SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Doripenem for Injection NAME OF ACTIVE INGREDIENT(S): Doripenem	Volume: Page:	

Protocol No.: JNJ-38174942: DORI-09

Title of Study: A Multicenter, Randomized, Open-Label, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem with that of Intravenous Piperacillin/Tazobactam in Hospital-Acquired Pneumonia

Coordinating Investigator: Eric Schroeder, 20375 W. 151st Street, Suite 451, Olathe, KS 66061, USA

Publication (Reference): None at the time of this report.

Study Initiation/Completion Dates: 14 June 2004 to 27 October 2006	**Phase of development:** 3

Primary Objective: To compare the clinical cure rate of intravenous (i.v.) doripenem vs. i.v. piperacillin/tazobactam at the Test of Cure visit (TOC) in subjects with hospital-acquired pneumonia (synonymous with nosocomial pneumonia, NP). The TOC visit was conducted 7 to 14 days after the completion of study drug therapy (i.v. and oral).

Secondary Objectives:

- Compare the clinical response rate of i.v. doripenem vs. i.v. piperacillin/tazobactam at the end of i.v. therapy (EOT[i.v.]) and late follow up (LFU) visits.
- Compare the per-subject microbiological response rate of i.v. doripenem vs. i.v. piperacillin/tazobactam at the TOC and LFU visits.
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- Compare the safety profile of i.v. doripenem with that of i.v. piperacillin/tazobactam.
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Methods: This was a Phase 3, multicenter, prospective, randomized (1:1), open-label study (but with in-house blinding) of doripenem 500 mg q8h i.v. 60-minute infusion versus piperacillin/tazobactam 4.5 g q6h i.v. 30 minute infusion in non-ventilated subjects and subjects with early-onset ventilator associated pneumonia (VAP)(< 5 days of mechanical ventilation). Randomization was stratified by mechanical ventilation association (non-ventilator associated vs. early-onset VAP), and severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II score ≤ 15 or > 15), and geographic region (North America, South America and Europe/Other). In all subjects, an adequate sputum specimen was collected within 24 hours of enrollment and prior to the initiation of study drug therapy. To allow for the hospital discharge of subjects who improved during the study, a transition from i.v. to oral antibacterial therapy was permitted. After 72 hours of i.v. study drug therapy (9 doses of doripenem or 12 doses of piperacillin/tazobactam), subjects could have been switched to oral study drug therapy (levofloxacin 750 mg daily) if they met all of the criteria, indicating sufficient clinical improvement. Although investigators had the option to switch to oral therapy, they were encouraged to continue i.v study drug for the entire duration of therapy. Adjunctive amikacin therapy was initiated with the initiation of i.v. study drug therapy for potential *Pseudomonas aeruginosa* infection, as indicated by the product label in some countries. If *P. aeruginosa* infection was confirmed, treatment with amikacin was to be continued in subjects assigned to the piperacillin/tazobactam arm (as per the product label) for approximately 5 days. In subjects assigned to doripenem, amikacin therapy was discontinued, at the discretion of the investigator, if the subject had improved clinically and the *P. aeruginosa* isolate was not resistant to meropenem. Concomitant vancomycin therapy was permitted for methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The sponsor assessed subject evaluability for primary and secondary endpoints in a blinded fashion.

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The TOC and LFU visits were scheduled at 7 to 14 days and 28 to 35 days after the final dose of study drug therapy, respectively.		
Number of Subjects (planned and analyzed): 440 planned (220 per treatment arm); 448 randomized (225 doripenem; 223 piperacillin/tazobactam), 444 received study drug therapy (ITT or safety); 253 were clinically evaluable (CE) at TOC (134 doripenem, 119 piperacillin/tazobactam), 167 were microbiologically evaluable (ME) at TOC (84 doripenem, 83 piperacillin/tazobactam); and 429 were included in the clinical modified Intent-to-treat (cMITT) (217 doripenem, 212 piperacillin/tazobactam) analysis set.		
Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥ 18 years with clinical evidence of NP who were hospitalized for ≥ 48 hours, or those with prior hospital admission of at least 48 hours who were discharged within the last 7 days.		
Test Product, Dose and Mode of Administration, Batch No.: Doripenem for Injection 500 mg administered by i.v. infusion over 1 hours q8h. See Table 2 in the body of the report for batch numbers.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Piperacillin/tazobactam 4.5 g administered by i.v. infusion over 30 minutes q6h. See Table 2 in the body of the report for batch numbers.		
Duration of Treatment: 7 to 14 days (i.v. only or i.v. plus oral)		
Criteria for Evaluation: **Efficacy**: The primary efficacy endpoint was the clinical cure rate at the TOC visit. The primary efficacy analyses were performed in the primary efficacy analysis set, CE at TOC, and in the co-primary cMITT (using the cMITT_1 analysis) analysis set. Secondary efficacy endpoints included clinical cure rate at TOC (in the ME at TOC analysis set); clinical cure rate in the cMITT analysis set (using the cMITT_2 analysis); per-subject favorable microbiological response (i.e., eradication or presumed eradication) in the ME at TOC. **Safety**: Safety was assessed through monitoring of adverse events (AEs), physical examinations, vital signs, and the measurement of clinical laboratory data (serum chemistry, hematology, and urinalysis) at a central laboratory.		
Statistical Methods: The primary efficacy analysis was to establish non-inferiority of doripenem to piperacillin/tazobactam at the TOC visit in the CE at TOC analysis set. Non-inferior efficacy of doripenem was concluded if the lower limit of the 2-sided 95% confidence interval (CI) for the difference in clinical cure rates (doripenem minus piperacillin/tazobactam) was ≥ –20%. The clinical cure rate at TOC in the mMITT analysis set was a co-primary analysis. The 2-sided 95% CI was calculated using the normal approximation to the difference of 2 binomial proportions with continuity correction.. Safety analyses were conducted in the ITT analysis set. Safety endpoints included the proportion of subjects in each treatment group with any treatment-emergent adverse events (TEAEs), the proportion who experienced any TEAE that resulted in discontinuation of study drug therapy, the proportion of serious adverse events (SAEs) observed during study drug therapy administration and up to 30 days post-therapy (i.v. and oral), and the proportion of subjects with laboratory abnormalities.		

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SUMMARY OF RESULTS AND CONCLUSIONS

Disposition And Demographic And Baseline Characteristics: In general, the demographics of the study population were well balanced between treatment groups and consistent with those of published studies. As seen in other trials, subjects were predominantly male. Higher risk subjects were well represented; 45% of subjects overall were ≥65 years old and 22% of these subjects ≥75 years old, 22% had early-onset VAP, and 25% had APACHE II scores of greater than 15. The frequency distribution of respiratory pathogens isolated at baseline was generally comparable in the 2 treatment arms. Overall, *P. aeruginosa* was the most common pathogen isolated in the ME population. The rate of resistance to the study drug received was notably higher to piperacillin/tazobactam in some important pathogens isolated at baseline, including *Klebsiella pneumoniae* (0%, doripenem; 34%, piperacillin/tazobactam) and *P. aeruginosa* (0%, doripenem; 50%, piperacillin/tazobactam).

Efficacy Results: The primary and co-primary analyses clearly showed that doripenem was non-inferior in efficacy to piperacillin/tazobactam in the treatment of NP.

	DORIPENEM			PIPERACILLIN/ TAZOBACTAM				
Clinical Cure Rates by Analysis Set	N	n	%	N	n	%	Diff (%)	95% CI
Primary Analysis Results								
Clinically Evaluable at TOC (TOC visit)	134	109	81.3	119	95	79.8	1.5	(-9.1; 12.1)
Clinical MITT (Using cMITT_1 Analysis)	213	148	69.5	209	134	64.1	5.4	(-4.1; 14.8)

Secondary efficacy analyses showed doripenem was clinically effective in the treatment of NP, and therapeutically non-inferior to piperacillin/tazobactam. The difference in outcomes between treatment groups in all analysis sets favored doripenem. The clinical cure rate in the mMITT analysis set, which includes subjects with resistant pathogens at baseline, was comparable between the two treatment arms. Because of the greater rate of baseline resistance to piperacillin/tazobactam, a difference between the two treatments arms would have been expected. However, such a difference was not seen, probably due to aminoglycoside adjunctive therapy, which was widely prescribed and may have made up for the lack of efficacy of the study drug against such resistant pathogens.

	DORIPENEM			PIPERACILLIN/ TAZOBACTAM				
Clinical Outcome by Analysis Set	N	n	%	N	n	%	Diff (%)	95% CI
Clinical Cure Rates - Secondary Analysis Set								
Microbiologically Evaluable at TOC	84	69	82.1	83	65	78.3	3.8	(-9.4; 17.1)
Clinical MITT (Using cMITT_2 Analysis)	217	154	71.0	212	143	67.5	3.5	(-5.7; 12.7)
Microbiological MITT	139	94	67.6	144	97	67.4	0.3	(-11.4; 11.9)

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The favorable per-subject microbiological response rate in the ME at TOC analysis set was high and similar between the 2 treatment arms in the ME at TOC analysis set (84.5% in doripenem-treated subjects and 80.7% in piperacillin/tazobactam-treated subjects). The difference between the favorable microbiological response rates (doripenem minus piperacillin/tazobactam) was 3.8% (2 sided 95% CI of –8.9% to 16.5%).

Relapse rates at the LFU were low in both treatment groups. There were no microbiological recurrences observed.

Safety Results: The total extent of exposure to study drug therapy was similar in both treatment arms for both the ITT and CE at TOC analysis sets. The median total duration of study drug therapy (i.v. plus oral) was 11 days in both the doripenem and piperacillin/tazobactam treatment arms for both analysis sets. In doripenem and piperacillin/tazobactam treatment arms, 54% and 59% of subjects, respectively, received only i.v. study drug therapy and in both groups were treated for a median of 10 days.

As can be seen in the incidence of TEAEs summarized below, the safety profiles of doripenem and piperacillin/tazobactam were similar.

Safety Outcome	DORIPENEM (N=223) n (%)	PIPERACILLIN/ TAZOBACTAM (N=221) n (%)	Total (N=444) n (%)
Any Treatment-Emergent Adverse Event (TEAE)	171 (76.7)	172 (77.8)	343 (77.3)
Any Study Drug Related TEAE	36 (16.1)	39 (17.6)	75 (16.9)
Any Serious TEAE	67 (30.0)	58 (26.2)	125 (28.2)
Discontinuation Due to TEAE	9 (4.0)	14 (6.3)	23 (5.2)
Discontinuation Due to Study Drug Related TEAE	3 (1.3)	3 (1.4)	6 (1.4)
Deaths	43 (19.3)	39 (17.6)	82 (18.5)

Diarrhea was the most frequently reported TEAE (~10% of subjects per treatment arm). Most events were mild or moderate in severity and were attributable to the index infection or complications of underlying medical conditions. No SAEs or AEs leading to death was considered related to study drug therapy. Although seizures are a concern in the carbapenem class, these were equally uncommon in both treatment groups (3 doripenem-treated subjects; 6 piperacillin/tazobactam-treated subjects). Likewise, the incidence of laboratory abnormalities was similar in the treatment arms and there were no unexpected safety signals in either treatment arm.

CONCLUSIONS:

The results of this study clearly demonstrated that the efficacy of doripenem was non-inferior to that of piperacillin/tazobactam and that the safety profiles were similar in subjects with NP.

Date of the report: 14 May 2007

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