SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Doripenem for Injection NAME OF ACTIVE INGREDIENT(S): Doripenem	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: JNJ-381740942: DORI-10 CR005386 **Title of Study:** A Multicenter, Randomized, Open-Label, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem with that of Intravenous Imipenem in Ventilator-Associated Pneumonia		
Coordinating Investigator: Professor Jean Chastre, M.D., Groupe Hospitalier Pitie Salpetriere, Paris, France		
Publication (Reference): None at the time of this report.		
Study Initiation/Completion Dates: 14 June 2004 to 05 October 2006		**Phase of development:** 3

Primary Objective:

- To compare the clinical response rate of intravenous (i.v.) doripenem vs. i.v. imipenem at the test-of-cure visit (TOC). The TOC visit was conducted 7 to 14 days after the completion of i.v. study drug therapy.

Secondary Objectives:

- To compare the per subject microbiological response rate of i.v. doripenem vs. i.v. imipenem at the TOC visit;
- To compare the emergence of study drug-resistant *Pseudomonas aeruginosa* after initiation of i.v. study drug therapy through the late follow-up (LFU) visit, in the i.v. doripenem group vs. the i.v. imipenem group;
- To compare the per pathogen microbiological outcome rate, and also the per pathogen clinical cure rate of i.v. doripenem vs. i.v. imipenem at the TOC visit;
- To compare the all-cause mortality rate at 28 days post start of therapy in i.v. doripenem group vs. i.v. imipenem group;
- To compare the safety profile of i.v. doripenem with that of i.v. imipenem.

Methodology: This was a Phase 3, multicenter, prospective, randomized (1:1), open-label study (but with in-house blinding) of doripenem 500 mg q8h i.v. 4-hour infusion versus imipenem 500 mg q6h i.v. 30-minute infusion or 1000 mg q8h i.v. 60-minute infusion, in the treatment of adults with VAP. Randomization was stratified by region (North America, South America, and Other) and within each region by duration of mechanical ventilation (early-onset VAP [defined as < 5 days] vs. late-onset VAP [defined as ≥ 5 days]) and severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score ≤ 15 or > 15). For subjects who met the criteria for VAP, a specimen of lower respiratory tract (LRT) secretions was obtained by endotracheal aspiration (or bronchoscopy, if scheduled) prior to inclusion in the study and randomization. Concomitant amikacin and vancomycin therapies were permitted for *P. aeruginosa* and for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, respectively. The TOC and LFU visits were scheduled at 7 to 14 days and 28 to 35 days after completion of i.v. study drug therapy, respectively.

SYNOPSIS (CONTINUED)

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Number of Subjects: 531 randomized (264 doripenem; 267 imipenem), 525 received study drug therapy (Intent-to-Treat [ITT]); 248 were clinically evaluable (CE) at TOC (126 doripenem, 122 imipenem); 226 were microbiologically evaluable (ME) at TOC (116 doripenem, 110 imipenem); and 501 were included in the clinical modified ITT (cMITT) (249 doripenem, 252 imipenem) analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects included male and female patients aged ≥ 18 years with clinical evidence of VAP, on mechanical ventilation for > 24 h or weaned from mechanical ventilation within 72 h, and requiring i.v. therapy. This included both early-onset and late-onset VAP.

Test Product, Dose and Mode of Administration: Doripenem for Injection 500 mg administered by i.v. infusion over 4 hours q8h.

Reference Therapy, Dose and Mode of Administration: Imipenem 500 mg administered by i.v. infusion over 30 minutes q6h or 1000 mg by i.v. infusion over 60 minutes q8h.

Duration of Treatment: 7 to 14 days of i.v. study drug therapy only.

Criteria for Evaluation:

- **Efficacy**: The clinical cure rate at the TOC visit (in the CE at TOC analysis set) and the clinical cure rate in the cMITT analysis set were the co-primary efficacy analyses, respectively. Key secondary efficacy endpoints included clinical cure rate at the TOC visit (in the ME at TOC analysis set); favorable per-subject microbiological response (i.e., eradication or presumed eradication) rate at the TOC visit (in the ME at TOC analysis set); and decreased susceptibility rates for *P. aeruginosa* that were isolated from post-baseline LRT culture specimens (in the cMITT analysis set).
- **Safety**: Safety was assessed through monitoring of adverse events (AEs), physical examinations, vital signs, and the collection of clinical laboratory data (serum chemistry, hematology, and urinalysis).

Statistical Methods: The primary efficacy analysis was to establish non-inferiority of doripenem to imipenem at the TOC visit in the CE at TOC analysis set. Non-inferior efficacy of doripenem was concluded if the lower limit of the 2-sided 95% confidence interval (CI) for the difference in clinical cure rates (doripenem minus imipenem) was ≥ -20%. The clinical cure rate in the cMITT analysis set was a co-primary analysis. Both co-primary analyses were conducted using normal approximation to the difference between 2 binomial distributions with continuity correction. Safety analyses were conducted in the ITT analysis set. Safety endpoints included the proportion of subjects in each treatment group with any treatment emergent AE (TEAE), the proportion who experienced any TEAE that resulted in discontinuation of study drug therapy, the proportion of serious adverse events (SAEs) observed during study drug therapy administration and up to 30 days post-therapy, and the proportion of subjects with laboratory abnormalities.

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DEMOGRAPHICS AND BASELINE CHARACTERISTICS

In general, the demographic and baseline characteristics of subjects assigned to the doripenem and the imipenem treatment arms were similar. The CE at TOC analysis set was predominantly male (nearly 80% overall) and Caucasian (86% overall); with a mean age of 51 years. High risk subjects were well represented in this study; almost 30% overall were ≥ 65 years old, 61% had late-onset VAP (ventilated ≥ 5 days), 52% had APACHE II scores of >15 and 21% had APACHE II scores of >20.

EFFICACY RESULTS:

The primary and co-primary analyses clearly showed that doripenem was not inferior to imipenem in the treatment of VAP.

	DORIPENEM			IMIPENEM				
	N	n	%	N	n	%	Diff (%)	95% CI
Primary Analysis Results								
Clinically Evaluable at TOC (TOC visit)	126	86	68.3	122	79	64.8	3.5	(-9.1; 16.1)
Clinical MITT	244	144	59.0	249	144	57.8	1.2	(-7.9; 10.3)

Key Secondary Analysis Results

The clinical cure rate in the ME at TOC analysis set was 69.0% in the doripenem treatment arm compared with 64.5% in the imipenem treatment arm (diff: 4.4%; CI: –8.7% to 17.6%).

Favorable per-subject microbiological response rate (eradication or presumed eradication of all baseline LRT pathogens) in the ME at TOC analysis set was 73.3% in the doripenem treatment arm compared with 67.3% in the imipenem treatment arm (diff: 6.0%; CI: –6.8% to 18.8%).

Overall, 14/25 (56%) of *P. aeruginosa* isolates in the imipenem arm were either resistant at baseline or became resistant on therapy compared with 5/28 (18%) in the doripenem arm.

All additional analyses confirmed the results of the primary and key secondary analyses.

SAFETY RESULTS:

As can be seen in the incidence of treatment-emergent adverse events (TEAE)s summarized below, the safety profiles of doripenem and imipenem were similar.

Safety Outcome	DORIPENEM (N=262) n (%)	IMIPENEM (N=263) n (%)	Total (N=525) n (%)
Any TEAE	249 (95.0)	238 (90.5)	487 (92.8)
Any Study Drug Related TEAE (a)	45 (17.2)	46 (17.5)	91 (17.3)
Any Serious TEAE	70 (26.7)	72 (27.4)	142 (27.0)
Any Study Drug Related Serious TEAE (a)	5 (1.9)	4 (1.5)	9 (1.7)
Discontinuation Due to TEAE	17 (6.5)	15 (5.7)	32 (6.1)
Discontinuation Due to Study Drug Related TEAE	8 (3.1)	7 (2.7)	15 (2.9)
Deaths	35 (13.4)	32 (12.2)	67 (12.8)

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The most frequently reported treatment-emergent adverse events were within the gastrointestinal system organ class (48%, doripenem; 45%, imipenem) and the infections and infestations system organ class (47%, doripenem; 44%, imipenem).

Likewise, the incidence of laboratory abnormalities was similar in the treatment arms and there were no unexpected safety signals in either treatment arm.

Although the number of seizures was low in both treatment arms (3 doripenem and 10 imipenem), the difference between the treatment arms is in keeping with preclinical data indicating a low propensity of doripenem to induce seizures. The potential lower risk of seizures with doripenem therapy compared with imipenem therapy may be particularly important in subjects with both known or previously unknown risk factors.

SUMMARY - CONCLUSIONS

- The primary and co-primary analyses clearly showed that doripenem was not inferior to imipenem in the treatment of VAP. All additional analyses confirmed these results.
- The clinical and microbiological success rates for infections caused by *Pseudomonas aeruginosa* were approximately twice as high in the doripenem than in the imipenem treatment arm (80% vs. 43% for clinical cure and 65% vs. 36% for microbiological outcome). However, the sample sizes were small and the differences did not reach statistical significance.
- Favorable per pathogen microbiological outcome rates and clinical cure rates were also higher for doripenem when *Klebsiella* spp or *Escherichia coli* were identified in the LRT at baseline. However, there were higher clinical cure rates in subjects with MSSA and *H. influenzae* infections treated with imipenem than with doripenem.
- The safety profiles of doripenem and imipenem were similar and there were no unexpected safety signals in either treatment arm.

In conclusion, the results of this study clearly demonstrated that the efficacy of doripenem was non-inferior to that of imipenem in treating ventilator-associated nosocomial pneumonia and that the safety profiles were similar.

Date of the report: 14 May 2007

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