 60 minutes. The reference therapy (placebo) consisted of normal saline solution, indistinguishable from doripenem. Treatments were administered in a double-blind manner.

Table 1. Doripenem Treatment Schedule

Cohort	n	Dosing regimen	Total amount of doripenem administered
A	6	500 mg doripenem Q12h for 7 days (13 infusions)	6500 mg
B	5*	500 mg doripenem Q8h for 7 days (19 infusions)	9500 mg
C	6	1000 mg doripenem Q12h for 7 days (13 infusions)	13000 mg
D	6	1000 mg doripenem Q8h for 7 days (19 infusions)	19000 mg

* One subject was withdrawn on Day 2 following infusion #4 of 500 mg doripenem.

Inclusion criteria
Healthy non-Asian (not from Japan, China, Malaysia, or of "Oriental" descent) male and female subjects, 18 - 65 years of age, with body mass index 18-30 kg/m^2, who gave written informed consent.

Pharmacokinetic assessment

Ten mL blood samples were drawn for quantification of doripenem at the following time-points:

Cohorts A and C:

Day 1 (first dose)	pre-dose, 15 minutes post-start of the first infusion for Cohort A; 30 minutes post-start of the first infusion for Cohort C, end of infusion, 5, 15, 30, 45 and 60 minutes post-end of infusion, and 3, 5, 8, and 12 hours post-start of the first infusion
Days 4,5,6,7 (first dose)	pre-infusion and 5 minutes post end of infusion
Day 7 (last dose = dose 13)	pre-dose; 15 minutes post-start of the last infusion for Cohort A; 30 minutes post-start of the last infusion for Cohort C, end of infusion, 5, 15, 30, 45 and 60 minutes post-end of infusion, and 3, 5, 8, and 12 hours post-start of infusion
Day 8	24 hours after the start of dose 13
Day 11	96 hours after the start of dose 13

Cohorts B and D:

Day 1 (first dose)	pre-dose, 15 minutes post-start of the first infusion for Cohort B; 30 minutes post-start of the first infusion for Cohort D, end of infusion, 5, 15, 30, 45 and 60 minutes post-end of infusion, and 3, 5, 8, and 12 hours post-start of infusion
Days 4,5,6,7 (first dose)	pre-infusion and 5 minutes post-end of infusion
Day 7 (last dose = dose 19)	pre-dose, 15 minutes post-start of the last infusion for Cohort B; 30 minutes post-start of the last infusion for Cohort D, end of infusion, 5, 15, 30, 45 and 60 minutes post-end of infusion, and 3, 5, 8, and 12 hours post start of infusion
Day 8	24 hours after the start of dose 19
Day 11	96 hours after the start of dose 19

Urine collection was performed according to the following schedule for the purposes of quantifying doripenem urinary excretion:

Cohort A and C:

- Day 7: 0-2, 2-4, 4-8, 8-12, 12-14, 14-16 and 16-24 hours from the start of the first infusion
- Day 8: 0-12 and 12-24 hours

Cohort B and D:

- Day 7: 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16 and 16-24 hours from the start of the first infusion
- Day 8: 0-12 and 12-24 hours

Analytical Methods

Plasma and urine doripenem concentrations were analyzed by [redacted] validated LC-MS/MS assay, including [redacted] and detection by tandem mass [redacted]s

spectrometry was used to quantify samples. The limit of quantitation for both human plasma and urine was established as [redacted] g/mL for this assay.

Pharmacokinetic Methods

The PK parameters of doripenem were estimated by non-compartmental analysis using WinNonlin® (Version 3.1). Actual blood sampling times were used for the estimation of all PK parameters. The time spent above the MIC (%T>MIC) was determined from the mean doripenem plasma concentration-time curve. The MIC values of interest were 1000, 2000 and 4000 ng/mL.

Plasma concentration-time profiles of doripenem after single intravenous administration were described by exponential functions using WinNonlin®. Mono-exponential and bi-exponential functions were fitted to the individual plasma doripenem concentration-time data. The most representative model was selected using an F-test (at the 5% level of significance) and the selected exponential function was applied to all subjects. The decision of whether or not to use weighting was based on the resulting residual plots. The pharmacokinetic parameters (Cmax, AUC0-∞, λz, t1/2, CL and Vss) derived from the compartmental model are reported.

AUC0-τ was tested for dose-proportionality using SAS® (Version 8.1). Those cohorts receiving the same dosing regimen, i.e. Cohorts A and C, and Cohorts B and D, were compared separately. Dose-proportionality of Cmax was not considered since the regimens differed in infusion duration.

The amount of doripenem recovered within each urine collection interval (Ae), the cumulative recovery and the fraction of the administered dose excreted in the urine, expressed as a percentage of the dose administered (Fe = Cumulative Ae/ Dose x 100), were determined.

Results:

Study Population

Four cohorts of 8 subjects enrolled in the study; 30 subjects completed participation. One withdrawn subject received 7 doses of placebo and the other received 4 infusions of 500 mg doripenem (Q8h). A summary of the demographic characteristics of subjects is presented in Table 2.

Table 2. Demographic Details by Treatment Group

Variable Statistic or Category	Doripenem 500 mg Q12h N = 6	Doripenem 500 mg Q8h N = 6	Doripenem 1000 mg Q12h N = 6	Doripenem 1000 mg Q8h N = 6	Placebo N = 8
Age (years)					
Mean	24.5	24.3	26.2	27.5	25.4
SD	2.59	3.67	6.24	5.09	5.78
Height (m)					
Mean	1.762	1.813	1.747	1.755	1.715
SD	0.0823	0.1157	0.0885	0.0961	0.0737
Weight (kg)					
Mean	70.33	74.68	73.12	70.47	73.11
SD	8.832	9.923	15.179	7.917	10.838

Variable Statistic or Category	Doripenem 500 mg Q12h N = 6	Doripenem 500 mg Q8h N = 6	Doripenem 1000 mg Q12h N = 6	Doripenem 1000 mg Q8h N = 6	Placebo N = 8
BMI (kg/m2)					
Mean	22.5	22.7	23.7	22.7	24.6
SD	1.22	1.21	3.01	1.63	1.92
Race	All subjects were white				
Gender					
Male	4	5	5	4	3
Female	2	1	1	2	5

Analytical Performance

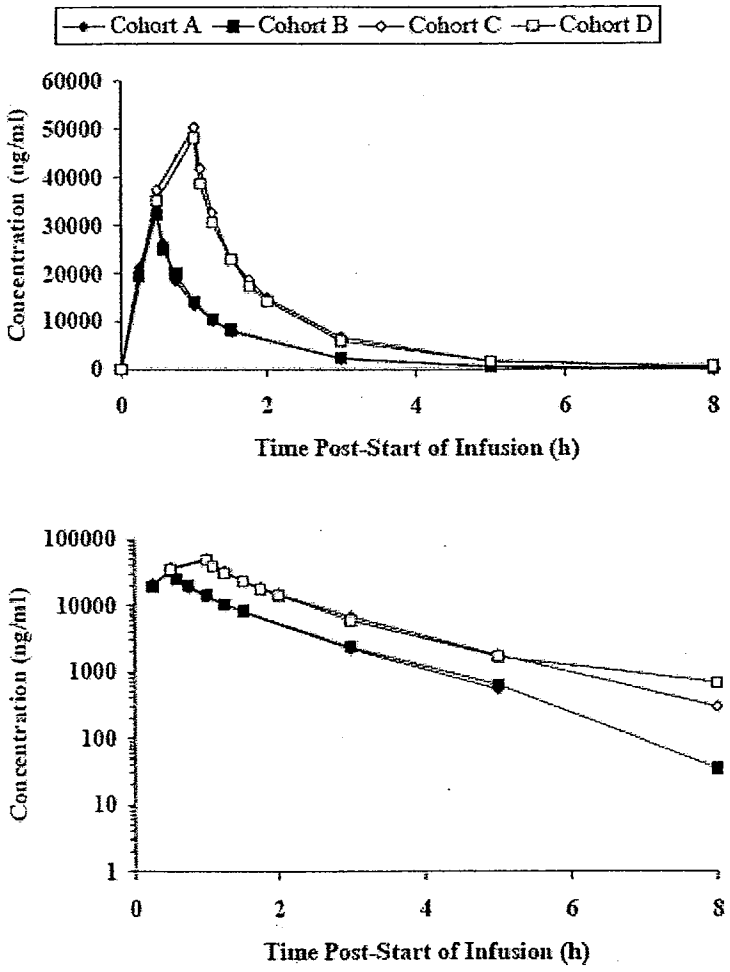
Pharmacokinetic Analysis

All 24 subjects who received at least one dose of active treatment were included in the PK analysis. The subject who was withdrawn from the study was included in the analysis up to the time of withdrawal.

Plasma Data

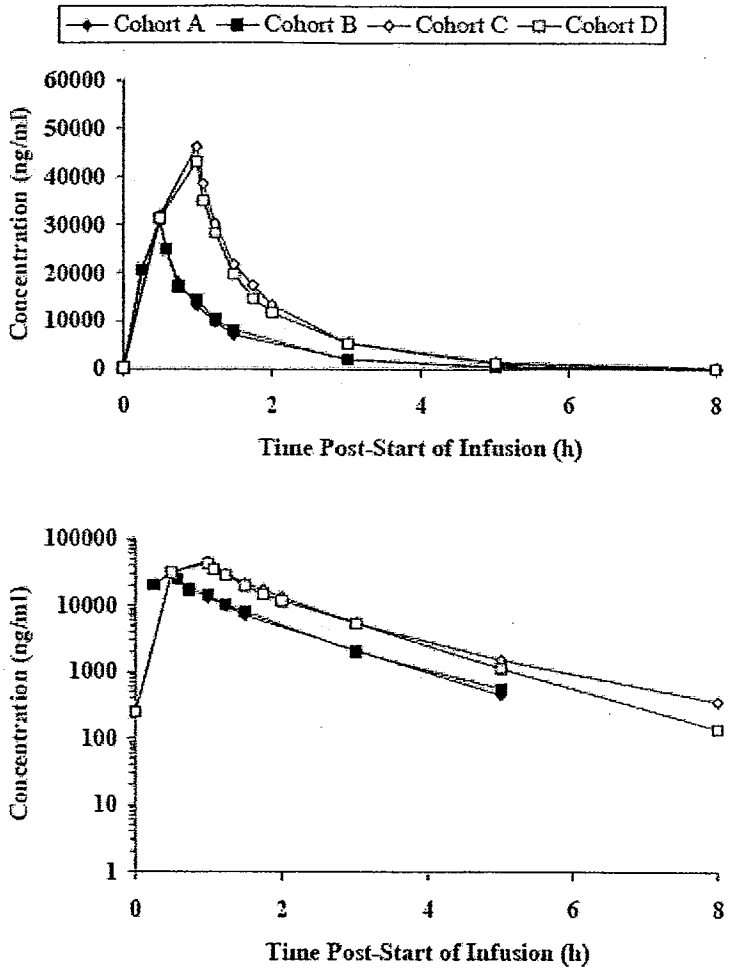
Mean plasma concentration-time curves from Day 1 and Day 7 of doripenem administration are presented in Figures 1 and 2. A summary of mean PK parameter values is provided in Tables 3 and 4. Following single (Day 1) and repeated (Day 7) twice- or three-times daily intravenous doses of doripenem, maximum plasma concentrations (Cmax) were generally attained at the end of the infusion. Thereafter, plasma doripenem concentrations declined in a bi-phasic manner with a mean apparent terminal half-life ranging from 0.8 to 1 h after single and repeated administration. The total plasma clearance of doripenem was 211 to 233 ml/min. The volume of distribution of doripenem at steady-state was 14 to 16 L, which is similar to the extracellular fluid volume of man (16 L).

Figure 1. Mean plasma concentration-time curves: Day 1



Cohort A: 500 mg Doripenem infused over 30 min twice-daily (Q12h)
Cohort B: 500 mg Doripenem infused over 30 min three-times daily (Q8h)
Cohort C: 1000 mg Doripenem infused over 1 h twice-daily (Q12h)
Cohort D: 1000 mg Doripenem infused over 1 h three-times daily (Q8h)

Figure 2. Mean plasma concentration-time curves: Day 7



Cohort A: 500 mg Doripenem infused over 30 min twice-daily (Q12h)
Cohort B: 500 mg Doripenem infused over 30 min three-times daily (Q8h)
Cohort C: 1000 mg Doripenem infused over 1 h twice-daily (Q12h)
Cohort D: 1000 mg Doripenem infused over 1 h three-times daily (Q8h)

Table 3. Pharmacokinetic parameters of doripenem (geometric mean [CV%]) on Day 1

Parameter	Cohort A 500 mg Q12h	Cohort B 500 mg Q8h	Cohort C 1000 mg Q12h	Cohort D 1000 mg Q8h
n	6	6	6	6
Cmax (ng/ml)	32982 (6.81)	31770 (18.8)	49335 (22.5)	47999 (8.75)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.5-0.58)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
AUC0-τ (ng·h/ml)	35869 (6.37)	36140 (16.7)	79300 (21.8)	75513 (10.6)

Parameter	Cohort A 500 mg Q12h	Cohort B 500 mg Q8h	Cohort C 1000 mg Q12h	Cohort D 1000 mg Q8h
AUC0-∞ (ng·h/ml)	35746 (6.34)	36144 (16.6)	79122 (21.9)	76484 (9.99)
t1/2 (h)	0.868 (8.06)	1.00 (22.6)	1.03 (11.7)	1.03 (24.2)
CL (ml/min)	233 (7.00)	231 (17.9)	211 (22.6)	218 (9.49)
Vss (ml)	13711 (10.4)	14773 (16.3)	14533 (20.7)	16404 (14.0)

[a] Median (min-max) data

Table 4. Pharmacokinetic parameters of doripenem (geometric mean [CV%]) on Day 7

Parameter	Cohort A 500 mg Q12h	Cohort B 500 mg Q8h	Cohort C 1000 mg Q12h	Cohort D 1000 mg Q8h
n	6	5 [b]	6	6
Cmax (ng/ml)	30250 (14.7)	31204 (11.5)	45934 (11.5)	42867 (9.20)
tmax (h)[a]	0.5 (0.5-0.5)	0.5 (0.5-0.5)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
AUC0-τ (ng·h/ml)	33687 (8.36)	35292 (12.5)	71016 (17.5)	65408 (9.48)
t1/2 (h)	0.824 (4.33)	0.869 (8.29)	1.13 (8.24)	0.932 (11.0)
Ro	0.939 (6.10)	0.923 (8.73)	0.896 (9.74)	0.866 (8.27)
CLR (ml/min)	156 (13.6)	164 (11.5)	156 (21.7)	179 (17.5)

[a] Median (min-max) data

[b] Subject 12 withdrew prior to Day 7 dosing

Pharmacodynamics

The T> MIC for MIC values of 1000, 2000 and 4000 ng/mL were determined using mean plasma concentration-time curves for each cohort. For carbapenem antibiotics, %T>MIC is the surrogate pharmacodynamic marker that correlates best with positive clinical outcomes. Results are provided in Table 5.

Table 5. Absolute Time above MIC on Days 1 and 7 (hours)

MIC	Day	Cohort A 500 mg Q12h	Cohort B 500 mg Q8h	Cohort C 1000 mg Q12h	Cohort D 1000 mg Q8h
1000 ng/ml	1	4.42	5.23	6.55	10.48
2000 ng/ml	1	3.19	3.39	4.88	6.52
4000 ng/ml	1	2.47	2.53	4.05	3.84
1000 ng/ml	7	4.33	4.39	6.29	5.36
2000 ng/ml	7	3.12	3.01	4.72	4.56
4000 ng/ml	7	2.38	2.46	3.68	3.59

Following single and repeat dosing with twice-daily doripenem doses of 500 mg and 1000 mg (Cohorts A and C), systemic exposure was approximately dose proportional for AUC(0-τ). The increase in Cmax was less than dose proportional, likely due to differences in infusion duration. Similar results were observed for every 8 hour dosing of doripenem (Cohorts B and D). There was no apparent accumulation of doripenem on repeated dosing, consistent with a short half-life relative to the dosing interval. Pre-dose doripenem concentrations were generally below the limit

of quantitation during the 7-day administration period, suggesting that each dose could be considered a discrete dose.

Compartmental PK Analysis

A bi-exponential function best represented the plasma doripenem concentration-time data. The pharmacokinetic parameters derived from the bi-exponential function were similar to those obtained following non-compartmental analysis (Table 6). The coefficients of variation of the mean pharmacokinetic parameters were relatively low, indicating that the subjects appeared to comprise a homogenous group.

Table 6. Pharmacokinetic Parameter Estimates of Doripenem Estimated by Compartmental Analysis (Geometric Mean [%CV])

Parameter	Cohort A 500 mg Q12h	Cohort B 500 mg Q8h	Cohort C 1000 mg Q12h	Cohort D 1000 mg Q8h
n	6	6	6	6
Cmax (ng/ml)	33050 (6.44)	31018 (15.4)	50485 (20.8)	48402 (9.01)
AUC0-∞ (ng.h/ml)	34513 (7.38)	34000 (16.4)	77732 (21.2)	73515 (11.6)
λz (/h)	0.862 (10.7)	0.818 (20.2)	0.754 (23.9)	0.819 (16.0)
t1/2 (h)	0.804 (10.6)	0.847 (24.7)	0.919 (23.5)	0.846 (14.7)
CL (ml/min)	241 (8.23)	245 (16.5)	214 (22.1)	227 (11.0)
Vss (ml)	13624 (8.18)	14352 (19.2)	13236 (20.0)	13376 (9.28)

Urinary Excretion

Urinary recovery profiles of doripenem for each of the 4 cohorts are shown in Figure 3 below. Maximum recovery of doripenem was attained within 6 hours following the start of infusion. Urinary recovery was 60 – 70% of the total dose (Table 7). Renal clearance of doripenem, as estimated on Day 7 of dosing, was an average of 156 – 179 ml/min.

Table 7. Urinary Excretion and Renal Clearance (Geometric Mean [%CV]): Day 7

Cohort		Fe (% Dose)	CL_R (ml/min)
A	500 mg q12h	63.1 (17.7)	156 (13.6)
B	500 mg q8h	69.5 (12.0)	164 (11.5)
C	1000 mg q12h	66.6 (12.3)	156 (21.7)
D	1000 mg q8h	70.7 (13.4)	179 (17.5)

Safety

In total, there were 67 treatment-emergent adverse events reported by 22 subjects (69% of the study population) during the course of the study. Of these, 49 were reported by 16 subjects receiving doripenem (67% of subjects on active treatment), and 18 were reported by 6 subjects receiving placebo (75% of placebo subjects). Of the 22 subjects reporting adverse events, 18 (56%) experienced at least one adverse event that was considered possibly or probably related to treatment. The majority of adverse events were mild in severity; five subjects (16%) reported adverse events of moderate severity (2/5 were in placebo group). There were no severe or serious adverse events.

The subject incidence of adverse events was relatively evenly spread between all dose groups, including placebo. Adverse events were least frequent in subjects receiving 1000 mg doripenem Q12h, with only one subject (17%) in this group reporting an adverse event (anorexia). The most common adverse event was headache (31%). Gastrointestinal disorders were also commonly reported, but no adverse events showed a clear relationship to dose or frequency of doripenem administration. One subject on active treatment (500 mg doripenem Q8h) was withdrawn from the study due to adverse events which had possible or probable relationships to treatment: diarrhea, abdominal cramps and a sensation of having a swollen throat.

Both the individual and mean biochemistry data indicate a trend for serum levels of the hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to increase following repeated administration of doripenem. Serum levels of these enzymes were generally observed to decrease towards normal by the follow up visit. This trend was especially noticeable in subjects receiving 1000 mg Q8h. A possible trend upward in hepatic transaminases (AST and ALT) was also noted in subjects in other active dose groups, but no such trend was apparent in subjects receiving placebo. No abnormalities were noted in gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALK).

Sponsor's Conclusions

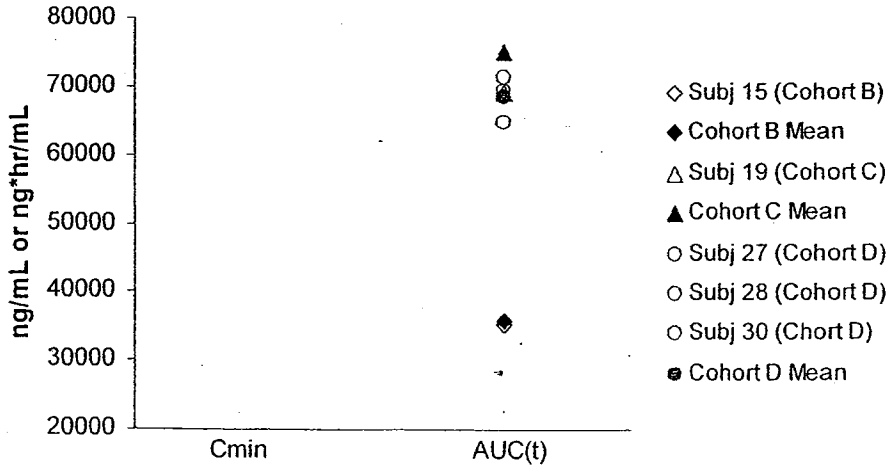
- There was no dose-response trend in adverse events; the subject incidence of adverse events was relatively evenly spread between the dose groups, including placebo.
- There was an apparent dose-response trend for serum levels of the hepatic enzymes AST and ALT to rise following repeated administration of doripenem. This trend was most pronounced in the high dose cohort (1000 mg Q8h) and was less clear for the lower dose cohorts. This trend was not observed in subjects receiving placebo. Observed abnormalities in hepatic transaminases appeared to be reversible. Except for liver function tests, there were no apparent trends in safety parameters.
- Following single and repeated twice- or three-times daily intravenous doses of doripenem to healthy subjects, maximum plasma concentrations were attained at the end of the infusion period. Thereafter, plasma doripenem concentrations declined in a bi-phasic manner with an apparent terminal half-life of approximately 0.8 to 1 h after single and repeated daily doses.
- Doripenem is a drug with an apparent volume of distribution at steady state nominally similar to the extracellular fluid volume of man. The total plasma clearance of doripenem was, on average, 211 to 233 ml/min which is low relative to hepatic blood flow. The short apparent terminal half-life of doripenem is a manifestation of the low total plasma clearance and small volume of distribution of doripenem.
- Doripenem did not accumulate in plasma on repeated dosing, which is consistent with a short half-life relative to the dosing interval.
- Pre-dose doripenem concentrations during the 7-day administration period were, in general, below the limit of quantification of the assay, consistent with a lack of accumulation of doripenem in plasma.
- Following single and repeated twice- and three-times daily intravenous doses of 500 and 1000 mg doripenem, the systemic exposure to doripenem, characterized by AUC0-τ and Cmax, increased with increasing dose levels. This increase in systemic exposure was approximately dose-proportional for AUC0-τ; however, there was a statistically significant less than dose proportional increase in Cmax over the dose range studied. This was most likely due to the different infusion duration of the higher dose level and the fact that steady state had not been attained.

- Urinary recovery of doripenem was essentially complete within 6 h post-start of infusion with 60 to 70% of the dose excreted unchanged, suggesting that up to 30% of the administered dose is subject to non-renal elimination. Renal clearance of doripenem was nominally similar to glomerular filtration rate in man, indicating no marked net secretion or reabsorption.
- Plasma doripenem concentration versus time profiles were best represented by a bi-exponential function with uniform weighting. The coefficients of variation of the mean pharmacokinetic parameters were relatively low (generally <20%) indicating that the subjects appeared to comprise a homogenous group. Pharmacokinetic parameters derived from the bi-exponential function were similar to those obtained from the non-compartmental analysis.

Reviewer assessment:
The urinary excretion results indicate the urinary recovery of doripenem is 60 – 70%. However, it is not clear what percent of the renal recovery may account for the ring-opened metabolite, as doripenem-M1 was not assessed in this study.
The Sponsor concludes that the renal clearance of doripenem (156 – 179 mL/min) is nominally similar to the GFR in man, suggesting no marked secretion or reabsorption. However, the renal clearance of doripenem actually exceeds that of a normal GFR (range 88 – 137), suggesting that doripenem undergoes renal secretion.

As stated by the Sponsor, there appears to be a dose-response trend for an increase in serum levels of AST and ALT following repeated administration of doripenem. One subject in Cohort B (17%), 1 subject in Cohort C (17%), and 3 subjects in Cohort D (50%) had increases in their hepatic enzymes, while there were no incidents of elevated enzymes in Cohort A or in placebo-treated patients. However, doripenem exposure in the 5 subjects with elevated liver enzymes does not appear to be increased relative to the cohort averages (figure below). Observed abnormalities were reversible in all cases in which follow-up labs were performed.

Figure 3. Doripenem Exposure in Subjects with Elevated Hepatic Enzymes Relative to Cohort Means



Study DORI- 04

A Phase 1, Double-Blind, Placebo-Controlled Study to Determine the Safety, Tolerability and Pharmacokinetics of Prolonged-Infusion Regimens of Doripenem in Healthy Subjects

Dates: April – June 2003

Study Sites: [redacted]

Objective:

To determine the pharmacokinetics of prolonged-infusion regimens of doripenem, to evaluate the safety and tolerability of the prolonged-infusion regimens, and to evaluate the predictive value of the pharmacokinetic simulation model utilized to determine study dose regimens.

Methods:

Study Design

DORI-04 was a Phase 1, double-blind, placebo-controlled, dose-finding study of prolonged-infusion IV dosing regimens of doripenem in healthy subjects of either sex between the ages of 18 and 65 years. Six subjects in each cohort were randomized to receive active drug, and two control subjects were randomized to receive normal saline placebo following the same dosage schedule as the actively dosed subjects. For analysis purposes subjects receiving placebo were grouped into a fourth cohort (Cohort D).

The dosage regimens were sequential; i.e., safety was evaluated in each cohort before enrolling in the next cohort. Subjects in all cohorts remained in the study center for the 10-day duration of the infusion schedule, and returned for follow-up visits 7 and 14 days after the end of last infusion.

Dose Selection

Doripenem exhibited bactericidal activity at %T>MIC for 27% to 43% of the dosing interval in an animal model, with gram negative organisms generally requiring longer intervals of time above the MIC. Susceptibility testing performed against worldwide isolates showed that typical pathogens for the majority of the targeted infection types have an MIC_{90} below 1.0 μg/mL, with some species of *S. pneumoniae* and *H. influenzae* having MIC_{90} values less than or equal to 2.0 μg/mL. However, some clinical isolates of certain species, such as MRSA, *P. aeruginosa* and *Acinetobacter spp.*, may have higher MICs.

[redacted] developed a population PK model for doripenem utilizing data collected from 24 subjects enrolled in the Phase I Study DORI-01. This analysis determined that a basic two-compartment model with first-order elimination, inter-individual variability of clearance and the central and peripheral volumes of distribution described using an exponential error model, and residual variability described as an additive plus constant coefficient of variation model best described the concentration-time profile of doripenem. The population PK model was then used to perform a Monte-Carlo simulation of many new dosing regimens: 250 –1000 mg bid with infusion durations ranging from 1-6 hours; 250-1000 mg t.i.d. with infusion durations ranging from 1-5 hours and 750-1500 mg qd with infusion durations ranging from 1-5 hours. Each dosing regimen was simulated for 5000 subjects with samples every 6 minutes over the inter-dose interval. The percentage of the dosing interval with a concentration over target MIC values of 0.25 μg/mL to 16 μg/mL was then calculated for each subject. Based upon the results of this simulation study, the following three dosing regimens were selected for study in this protocol: Cohort A, 500 mg q8h infused over 4 hours, Cohort B, 1000 mg q12h infused over 6 hours, and Cohort C, 1000 mg q8h infused over 4 hours. The simulations indicated that these

dosing regimens should result in concentration-time profiles that would provide the microbiologic activity required to successfully treat more serious infections caused by organisms with somewhat higher MIC values of 4 or 8 µg/mL. Furthermore, prolonged infusion regimens may increase drug concentrations in tissues such as the lung, thus enhancing the probability of a positive clinical outcome. The following table summarizes the mean of the simulated percent of the dosing interval that plasma concentrations of doripenem were expected to be above the target MIC and the percent of subjects with time above the target MIC for at least 40% of the dosing interval for each cohort.

	Cohort A	**Cohort B**		**Cohort C**
Total Daily Dose	**1500 mg**	**2000 mg**		**3000 mg**
Target MIC	≤ 4.0 µg/mL	≤ 4.0 µg/mL	≤ 8.0 µg/mL	≤ 8.0 µg/mL
Mean % T > Target MIC	49%	54%	37%	49%
% Subjects with T > Target MIC at Least 40% of the Dosing Interval	99%	100%	46%	99%

Test Product

Subjects were administered multiple IV infusions of the following test and placebo products according to a randomization scheme generated at Peninsula Pharmaceutical Products, Inc. (PPI):
Active Drug: Doripenem for Injection, 500 mg/vial; Manufactured by Peninsula Pharmaceuticals, Inc./ —, Lot No.: CF2066; Expiration date: March 2004.
Placebo: Placebo 0.9% Sodium Chloride Injection USP 250 mL; Manufactured by Peninsula Pharmaceuticals, Inc./ —.; Lot No.: J3C483; Expiration date: March 2005.
Duration of dosing: In each cohort, study drug was administered for 10 days (q8h and q12h).

Table 1. Doripenem Treatment Schedule

Cohort	**Dose**	**N =**	**Dosing regimen**
A	500 mg	6 (active) 2 (placebo)	q8h over 4 hours
B	1000 mg	6 (active) 2 (placebo)	q12h over 6 hours
C	1000 mg	6 (active) 2 (placebo)	q8h over 4 hours

Inclusion Criteria

Subjects were included in the study if they were healthy males or females (non-pregnant) between 18 and 65 years of age, judged to be in good health based on physical exam and laboratory screening, and with a body mass index (BMI) between 18 and 30.

Drug Concentration Measurements

Five mL blood samples were drawn for quantification of doripenem and the M1 metabolite at the following time-points:
Cohorts A and C (4 hour duration of infusion): hour 0 (predose), and at 2, 4, 4.5, 5.25, 6.25 and 7.5 hours post-start of the first infusion on Days 1 and 7.
Cohort B (6 hour duration of infusion): hour 0 (pre-dose) and at 3, 6, 6.5, 7.25, 8.25 and 9.5 hours post-start of the first infusion on Days 1 and 7.

A total of 14 blood samples (70 mL each) were drawn from each subject during the study for drug analysis. Samples were drawn and processed under fluorescent lighting at room temperature.

Plasma samples were separated by centrifugation and frozen at -80°C until packed on dry ice and sent for analysis.

Urine collection was performed according to the following schedule for the purposes of quantifying doripenem and the M1 metabolite in urinary excretion:

Day 1 (first dose): 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16 and 16-24 hours from the start of first infusion for the treatment arms evaluating a 4 hour duration of infusion (Cohorts A and C) and 0-2, 2-4, 4-8, 8- 12, 12-14, 14-16 and 16-24 hours from the start of first infusion for the treatment arm evaluating a 6 hour duration of infusion.
Day 7: All cohorts: 0-12 and 12-24 hours.

Analytical Methods
Analyses of doripenem in plasma and urine were performed at [redacted], using a validated LC/MS/MS method. The major metabolite of doripenem (doripenem-M1) was assayed in plasma and urine at [redacted] using a validated LC/MS/MS method.

Pharmacokinetic Methods
Noncompartmental PK analysis of plasma data was performed using WinNonlin PRO v. 3.2 (model 202). PK parameters were calculated using the actual sampling time and the actual duration of individual infusions, and for each plasma concentration-time curve on Days 1 and 7.

PK parameters in urine were calculated in SAS® (v.8.2) for OpenVMS, using actual durations of the collection intervals. The following parameters were determined for parent and metabolite for each subject: AE (amount excreted), Re (maximum rate of excretion), Tmax (Time of maximum rate of excretion), Fe (fraction of dose excreted in urine during the first dosing interval).

Results:
Study Population
The study population consisted of 14 males and 10 females, with a mean age of 35 years. A summary of the demographic characteristics of subjects is presented in Table 2.

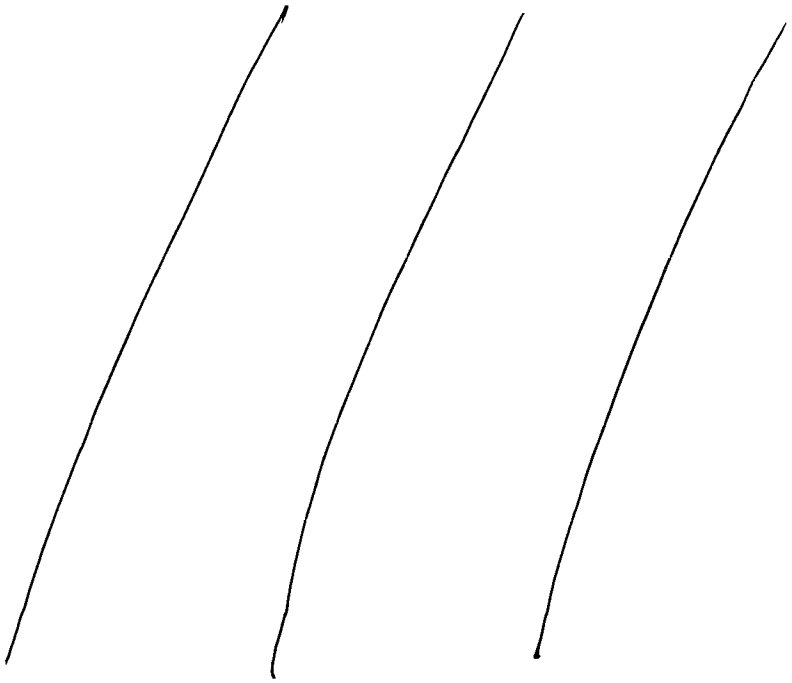
Table 2. Demographic Details by Treatment Group

Variable	Characteristic	All subjects (N=24)	Subjects who received active treatment (N=18)	Cohort A* (N=6) (500 mg q8h IV Infusion Over 4 Hours)	Cohort B* (N=6) (1000 mg q12h IV Infusion Over 6 Hours)	Cohort C* (N=6) (1000 mg q8h IV Infusion Over 4 Hours)
Gender	Male Female	14 (58.3%) 10 (41.7%)	13 (72.2%) 5 (27.8%)	3 (50%) 3 (50%)	5 (83.3%) 1 (16.7%)	5 (83.3%) 1 (16.7%)
Race/Ethnicity	Caucasian Hispanic	8 (33.3%) 16 (66.7%)	8 (44.4%) 10 (55.6%)	3 (50%) 3 (50%)	2 (33.3%) 4 (66.7%)	3 (50%) 3 (50%)
Age (years)	Mean (SD) Median (Minimum-maximum)	34.6 (9.2) 34.5 (20 – 53)	34.2 (10.2) 32.0 (20 – 53)	33.3 (8.5) 31.0 (25 - 48)	36.8 (12.3) 36.0 (22 - 53)	33.3 (10.4) 34.5 (20 - 48)

Variable	Characteristic	All subjects (N=24)	Subjects who received active treatment (N=18)	Cohort A* (N=6) (500 mg q8h IV Infusion Over 4 Hours)	Cohort B* (N=6) (1000 mg q12h IV Infusion Over 6 Hours)	Cohort C* (N=6) (1000 mg q8h IV Infusion Over 4 Hours)
Weight (kg)	Mean (SD) Median Minimum-maximum	75.9 (10.9) 74.5 (56.8 –100.3)	77.3 (12.0) 79.7 (56.8 – 100.3)	71.0 (6.9) 70.4 (62.7 - 82.6)	75.8 (17.7) 73.8 (56.8 - 100.3)	84.8 (3.9) 84.2 (80.4 – 89.9)
Height (cm)	Mean (SD) Median (Minimum-maximum)	171.3 (9.4) 170.5 (156 – 196)	173.2 (9.6) 174.5 (159 – 196)	167.8 (6.2) 168.0 (159 - 175)	173.5 (14.4) 172.0 (159 - 196)	177.7 (4.7) 178.5 (169 – 183)
BMI	Mean (SD) Median (Minimum-maximum)	25.8 (2.24) 26.0 (20.4 – 29.6)	25.7 (2.5) 26.0 (20.4 – 29.6)	25.4 (2.9) 25.9 (20.4 - 28.8)	24.9 (2.6) 25.2 (21.5 - 28.5)	26.9 (1.8) 26.5 (24.9 – 29.6)
Creatinine Clearance	Mean (SD) Median (Minimum-maximum)	125.0 (23.0) 121.6 (94.9 –191.1)	125.8 (25.3) 121.6 (94.9 – 191.1)	122.3 (21.4) 122.2 (94.9-159.4)	115.2 (24.4) 110.8 (95.6 -161.5)	139.7 (27.3) 133.1 (114.1-191.1)

* Only subjects who received the active treatment are included

Analytical Performance



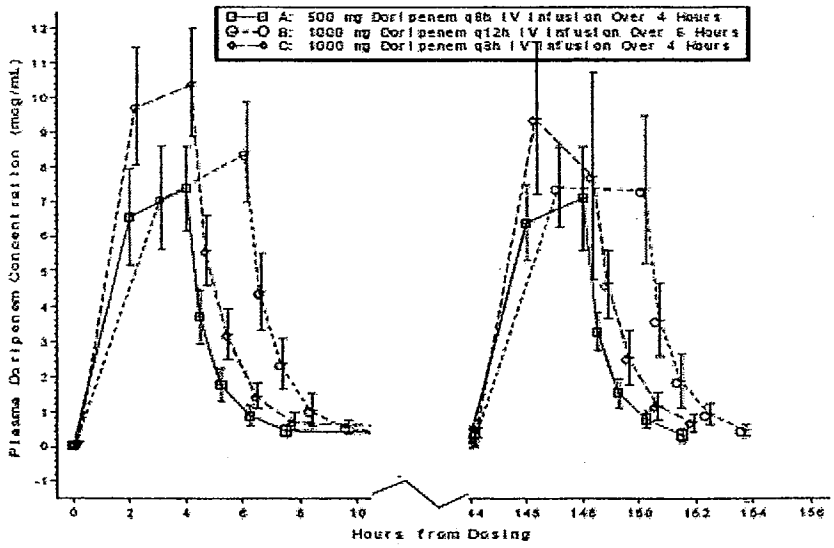
Pharmacokinetic Analysis of Doripenem

Data from all 18 subjects who received active treatment were included in the pharmacokinetic analysis. Subject No. 5, who completed only Day 1, was used in the analysis for Day 1 only.

Doripenem in Plasma

Mean plasma concentration-time curves of doripenem are presented on linear and log scales in Figures 1 and 2 below. Pharmacokinetic parameter values for doripenem are shown in Table 3.

Figure 1. Mean (SD) plasma doripenem concentration-time curves (linear scale) (n=6 per group)



Plots for Cohorts B and C are shifted to the right for ease of reading.

Project AA04843

Figure 2. Mean (SD) plasma doripenem concentration-time curves (log scale) (n=6 per group)

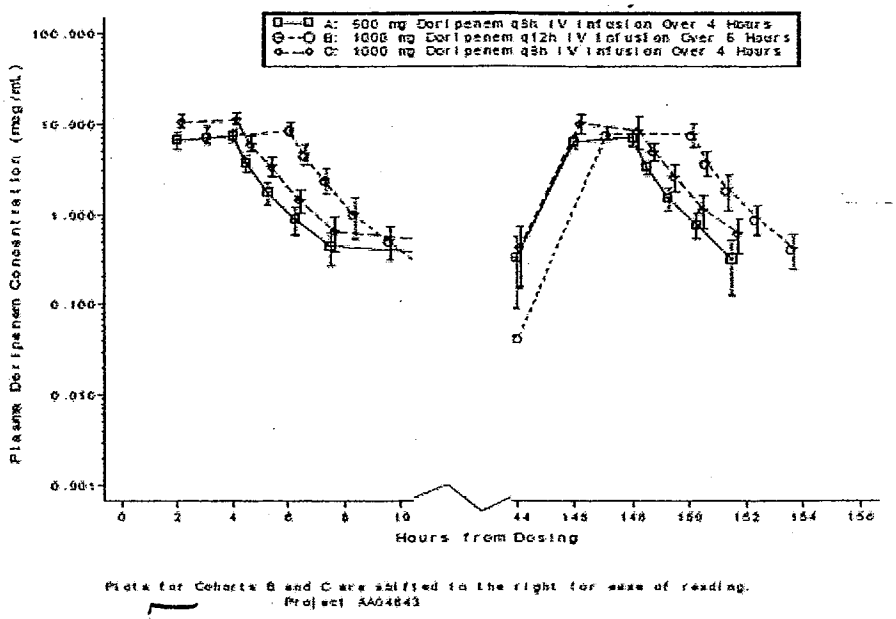


Table 3. Pharmacokinetic parameters of doripenem in plasma (N, Mean [SD] and Median [Min-Max])

	Cohort A 500 mg Doripenem q8h IV Infusion Over 4 hours		Cohort B 1000 mg Doripenem q12h IV Infusion Over 6 hours		Cohort C 1000 mg Doripenem q8h IV Infusion Over 4 hours	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Cmax (mcg/mL)	6 7.4141 (1.22191) 7.718 (5.158-8.682)	5 7.1624 (1.45221) 7.528 (4.774-8.648)	6 8.3046 (1.43517) 8.489 (6.589-10.123)	6 7.7609 (1.29656) 7.785 (6.318-9.087)	6 10.6403 (1.07844) 11.060 (8.572-11.562)	6 9.3166 (2.10299) 9.575 (5.496-11.361)
Tmax (hr)	6 3.345 (1.0416) 4.01 (2.00-4.04)	5 3.207 (1.0981) 4.00 (2.00-4.01)	6 6.013 (0.0100) 6.01 (6.01-6.03)	6 5.508 (1.2287) 6.01 (3.00-6.01)	6 3.005 (1.0887) 3.01 (2.01-4.00)	6 3.001 (1.0956) 3.00 (2.00-4.00)
AUC(0-t) (mcg*hr/mL)	6 27.76 (4.526) 29.5 (20.1-31.4)	—	6 41.61 (7.119) 41.1 (32.8-52.7)	—	6 39.73 (5.318) 41.1 (32.8-44.7)	—

	Cohort A 500 mg Doripenem q8h IV Infusion Over 4 hours		Cohort B 1000 mg Doripenem q12h IV Infusion Over 6 hours		Cohort C 1000 mg Doripenem q8h IV Infusion Over 4 hours	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
AUC(0-inf)* (mcg*hr/mL)	6 28.49 (4.770) 30.1 (20.4-32.6)	N/A	6 42.33 (7.226) 42.1 (33.2-53.3)	N/A	6 40.57 (5.606) 42.4 (33.1-45.7)	N/A
AUCss(0-tau) (mcg*hr/mL)	N/A	5 26.53 (4.944) 29.0 (18.3-30.6)	N/A	6 40.12 (8.206) 40.1 (31.0-48.3)	N/A	5 35.72 (6.219) 35.9 (27.9-44.2)
T1/2 (hr)	6 1.0530 (0.25373) 1.055 (0.645-1.343)	5 1.0431 (0.25517) 1.063 (0.670-1.372)	6 0.9915 (0.13556) 0.968 (0.848-1.214)	6 1.0928 (0.29637) 1.065 (0.814-1.653)	6 0.9399 (0.14830) 0.965 (0.739-1.077)	6 1.0359 (0.22868) 1.078 (0.762-1.333)
λz (1/hr)	6 0.6981 (0.20358) 0.660 (0.516-1.075)	5 0.7027 (0.20031) 0.652 (0.505-1.035)	6 0.7095 (0.09168) 0.719 (0.571-0.817)	6 0.6671 (0.14931) 0.651 (0.419-0.851)	6 0.7538 (0.12449) 0.725 (0.643-0.938)	6 0.6991 (0.16466) 0.644 (0.520-0.910)
CL (CLss) (L/hr)	6 18.04 (3.547) 16.6 (15.4-24.5)	5 19.52 (4.512) 17.2 (16.3-27.3)	6 24.20 (4.107) 23.8 (18.7-30.1)	6 25.83 (5.333) 25.5 (20.7-32.3)	6 25.07 (3.669) 23.7 (21.9-30.2)	5 28.69 (5.057) 27.8 (22.6-35.8)
Vss (L)	6 24.97 (3.972) 24.2 (19.5-30.9)	N/A	6 42.48(8.645) 41.8 (31.2-55.5)	N/A	6 34.92(5.509) 34.9 (28.8-44.1)	N/A
MRT (hr)	6 1.395 (0.1377) 1.41 (1.23-1.59)	N/A	6 1.764 (0.2952) 1.68 (1.51-2.34)	N/A	6 1.399 (0.1618) 1.36 (1.20-1.65)	N/A
Cavg (mcg/mL)	N/A	5 3.3157 (0.61801) 3.629 (2.289-3.825)	N/A	6 3.3433 (0.68386) 3.341 (2.582-4.027)	N/A	5 4.4656 (0.77736) 4.491 (3.490-5.529)

The ratio of the doripenem dose of Cohort C to Cohort A was 2, whereas the ratios of the mean Cmax and AUC(0-t) on Day 1 were approximately 1.4 and the ratios on Day 7 were