

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There were no studies conducted to assess the potential for study drug abuse. Generally, antibiotics represent a therapeutic class with a limited history of abuse potential and withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

There were no human reproduction studies conducted.

Two pregnant women may have been exposed to study drug therapy during the first month of fetal gestation. One pregnancy was ectopic and terminated surgically and the second pregnancy was spontaneously aborted. Both women had concurrent medical events associated with an increased risk for adverse pregnancy outcome, however, the relationship between study drug exposure and pregnancy outcome cannot be definitively determined.

7.1.15 Assessment of Effect on Growth

Not applicable to this adult study which only enrolled patients over the age of 18.

7.1.16 Overdose Experience

For the purposes of this safety analysis, in the Phase 2/3 studies, any dose of doripenem >1g, or a total daily dose >3g was considered a potential "overdose." No subjects received such dosages and thus the effects of doripenem overdose in humans remains unknown.

7.1.17 Postmarketing Experience

Doripenem is an injectable carbapenem antibiotic manufactured by Shionogi & Co., Ltd., Osaka, Japan. Peninsula Pharmaceuticals has obtained an exclusive license for the development and commercialization of doripenem in North America, South America, and Europe. Doripenem has been studied by Shionogi in Japan in Phase 3 studies in the indications of urinary tract infections and respiratory infections; doses lower than those proposed for U.S. trials have been used (250 mg bid x 7 days).

The Applicant has included a report of post-marketing experience in its Integrated Summary of Safety. The report included a cumulative review of the post-marketing experience based on a search of the company's worldwide safety database (SCEPTRE). The search included all spontaneously reported confirmed cases of adverse events reported as of August 31, 2006. There were 49 confirmed cases with doripenem as a suspect drug. Among the 49 cases, there were 29 (59%) serious cases and 20 (41%) non-serious cases. The patient demographics included 30 males, 18 females, and one patient whose gender was not known. The Applicant provided a review of the 49 cases and supports the inclusion of anaphylaxis as an adverse event in the post-marketing section of the product labeling. Although only one case of anaphylactoid reaction was

reported, the case describes the event in sufficient detail to conclude that anaphylaxis may occur with the use of doripenem.

The Applicant has subsequently submitted a 4 month updated safety report that has been reviewed by Dr. Alfred Sorbello, FDA Medical Officer. For the overall safety review of doripenem, which includes the results from studies DORI-03, DORI-05, DORI-06, DORI-07, and DORI-08, please see the safety review by Dr. Alfred Sorbello.

7.2 Adequacy of Patient Exposure and Safety Assessments

Within the context of adult patients with complicated urinary tract infections, including pyelonephritis, the extent and duration of exposure needed to assess safety was limited. The study protocol called for a possible switch from IV doripenem (500 mg q8h) to oral levofloxacin (250 mg q24h) after 9 doses of the doripenem, provided that the patient showed signs of clinical improvement. Those patients who did not improve at that point were allowed to remain on IV doripenem for up to 10 days. Patients who were bacteremic at baseline could be treated for up to 14 days with doripenem.

Therefore, the safety data for those patients who received only IV doripenem without a switch to levofloxacin is very limited.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The dosage regimen for doripenem used in Study DORI-06 was 500 mg q8h for 10 days. After \geq 9 doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h). The study provided adequate patient exposure and safety assessments for the cUTI indication. The safety dataset for this NDA was based on the safety analysis of Study DORI-05, which was a multi-center, randomized, controlled study. The safety analysis included all patients who received at least one dose of study drug. There were 423 patients who received at least one dose of doripenem (500 mg q8h).

Adverse events were recorded daily during study drug administration, at the EOT(IV), TOC, and LFU visits. Laboratory testing was conducted at study entry, Study Day 3, EOT(IV), TOC, and LFU.

The Applicant conducted a second clinical trial (DORI-05), which also looked at the safety and efficacy of doripenem in treating 376 patients with complicated urinary tract infections.

7.2.1.2 Demographics

See Table 3 in section 6.1.4.1.

7.2.1.3 Extent of exposure (dose/duration)

See Table 7 in section 6.1.4.6.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The Applicant performed a Phase II, dose-finding study (DORI-03) for the purpose of determining the best dosing regimen to be used in later Phase III studies. It was a multi-center, randomized, double-blind, dose finding study of two intravenous (IV) dosing regimens of doripenem (250 mg q8h and 500 mg q8h) for 7 to 14 days in the treatment of complicated urinary tract infections (cUTI) in adults. One hundred twenty-one subjects were randomized to receive either one of the two doses for 7 -14 days in the treatment of cUTI in adults. One hundred patients were evaluable for microbiological assessment. The cure rate for this group (ME at TOC) was 64.2% (34/53) for the group that received 250 mg compared to 68.1% (32/47) for the group that received 500 mg. Thus, the Applicant selected the higher, 500 mg dose to be used in subsequent comparative and non-comparative studies.

The Applicant conducted a second clinical trial (DORI-05, which also looked at the safety and efficacy of doripenem in treating 376 patients with complicated urinary tract infections.

7.2.2.2 Postmarketing experience

Please refer to section 7.1.17 of this review for further information on post-marketing experience with doripenem.

7.2.2.3 Literature

Please refer to section 7.2.2.3 in the review of Study DORI-05 for information concerning the articles submitted by the Applicant.

7.2.3 Adequacy of Overall Clinical Experience

Within the context of adult patients with complicated urinary tract infections, including pyelonephritis, the extent and duration of exposure needed to assess safety was limited. The study protocol called for a possible switch from IV doripenem (500 mg q8h) to oral levofloxacin (250 mg q24h) after 9 doses of the doripenem, provided that the patient showed signs of clinical improvement. Those patients who did not improve at that point were allowed to remain on IV doripenem for up to 10 days. Patients who were bacteremic at baseline could be treated for up to 14 days with doripenem.

Therefore, the safety data for those patients who received only IV doripenem without a switch to levofloxacin is very limited.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal toxicity data and assays for mutagenicity potential were included in the IND submissions (IND 64,416). Please see the reviews by Dr. Amy C. Nostrandt, D.V.M., Ph.D., dated January 22, 2003 and June 27, 2003.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of patients with regard to monitoring vital signs, laboratory testing, and observation of adverse events was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Applicant conducted four pharmacokinetics studies (R1411, R1412, R1414, and R1417) in healthy volunteers. In addition, two Phase I clinical studies in healthy volunteers (DORI-01) and in subjects with renal impairment (DORI-02) were conducted. DORI-01 was a randomized, multiple-dose, dose-escalation study with 4 cohorts containing male and female subjects. Blood and urine samples were collected throughout the study for pharmacokinetic analysis.

DORI-02 was an open-label, controlled study, to evaluate the safety, tolerability, and pharmacokinetics of doripenem administered intravenously to subjects with mild (CL_{CR} 51-79 mL/min), moderate CL_{CR} 31-50 mL/min), and end stage renal impairment requiring hemodialysis. All subjects received a single IV dose of doripenem, 500 mg administered over 30 minutes. Subjects with renal impairment were matched (for age and body weight) in a ratio of 3:1 with control subjects who have normal renal function. Please see Clinical Pharmacology & Biopharmaceutics Review for IND 64,416 by Dr. Charles Bonapace, dated November 6, 2002.

Also, a dose finding clinical study (DORI-03) involving 100 patients with cUTI was completed.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Applicant adequately evaluated patients for potential drug class-related adverse events, including, but not limited to observing for episodes of seizure, allergies, worsening of renal function, liver dysfunction, and neutropenia.

7.2.8 Assessment of Quality and Completeness of Data

The data available were adequate for conducting the safety review for doripenem.

7.2.9 Additional Submissions, Including Safety Update

A four month safety update was submitted by the Applicant, which included data from an ongoing nosocomial pneumonia studies and updated post-marketing data. Please see Dr. Sorbello's review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Overall, the administration of doripenem (500 mg) by IV infusion over 1 hour q8h was generally safe and well tolerated in patients aged 18 years or older with cUTI or pyelonephritis.

There were four deaths in the study that appeared to be unrelated to therapy with doripenem. One patient died before starting study drug therapy and three died after receiving at least one dose of doripenem. All treatment emergent adverse events leading to death were single events; respiratory failure, ventricular arrhythmia, and bladder neoplasm.

Serious adverse events were reported in 39 (9%) patients. The most frequently reported SAE was urinary tract infections with 6 (1.4%) cases reported. There were three SAEs, occurring in two patients, that were considered possibly related to study drug therapy: atrial flutter in one and atrial fibrillation and renal impairment in the second patient.

Headache was the most frequently reported adverse event (19%) and was the most commonly reported adverse event with onset during IV therapy (16%). Phlebitis was the next most commonly reported adverse event during IV therapy administration (8%).

With the exception of headache, the most frequently reported treatment-emergent adverse events were within the gastrointestinal (GI) system organ class. Constipation, diarrhea, vomiting, upper abdominal pain, and nausea were reported by 4% or more of patients overall.

There were two pregnant women who may have been exposed to study drug therapy during the first month of fetal gestation. One pregnancy was ectopic and terminated surgically and the second pregnancy was spontaneously aborted.

Elevations in liver enzyme levels did occur in the study with two patients meeting the criteria to fulfill Hy's rule after receiving 2-3 days of IV doripenem. Neither event was likely to be related to doripenem as both patients had confounding medical events that could have contributed significantly to the observed liver findings.

There were no unexpected clinically significant changes in vital sign measurements observed during the study.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There was no pooling of data in this study.

7.4.2 Explorations for Predictive Factors

Not applicable to this study.

7.4.3 Causality Determination

Not applicable to this study.

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9/27/2007 10:12:06 AM
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Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review

IND or NDA	22106
Brand Name	N/A
Generic Name	Doripenem monohydrate
Sponsor	Johnson and Johnson
Indication	Treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis
Dosage Form	Solution for injection
Therapeutic Dose	500 mg q8h by intravenous infusion over 1 h
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Maximum tested dose 1000 mg q8h x 10 days
Application Submission Date	12 December 2006
Review Classification	Standard NDA
Date Consult Received	26 January 2007
Date Consult Due	26 March 2007
Clinical Division	DAIOP / HFD 520
PDUFA Date	12 October 2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Two doses of doripenem administered by IV infusion over 60 minutes were evaluated: 500 mg and 1000 mg. At the suprathreshold dose (1000 mg), doripenem plasma concentrations were 2-fold higher than peak concentrations following the 500 mg dose. The 1000 mg dose covers the expected increase in doripenem and doripenem-M-1 plasma concentrations due to renal impairment (Study DORI-02).

Two methods of analyses were used to analyze the Fridericia-corrected QT values, the Sponsor's predefined method using mixed effects model on the change from time-matched baseline QTcF values and the Statistical Reviewer's method of analyzing raw mean difference on change from baseline between drug and placebo based on the ICH E14 criteria. Both analysis methods gave similar results.

- Moxifloxacin was demonstrated to be an active positive control and prolongs QTc as anticipated (Table 7).
- The upper limit of the two-sided 90% CI for the mean difference between doripenem (for both doses of 500 mg and 1,000 mg) and placebo was under 5 milliseconds at all time points which is below the value of 10 ms, which is identified as the threshold for regulatory concern in the ICH E14 guideline.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

There were no questions to be addressed.

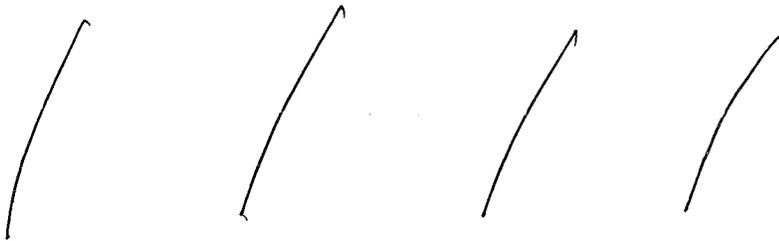
1.3 REVIEWER'S COMMENTS

- This study was a 4 treatment, 4 period, 4 sequence crossover design. The sponsor proposed a 4-way latin-square design in which each treatment follows every other treatment an equal number of times. This type of a design minimizes the carry-over effect of a given treatment, if any. Both doses of doripenem (500 mg I.V. and 1,000 mg I.V) as well as the placebo and active control were blinded using a double-dummy double-blind design (oral placebo to match oral moxifloxacin and i.v. placebo to match i.v. doripenem). The statistical reviewer concludes that this was an adequately designed thorough QT study.

2 PROPOSED LABEL

The sponsor did not include any labeling for QT. **The following recommendations are suggestions for labeling only and are open to modification pending further discussion with the review division. We defer all final labeling decisions to the review division.**

12. 2 Pharmacodynamics



3 BACKGROUND

3.1 INDICATION

Treatment of complicated intra-abdominal infections and complicated urinary tract infections, including _____ pyelonephritis

3.2 DRUG CLASS

Carbapenem class of beta-lactams

3.3 MARKET APPROVAL STATUS

Doripenem is a new chemical entity and is not approved in the US.

3.4 PRECLINICAL INFORMATION

The sponsor reported the following information in Section 2.6.2, Pharmacology Summary.

"Doripenem was assessed for its effects on the activating component of delayed rectifier potassium current (IKr) in HERG-transfected Chinese hamster ovary cells (CHO-K1). The resting membrane potential was set at -80 mV on the

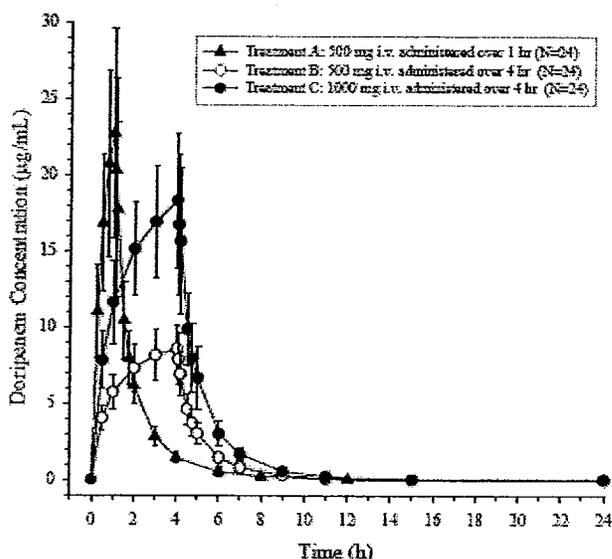
whole-cell clamp mode. Effects of doripenem on peak tail currents were assessed under two different depolarization pulse conditions (+20 mV, +60 mV) for each concentration of 3, 30 and 300 μ M. Although 30 μ M caused a statistically significant decrease at +60 mV, the change was small (approximately 10%) and not dose-dependent. No significant changes were observed for doripenem at any of the other dose and test conditions. Thus doripenem can be considered to be inactive as blocker of HERG-potassium channels."

3.5 PREVIOUS CLINICAL EXPERIENCE

Doripenem monohydrate has not been marketed in the USA so there is no previous clinical experience.

3.6 CLINICAL PHARMACOLOGY

Figure 1. Mean Plasma Concentration vs. Time Profiles After Single Doses of Doripenem (Study DORI-NOS-1004)



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Mean \pm SD data are shown.

Source: Mod5.3.3.1\DORI-NOS-1004\Sec11.4.1.1 (Figure 11.4.1.1:1).

(Sponsor's Figure 2, Clinical Summary 2.7.2 page 31)

Table 1 summarizes the key features of doripenem's clinical pharmacology.

Table 1 Highlights of Clinical Pharmacology (Data Compiled by Reviewer)

Therapeutic dose	500 mg x — q8h for CLcr \geq 51 ml/min Dose adjustments: Moderate renal impairment: 250 mg q8h Severe renal impairment: 250 mg q12h	
Maximum tolerated dose	N/A	
Principal adverse events	N/A	
Maximum dose tested	Single Dose	N/A
	Multiple Dose	N/A

Exposures Achieved at Maximum Tested Dose	Single Dose	N/A
	Multiple Dose	N/A
Range of linear PK	Linear and time-independent pharmacokinetics across the dose range of 125 to 1000 mg (Clinical Summary 2.7.2)	
Accumulation at steady state	No appreciable accumulation with q8h dosing (Clinical Summary 2.7.2)	
Metabolites	Doripenem dicarboxylate	
Absorption	Absolute/Relative Bioavailability	N/A
	Tmax	N/A
Distribution	Vss	16.6 L
	% bound	8.1% binding to serum proteins (Clinical Summary 2.7.2)
Elimination	Route	<ul style="list-style-type: none"> • Primary route: renal (glomerular filtration and active tubular secretion) • Beta-lactam ring cleavage to doripenem dicarboxylate (Clinical Summary 2.7.2)
	Terminal t _{1/2}	<ul style="list-style-type: none"> • 1.2 h • Mean (%CV) for metabolites
	CL	CL: 15.9 L/h CLr: 10.2 L/h (Clinical Summary 2.7.2)
Intrinsic Factors	Age	Cmax and AUC were 23% and 49% higher in elderly subjects with normal age-appropriate renal function. (Clinical Summary 2.7.2)
	Sex	Cmax and AUC were 15% and 13% higher in females. (Clinical Summary 2.7.2)
	Race	CL is 14% higher in subjects of Hispanic or Latino ancestry. (Clinical Summary 2.7.2)
	Hepatic & Renal Impairment	Hepatic impairment: not studied. Renal impairment: Increased AUC _{0-inf} from 61% (mild renal impairment) to 510% (severe renal impairment). ESRD also showed increase of 270% to 730%. The sponsor is suggested dose reduction in these patients. (Clinical Summary 2.7.2)
Extrinsic Factors	Drug interactions	Probenecid Interaction: Cmax: 15% increase AUC: 75% increase (Clinical Summary 2.7.2)

	Food Effects	As doripenem is administered intravenously, no studies were performed.
Expected High Clinical Exposure Scenario	Elderly subject with low CLcr.	

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW (SUBMITTED MATERIALS)

The sponsor submitted a 'thorough QTc study.'

4.2 QT STUDY

4.2.1 Title

A Randomized, Double-Blind, Placebo- and Positive-Controlled Crossover Study Evaluating Electrocardiogram Intervals in Healthy Adults Receiving Multiple Intravenous Infusions of Doripenem at Therapeutic and Supratherapeutic Doses

4.2.2 Protocol Number

DORI-NOS-1001

4.2.3 Objectives

The primary objective of this study was to assess the effects of doripenem on the QT/QTc interval duration at therapeutic and supratherapeutic doses in healthy adults.

The secondary objectives of this study were to assess the safety and tolerability of doripenem, to characterize the multiple-dose pharmacokinetics of doripenem, and to describe the effect of doripenem on other 12-lead ECG intervals (e.g., RR analyzed as heart rate, QRS, PR).

4.2.4 Design

4.2.4.1 Description

This was a randomized, double-blind, placebo- and positive-controlled, double-dummy, 4-way crossover study evaluating electrocardiogram intervals in healthy adults receiving multiple doses of doripenem i.v. infusions at therapeutic (500 mg) and supratherapeutic (1,000 mg) doses.

A total of 4 doses of doripenem administered every 8 hours as 1 hour intravenous infusions on Days 1 and 2 were to be evaluated. Moxifloxacin as a single oral 400-mg dose administered on Day 2 was chosen as positive control for the evaluation of QT/QTc interval prolongation. In order to blind the test drug doripenem i.v. and positive control moxifloxacin (oral), a double-dummy design was utilized using matching placebo in both i.v. (to blind doripenem) and oral (to blind moxifloxacin) forms.

The proposed study design is shown in Figure 2, where treatments are as follows:

- Treatment A = doripenem 500 mg i.v. on Day 1, and
doripenem 500 mg i.v. + oral placebo on Day 2
- Treatment B = doripenem 1000 mg i.v. on Day 1, and
doripenem 1000 mg i.v. + oral placebo on Day 2
- Treatment C = placebo i.v. on Day 1, and
placebo i.v. + oral placebo on Day 2
- Treatment D = placebo i.v. on Day 1, and
placebo i.v. + oral moxifloxacin 400 mg

Figure 2. Study Design

Sequence:	Period 1 Treatment	Period 2 Treatment	Period 3 Treatment	Period 4 Treatment	
Randomization	1	A	D	B	C
	2	B	A	C	D
	3	C	B	D	A
	4	D	C	A	B

Screening (up to 21 days before baseline)	Double-Blind Treatment Phase ^a (at least 7-day washout period between treatments)	Follow-up Telephone Contact (approx. 2 weeks after last dose)
Day -2 ^b		End of Study Assessments ^c

^a Treatments A, B (doripenem 500mg or 1000 mg and oral placebo, respectively), C (i.v. placebo and oral placebo), and D (moxifloxacin and i.v. placebo) were administered on Days 1 and 2 of each period as described in Section 3.1, Overview of Study Design. Serial ECGs were recorded at corresponding time points on Days -1 and 2 of each treatment period as specified in the protocol. Venous blood samples were collected for determination of plasma concentrations of doripenem, doripenem-M-1, and moxifloxacin on Day 2 of each treatment period at times specified in the protocol.

^b Subjects were admitted to the clinical testing facility no later than noon on Day -2 before each period and stayed through completion of all appropriate study evaluations. A washout period of at least 7 days occurred between Day 2 of each treatment period and Day 1 of the subsequent treatment period.

^c End of study procedures were performed on Day 3 of Period 4 or upon early withdrawal from the study.

(Sponsor's Figure 1, page 23)

4.2.4.2 Sponsor's Justification for Design -

The study used a crossover design with subjects serving as their own controls and thus, allowing for use of intra-subject variance in the comparison of treatment effects and facilitation of the heart rate QTc correction approach based on individual subject data.

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4.2.4.3 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.4.4 Blinding

All treatment arms were double-blinded (i.e., investigators and subjects were blinded). The pharmacist who was responsible for preparation of the study drug for each subject was not blinded. A site monitor who was responsible for drug accountability and for monitoring the pharmacist was also not blinded.

4.2.5 Study Subjects

Healthy males and females between 18 and 65 years of age, inclusive, with normal 12-lead ECG at screening and baseline, and with no relevant history of cardiovascular diseases were eligible for enrollment in this study. A total of 60 subjects (32 men and 28 women) were planned for enrollment, so that at least 52 subjects will complete the study.

4.2.6 Dosing Regimens

4.2.6.1 Treatment Arms

Subjects received the treatments listed in Table 2 according to assigned treatment sequence. Each treatment period was separated by a minimum of 7-day washout period.

Table 2. Treatment Schedule

	Treatment	Day 1	Day 2
A	i.v. infusion ^a oral ^b	doripenem (500 mg) -	doripenem (500 mg) placebo
B	i.v. infusion ^a oral ^b	doripenem (1000 mg) -	doripenem (1000 mg) placebo
C	i.v. infusion ^a oral ^b	placebo -	placebo placebo
D	i.v. infusion ^a oral ^b	placebo -	placebo moxifloxacin (400 mg)

^a Intravenous infusions were administered over 1 hour starting at approximately 8:00 a.m., 4:00 p.m., and midnight on Day 1 and at approximately 8:00 a.m. on Day 2.

^b On Day 2, a single oral dose of moxifloxacin 400 mg or placebo was administered with 180 mL of noncarbonated water at approximately 8:00 a.m. immediately before the i.v. infusion.

(Sponsor's Table 1, page 22)

4.2.6.2 Sponsor's Justification for Doses

In clinical trials of doripenem for the treatment of moderate to severe infections, the proposed dosing regimen is 500 mg doripenem administered as a 1-hour or 4-hour infusion every 8 hours, with the 1-hour infusion regimen generating a higher steady state C_{max} (21 µg/mL). Thus the 500-mg dose infused over 1 hour every 8 hours has been selected as the therapeutic dose for the present study. The supratherapeutic dose selected

for this study, 1,000 mg infused over 1 hour every 8 hours, corresponds to the highest dose tested in Phase 1 clinical studies. This dose regimen was well tolerated in healthy subjects and had a steady-state C_{max} of 43 µg/mL or 98 µM. This doripenem concentration is approximately one-third of the highest concentration tested (300 µM) in in vitro cardiovascular safety studies in which no toxicity was detected.

4.2.6.3 Instructions with regard to meals

Subjects fasted for at least 8 hours before the first ECG measurement on Day -1 and before initiation of the morning i.v. infusion on Days 1 and 2. On Days -1, 1 and 2, subjects received standardized lunch, dinner and light snack at approximately 12:00 p.m., 5:00 p.m. and 8:00 p.m. (approximately 4, 9 and 12 hours, respectively, after the initiation of the morning dose on Days 1 and 2). The timing of the meals and snack were kept the same on all study days, including Day -1.

4.2.6.4 Study Assessments

- ECGs were obtained in triplicate at each time point
- ECGs were collected first, followed by PK blood sample

Table 3. Highlights of Schedule of Interventions

Study Day	0 (Baseline)	1	2
Intervention	No treatment	Single dose	Single dose
12-Lead ECGs	Record ECGs [#]	Record ECGs ^{##}	Record ECGs [#]
PK Samples for drug	None collected	Collected ^{###}	Collected ^{###}

[#]0, 0.5, 1.0, 1.25, 2, 3, 4, 6 and 8 hours after the initiation of i.v. infusion

^{##}0, 8, 16 hour (pre-dose for each of the three i.v. infusions)

^{###}0, 0.25, 0.5, 1.0, 1.25, 2, 3, 4, 6, 8 and 12 hours after the initiation of i.v. infusion

4.2.6.5 Sponsor's justification for sampling schedule

Not provided.

4.2.6.6 Baseline

Time-matched baseline was used. At each time point of measurement, for each subject, the baseline ECG intervals were the ECG values obtained at the corresponding time point on Day -1 of that period.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Statistical Analyses

4.2.8.1.1 Primary Analysis

The primary pharmacodynamic (PD) parameter of interest for statistical analysis was ΔQT_c , i.e., change from baseline in corrected QT interval (QT_c) at time $t = QT_c$ value at time $t -$ baseline QT_c value at time t . The primary method for calculating the corrected QT interval in this study was Fridericia correction (QT_{cF}) defined as

$$QT_{cF} = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

The PD analysis set included all subjects who were randomly assigned to treatments, received study drug and had at least one post baseline QT measurement, and provided ECG parameter information.

The null hypothesis tested was that the difference in mean ΔQT_{cF} between each dose of doripenem (1,000 mg every 8 hours or 500 mg every 8 hours) and placebo is greater than or equal to 10 milliseconds, against the alternative hypothesis that the difference in mean ΔQT_{cF} between study drug and placebo is less than 10 milliseconds. The hypothesis will be tested at each time point of measurement.

The null hypothesis for doripenem 1000 mg dose vs. placebo will be tested first. If the null hypothesis for 1000 mg dose is rejected at every time point of measurement, it will be concluded that doripenem is non-inferior to placebo. The null hypothesis for doripenem 500 mg dose vs. placebo will be tested only if the null hypothesis for 1000 mg dose vs. placebo is not rejected for at least one time point of measurement.

The primary analysis was based on a mixed effects model fitted to the primary PD parameter, ΔQT_{cF} as the dependent variable, and sequence, treatment, period, time point of measurement and subject as a random effect.

Table 4 shows the summary of least square means from mixed effects model for comparison of mean ΔQT_{cF} of the following pairs:

1. moxifloxacin versus placebo;
2. doripenem 500 mg versus placebo; and
3. doripenem 1,000 mg versus placebo.

Table 4: Mean Change from Baseline in QTc: Least Square Mean Differences based on Mixed Effects Model

Time Point	Placebo/Moxifloxacin vs.			Dori 500 mg/Placebo vs.			Dori 1000 mg/Placebo vs.		
	Placebo/Placebo			Placebo/Placebo			Placebo/Placebo		
	L.S.Mean	SE	90% CI	L.S.Mean	SE	90% CI	L.S.Mean	SE	90% CI
0h	1.3	1.68	(-1.48; 4.05)	1.2	1.68	(-1.52; 4.01)	1.1	1.67	(-1.61; 3.90)
0.5h	4.1	1.70	(1.35; 6.93)	-0.8	1.69	(-3.58; 1.98)	1.0	1.69	(-1.75; 3.80)
1h	7.7	1.68	(4.89; 10.42)	0.1	1.69	(-2.67; 2.89)	-0.5	1.68	(-3.25; 2.29)
1.25h	10.2	1.68	(7.41; 12.95)	0.7	1.68	(-2.05; 3.49)	-0.3	1.68	(-3.07; 2.46)
2h	11.0	1.68	(8.26; 13.80)	0.3	1.68	(-2.47; 3.07)	1.1	1.68	(-1.68; 3.85)
3h	12.6	1.68	(9.86; 15.39)	-0.2	1.68	(-2.99; 2.54)	-2.1	1.68	(-4.83; 0.70)
4h	12.3	1.68	(9.56; 15.09)	-0.8	1.68	(-3.60; 1.93)	-1.5	1.68	(-4.26; 1.27)
6h	10.5	1.68	(7.69; 13.22)	0.1	1.68	(-2.67; 2.86)	-0.9	1.68	(-3.65; 1.88)
8h	11.1	1.68	(8.33; 13.86)	-1.0	1.68	(-3.79; 1.74)	-1.8	1.68	(-4.58; 0.95)

Note: Mixed effect models were fitted using ΔQTc as the dependent variable, sequence, treatment, period, time point of measurement, and treatment by time point of measurement interaction as factors, and subject as a random effect. Using the least-square means and estimated intra-subject variances, 90% confidence interval was calculated for inter-group differences.

Assay sensitivity was established if at any given time point the lower limit of the two-sided 90% confidence interval for moxifloxacin minus placebo was above 0 ms.

The mean effect of doripenem was considered "negative" if at all time points the upper limit of the two-sided 90% confidence interval for doripenem minus placebo fell below 10 ms.

Cross reference: Appendix 3.9.6

(Sponsor's Table 10, Page 59)

As shown in Table 4, the assay sensitivity for moxifloxacin as a positive control was established because the lower limit of the 90% confidence interval for the mean difference in $\Delta QTcF$ between moxifloxacin and placebo was above 0 milliseconds for at least one post-dose time points. In fact the lower limit of the 90% CI was above 0 ms for each post-dose time point starting from 0.5 hours through 8 hours post-dose and the mean differences ranged from 4.1 ms to 12.6 ms.

The upper limit of the two-sided 90% CI for the mean difference between doripenem (for both doses of 500 mg and 1,000 mg) and placebo was under 5 milliseconds at all time points which is below the predefined limit of 10 ms. Therefore, the effect of doripenem (both doses) on QT/QTc prolongation was non-inferior to, or no worse than, that of placebo.

4.2.8.1.2 Categorical Analysis

Table 5 shows the number of subjects with Fridericia-corrected QT values, QTcF, greater than 450 ms, 480 ms, or 500 ms.

Table 5: Number of Subjects with QTcF values greater than 450 ms, 480 ms, or 500 ms

(Study DORI-NOS-1001: Safety Analysis Set)

Day	Placebo i.v./ Placebo Oral (N=58) n (%)	Placebo i.v./ Moxifloxacin Oral (N=58) n (%)	Dori 500 mg i.v./ Placebo Oral (N=58) n (%)	Dori 1000 mg i.v./ Placebo Oral (N=59) n (%)
Total	0	1 (2)	0	1 (2)
Day -1	0	0	0	1 (2)
QTcF (ms)				
>450	0	0	0	1 (2)
>480	0	0	0	0
>500	0	0	0	0
Day 2	0	1 (2)	0	0
QTcF (ms)				
>450	0	1 (2)	0	0
>480	0	0	0	0
>500	0	0	0	0

Cross-reference: Appendix 3.9.2

(Sponsor's Table 11, Page 60.)

- No subject had a QTcF value greater than 480 ms in any treatment at any time point. No subject had a post dose QTcF greater than 450 ms after receiving either doses of doripenem or placebo treatment at any time point.
- There were two occurrences of QTcF values greater than 450 ms, both in female subjects: Subject 600009 (452.0 ms) at 8 h post dose after receiving moxifloxacin, and Subject 600039 (450.7 ms) before receiving doripenem 1000 mg at 4 h on Day -1 (baseline).

Table 6 shows the number of subjects with maximum changes from baseline in QTcF that were greater than or equal to 30 ms or 60 ms

Table 6: Number of Subjects with Maximum Changes from Baseline in QTcF greater than or equal to 30 ms or 60 ms

(Study DORI-NOS-1001: Safety Analysis Set)

Parameter	Placebo i.v./ Placebo Oral (N=58) n (%)	Placebo i.v./ Moxifloxacin Oral (N=58) n (%)	Dori 500 mg i.v./ Placebo Oral (N=58) n (%)	Dori 1000 mg i.v./ Placebo Oral (N=59) n (%)
Total	0	5 (9)	0	1 (2)
QTcF (ms)				
≥30	0	5 (9)	0	1 (2)
≥60	0	0	0	0

Cross-reference: Appendix 3.9.2

(Sponsor's Table 12, Page 60).

- No subject had a time-matched Δ QTcF exceeding 60 ms in any treatment at any time point. Δ QTcF values greater than 30 ms were seen in 5 subjects during moxifloxacin treatment and one subject during doripenem 1000 mg treatment, respectively (Table 6). Subject 600032 experienced a time-matched QTcF increase of 40.3 ms (354.0 ms to 394.3 ms) at 0 h (predose) on Day 2 of doripenem 1000 mg treatment. No

additional increases ≥ 30 ms were observed for this subject at any subsequent time points.

4.2.8.1.3 Additional Analyses

The Sponsor conducted additional analyses similar to the primary analysis and categorical analysis using other correction methods for QT, namely, Bazett's correction, Population correction and Individual correction. The results with these correction methods were similar to the Fridericia's correction method used for the primary and categorical analyses.

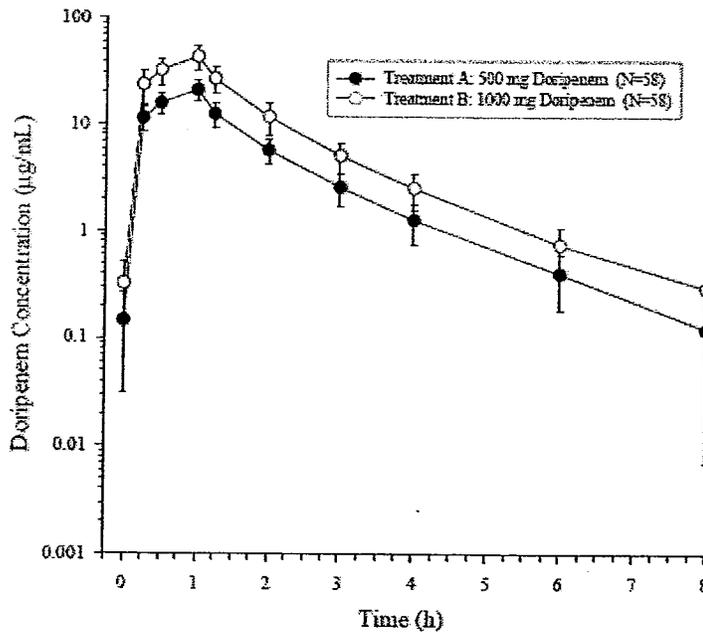
4.2.8.2 Safety Analysis

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

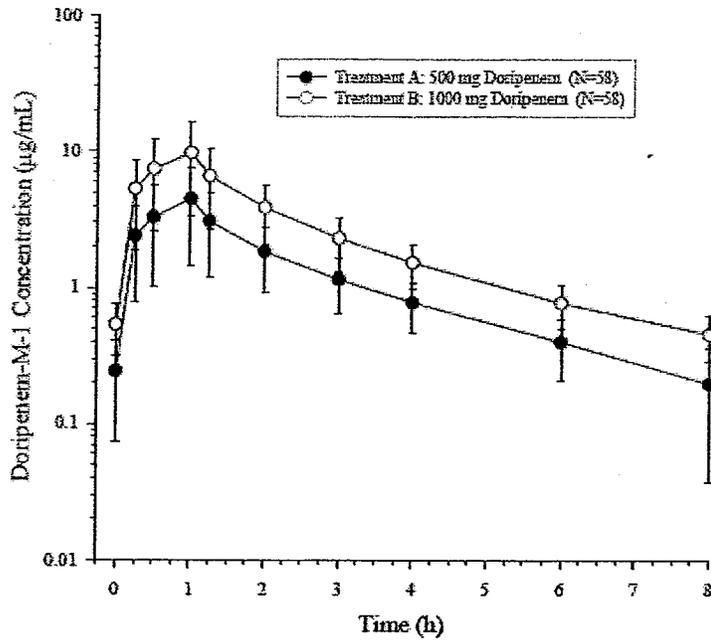
The mean plasma doripenem concentration time profiles for the 500 mg and 1000 mg doses are presented in Figure 3 (doripenem) and Figure 4 (doripenem-M-1). Peak plasma concentrations occurred at the end of infusion (median T_{max} = 1 h).

Figure 3. Mean (SD) Doripenem Plasma Concentration-Time Profiles



(Sponsor's Figure 2, page 49)

Figure 4. Mean (SD) Doripenem-M-1 Plasma Concentration-Time Profiles

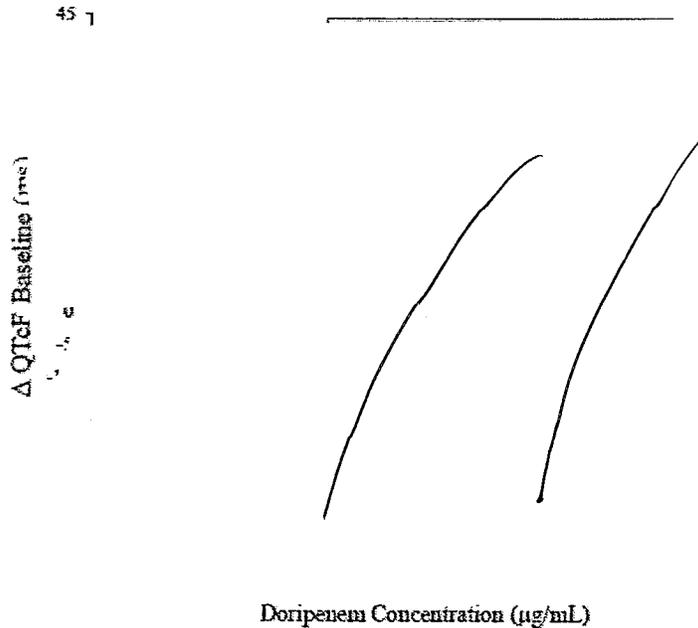


(Sponsor's Figure 3, page 51)

4.2.8.3.2 Exposure-Response Analysis

Figure 5 shows no apparent relationship was observed between Δ QTcF and doripenem plasma concentration.

Figure 5. Individual Δ QTcF vs. Doripenem Plasma Concentrations



(Sponsor's Figure 9, page 65)

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The Statistical Reviewer's evaluation is based on the sponsor's data and in accordance with ICH E14 guideline on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

The Statistical Reviewer used the following data set submitted in the NDA to carry out some of the independent analyses for statistical evaluation of the results:

\\cdsesub1\EVSPROD\NDA022106\0000\m5\datasets\dori-nos-1001\analysis\KECG2.XPT . This dataset is described in the \\cdsesub1\EVSPROD\NDA022106\0000\m5\datasets\dori-nos-1001\analysis\define.pdf file and it includes average values of the triplicate ECG measurements as well as the other derived ECG parameters and variables.

The statistical analysis consists of two parts: inferential analysis and categorical analysis. The former is performed by Statistical Reviewer, _____ and the latter by Regulatory Health Project Coordinator, Michael Li.

5.1.1 INFERENCE ANALYSIS

The Sponsor reported the primary analysis results based on a mixed effects model with the PD parameter of $\Delta QTcF$ as the dependent variable, and the independent variables being sequence, treatment, period, time point of measurement and subject. The Sponsor's analysis was the predefined analysis. To verify the Sponsor's results, the Statistical Reviewer performed additional analyses based on the time-matched raw mean difference in $QTcF$ of the drug and placebo after baseline adjustment at each time point.

In this study the time points of measurement were 0h, 0.5h, 1h, 1.25h, 2h, 3h, 4h, 6h, and 8h. The calculations for the Statistical Reviewer's analysis were done as follows:

1. Change from baseline in Fridericia-corrected QTc values were calculated for each subject at each time point of measurement for each of the treatment groups, doripenem 500 mg, doripenem 1000 mg, moxifloxacin 400 mg, and placebo. This is $\Delta QTcF(t,i)$, where t is time point of measurement and i is the index for i^{th} subject.
2. Difference of change from time-matched baseline in $QTcF$ for each dose of doripenem, or moxifloxacin vs. change from time-matched baseline $QTcF$ values for placebo was calculated. This is $\Delta \Delta_{D-P} QTcF(t,i) = \Delta_D QTcF(t,i) - \Delta_P QTcF(t,i)$, where D refers to the drug and P refers to Placebo.
3. Then, the endpoint of interest is the average of the above values over all subjects at

time point t . This is $\Delta \Delta_{D-P} QTcF(t) = \sum_N^{i=1} \frac{\Delta \Delta_{D-P} QTcF(t,i)}{N}$

4. If the upper bound of one-sided 95% confidence interval at each time point t is less than 10 ms, the study can be confirmed to be a negative QT study.

Table 7 shows the mean difference in change from time-matched baseline in QTcF values between drug and placebo at each time point of measurement in the study.

Table 7: ICH E14 Analysis—Mean Difference between Drug and Placebo of Change from Time-Matched Baseline QTcF values.

Time Point	Placebo/Moxifloxacin vs. Placebo/Placebo				Doripenem 500 mg/Placebo vs. Placebo/Placebo				Doripenem 1000 mg/Placebo vs. Placebo/Placebo			
	N	Raw Mean	SE	Lower bound of 1-sided 95% CI	N	Raw Mean	SE	Upper bound of 1-sided 95% CI	N	Raw Mean	SE	Upper bound of 1-sided 95% CI
0h	57	1.3	1.42	-1.0	57	1.1	1.52	3.6	58	0.9	1.56	3.5
0.5h	55	4.1	1.49	1.7	56	-0.7	1.24	1.3	56	1	1.54	3.5
1h	57	7.7	1.66	5.0	56	0.2	1.23	2.2	57	-0.2	1.58	2.4
1.25h	57	10.3	1.79	7.4	57	0.2	1.41	2.5	57	-0.1	1.72	2.7
2h	57	11	1.66	8.3	57	0.4	1.49	2.9	57	1.4	1.83	4.4
3h	57	12.8	1.75	9.9	57	-0.4	1.31	1.8	57	-2	1.52	0.5
4h	57	12.5	1.60	9.9	57	-1	1.42	1.3	57	-1.5	1.52	1.0
6h	57	10.5	2.07	7.1	57	0	1.89	3.1	57	-0.8	2.42	3.2
8h	57	11.4	1.77	8.5	57	-0.8	1.51	1.7	57	-1.7	1.80	1.3

N=Number of subjects with non-missing time-matched ECG values; SE = Standard Error ; CI = Confidence Interval; h=hour

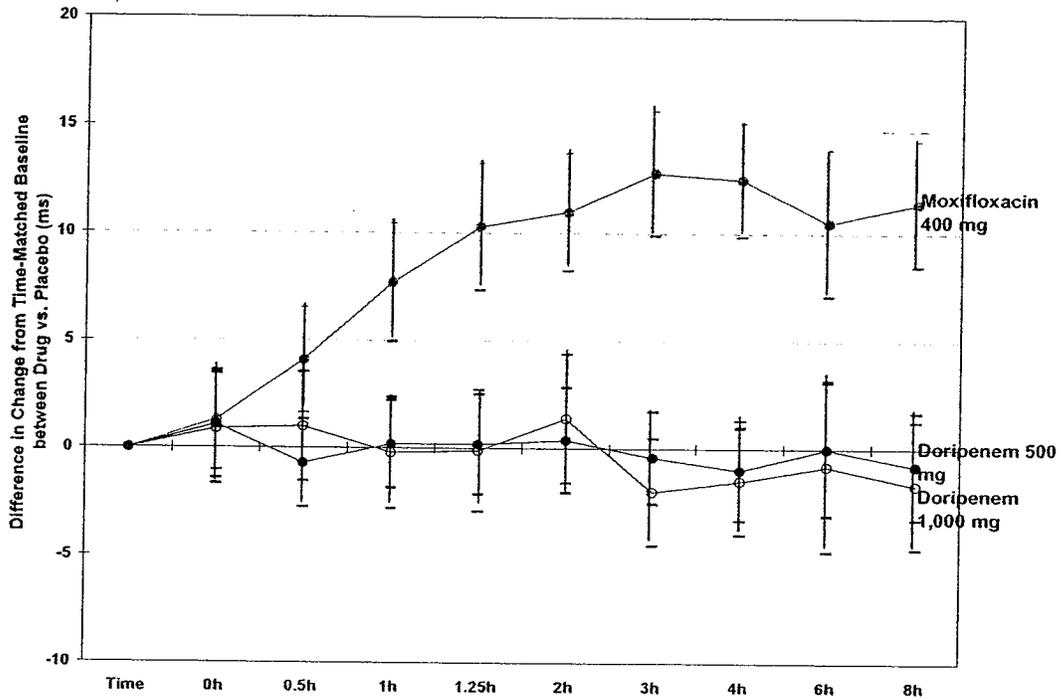
Source: FDA Statistical Reviewer's Analysis

Based on the above analysis (Table 7), the Statistical Reviewer makes the following conclusions:

- The lower bound of the one-sided 95% Confidence Interval on the raw mean difference in change from time-matched baseline between the moxifloxacin treatment group and placebo was 5 ms or higher at several time points of measurement post dose, namely, at 1h, 1.25h, 2h, 3h, 4h, 6h, and 8h. This analysis has validated the study. No multiple time point adjustment was performed for the moxifloxacin effect.
- In both doripenem dose groups (500 mg and 1,000 mg), the upper bound of the 95% CI on the raw mean difference in change from time-matched baseline between doripenem treatment group and placebo was less than 10 ms at all time points of measurement post dose.
- Therefore, this Statistical Reviewer's analysis confirms the Sponsor's results that this is a negative thorough QTc study. There is no evidence that doripenem at either doses of 500 mg or 1,000 mg prolongs the QTc interval.

Figure 6 shows a graphical depiction of the mean (and two-sided 90% CI) difference in change from time-matched baseline in QTcF values between drug versus placebo.

Figure 6: Mean and 90% CI of the difference in change from time-matched baseline in QTcF values between drug and placebo



(Source: FDA Statistical Reviewer's Analysis)

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5.1.2 CATEGORICAL ANALYSIS

The results for the categorical analysis are presented in the following tables.

Table 8: Frequency for QTcF > 450 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline- Dori 1000 mg IV/Pbo Oral	59	3	5.08	1593	8	0.50
Baseline- Dori 500 mg IV/Pbo Oral	58	0	0.00	1566	0	0.00
Baseline- Pbo IV/Moxi 400 mg Oral	58	1	1.72	1566	1	0.06
Baseline- Pbo IV/Pbo Oral	58	2	3.45	1566	2	0.13
Dori 1000 mg IV/Pbo Oral	59	2	3.39	1569	4	0.25
Dori 500 mg IV/Pbo Oral	58	0	0.00	1563	0	0.00
Pbo IV/Moxi 400 mg Oral	58	3	5.17	1562	6	0.38
Pbo IV/Pbo Oral	58	0	0.00	1563	0	0.00

Table 9: Frequency for QTcF > 500 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline- Dori 1000 mg IV/Pbo Oral	59	0	0.00	1593	0	0.00
Baseline- Dori 500 mg IV/Pbo Oral	58	0	0.00	1566	0	0.00
Baseline- Pbo IV/Moxi 400 mg Oral	58	0	0.00	1566	0	0.00
Baseline- Pbo IV/Pbo Oral	58	0	0.00	1566	0	0.00
Dori 1000 mg IV/Pbo Oral	59	0	0.00	1569	0	0.00
Dori 500 mg IV/Pbo Oral	58	0	0.00	1563	0	0.00
Pbo IV/Moxi 400 mg Oral	58	0	0.00	1562	0	0.00
Pbo IV/Pbo Oral	58	0	0.00	1563	0	0.00

Table 10: Frequency for Δ QTcF: 30 ~ 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Dori 1000 mg IV/Pbo Oral	59	2	3.39	1569	6	0.38
Dori 500 mg IV/Pbo Oral	58	5	8.62	1563	6	0.38
Pbo IV/Moxi 400 mg Oral	58	16	27.59	1562	34	2.18
Pbo IV/Pbo Oral	58	3	5.17	1563	3	0.19

Table 11: Frequency for $\Delta\text{QTcF} > 60$ ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Dori 1000 mg IV/Pbo Oral	59	0	0.00	1569	0	0.00
Dori 500 mg IV/Pbo Oral	58	0	0.00	1563	0	0.00
Pbo IV/Moxi 400 mg Oral	58	0	0.00	1562	0	0.00
Pbo IV/Pbo Oral	58	0	0.00	1563	0	0.00

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

- No additional analyses were conducted by the reviewer.
- The doses evaluated in the study are acceptable. The observed mean C_{max} for the suprathreshold dose was 44 µg/ml (SD = 11) for doripenem and 9.81 µg/ml (SD=6.45) for doripenem-M-1. These values cover the expected increase in C_{max} of both doripenem and the M1 metabolite in patients with renal impairment without dose adjustments (Table 12 and Figure 7). The sponsor is requesting dose adjustment in subjects with moderate to severe renal impairment (Table 1).

Table 12. Mean (SD) PK Parameters of Doripenem after a Single Dose of 500 mg (Study DORI-02)

PK Parameter	Groups A-D Normal	Group A Mild	Group B Moderate	Group C ESRI (Pre)	Group C ESRI (Post)	Group D Severe
N	8	6	6	3	3	6
C _{max} (µg/mL)	31.7 (9.20)	41.3 (9.42)	38.5 (5.95)	15.5 (1.96)	33.7 (5.50)	36.4 (6.28)
t _{max} (hr) ^a	0.5 (0.50-0.50)	0.5 (0.50-0.50)	0.5 (0.25-0.50)	0.25 (0.25-0.25) ^b	0.5 (0.50-0.50)	0.5 (0.25-0.75)
AUC _∞ (µg·hr/mL)	37.3 (5.35)	61.4 (18.0)	106 (18.6)	99.9 (8.46) ^c	287 (118)	190 (26.4)
t _{1/2} (hr)	1.11 (0.192)	1.31 (0.377)	2.67 (0.638)	8.87 (1.59)	6.27 (1.10)	4.62 (0.496)
CL (L/hr)	13.7 (1.98)	8.64 (2.05)	4.84 (0.750)	5.03 (0.427) ^d	1.99 (0.906)	2.68 (0.389)
V _d (L)	16.5 (3.57)	13.3 (5.07)	15.7 (3.33)	51.7 (9.09) ^d	16.9 (3.67)	16.8 (2.77)

Pre = pre-dialysis infusion, Post = post dialysis infusion.

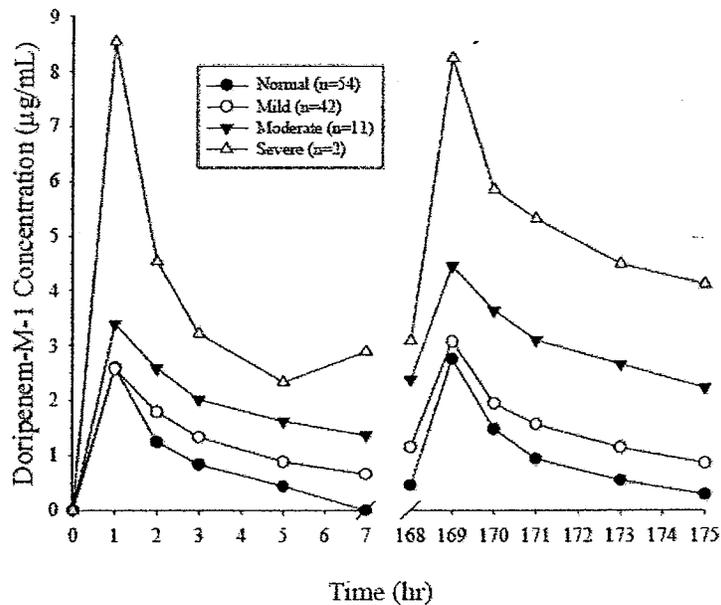
^a Median (range); ^b Underestimate, no samples were taken at end of infusion.

^c Likely to be overestimated; ^d Likely to be underestimated.

Source: Mod5.3.3\DORI-02\Appendix 12 (Tables 1.11, 1.13, 1.15, 1.17, 1.18).

(Sponsor's Table 29 on page 55 of Clinical Pharmacology Summary)

Figure 7. Mean Plasma Concentration vs. Time Profile in Patients from the Phase 2 cUTI Study (DORI-03)



Note: Plasma concentrations have been normalized to a 500 mg dose
(Sponsor's Figure 12, page 83 of Clinical Pharmacology Summary)

5.3 MEDICAL ASSESSMENTS

5.3.1 ADVERSE EVENTS

None of the following events were observed during the trial: torsades de pointes, sudden death ventricular tachycardia or fibrillation, syncope or seizures (Appendix 3.6 "Adverse Events"). No deaths or serious adverse events occurred. No subject withdrew from the study due to an adverse event.

No significant changes in vital signs were noted.

5.3.2 ECG WAREHOUSE

No independent review of ECG tracings was performed.

APPENDIX

5.4 TABLE OF STUDY ASSESSMENTS

Table 4: Serial ECGs, PK Blood Sample, and Vital Signs Collection Schedule (Study DORI-NOS-1001)

Study Day	Time (h)	Serial 12-Lead ECG ^{a,b}	PK Samples ^{b,c}	Comments
-2				Sitting vital signs taken
-1	0 (predose)	X		The 0h time on Day -1 corresponded to the 0h time on Day 2.
	0.5	X		
	1.0	X		
	1.25	X		
	2	X		
	3	X		
	4	X		
	6	X		
	8	X		
1	0 (predose)		X	1-hour i.v. infusion from ≈8:00 a.m. to ≈9:00 a.m.
	8		X	1-hour i.v. infusion from ≈4:00 p.m. to ≈5:00 p.m.
	16		X	1-hour i.v. infusion from ≈midnight to ≈1:00 a.m.
2	0 (predose)	X	X	<ul style="list-style-type: none"> The 0h time on Day 2 corresponded to the 0h time on Day -1. Single dose of oral study drug administered at ≈8:00 a.m. with 180 mL of noncarbonated water under fasted conditions immediately before i.v. infusion. 1-hour i.v. infusion for Day 2 from ≈8:00 a.m. to ≈9:00 a.m.
	0.25		X	
	0.5	X	X	
	1.0	X	X	ECG first, then PK blood sample collection immediately before completion of infusion
	1.25	X	X	
	2	X	X	
	3	X	X ^d	
	4	X	X	
	6	X	X	
	8	X	X	
	12		X	
3				Sitting vital signs taken

^a Three 10-second ECGs were recorded at 60-second intervals for each time point. ECGs were read centrally. Subjects were to rest in a supine position for at least 5 minutes before each ECG recording.

^b At the scheduled time point, the following order took place: ECG was collected first, then the PK blood sample. The PK blood sample had to be collected within 5 minutes after the last of the triplicate ECG recordings.

^c A 3-mL blood sample was collected for the determination of the plasma concentrations of doripenem and doripenem-M-1.

^d One additional 3-mL blood sample was collected for the determination of the plasma concentrations of moxifloxacin.

Cross Reference: Appendix 1.1

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Rafia Bhore
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Stephen Grant
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