Name of Company: Peninsula Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: Doripenem for Injection		
Name of Active Ingredient(s): Doripenem		

Title of Study: A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem with that of Meropenem in Complicated Intra-abdominal Infections (JNJ-38 174942; DORI-08 CR005389)

Number of Study Center(s): A total of 44 centers (21 in the United States, 10 in Europe, 10 in South America, and 3 in Canada) randomized 486 patients in this study.

Publication (reference): None.

Study Initiation/Completion Dates: Date study initiated: 03 May 2004; Date study completed: 27 March 2006

Phase of Development: 3

Primary Objective: To compare the clinical response of doripenem vs. meropenem in hospitalized patients with complicated intra-abdominal infections (cIAI) at the test-of-cure (TOC) visit (4 to 6 weeks after the completion of study drug therapy).
Secondary Objectives: To compare 1) the microbiological response at the TOC visit; 2) the safety profile of doripenem with that of meropenem.

Methods: This was a Phase 3, multicenter, prospective, randomized, double-blind, double-dummy study of doripenem, administered as a 1-hour IV infusion (500 mg q8h) vs. meropenem, administered as a 3- to 5-minute IV bolus (1 g q8h) in the treatment of cIAI in adults. The study was blinded using either placebo meropenem for patients receiving doripenem or placebo doripenem for patients receiving meropenem. Randomization was stratified by region (North America, South America, or Europe) and within each region by primary site of infection (complicated localized appendicitis vs. diagnosis of other sites of intra-abdominal infections [IAIs]) and severity of illness (APACHE II score ≤10 or >10). Intra-abdominal culture specimens (both aerobic and anaerobic) were collected at the time of the initial procedure (within 24 hours of enrollment). Blood culture samples were drawn from all patients. After ≥9 doses of IV study drug therapy (or equivalent if dose adjusted for renal impairment), patients could have switched to oral amoxicillin/clavulanate therapy (875/125 mg twice daily) if the following criteria were met: temperature and WBC count were decreasing relative to baseline values (if increased at baseline); cIAI signs and/or symptoms were absent/improved relative to those at baseline; and normal bowel function had returned.

Number of Patients (planned and analyzed): 472 planned (236 per treatment arm); 486 randomized (249 doripenem, 237 meropenem), 475 received study drug therapy (ITT or safety; 242 doripenem, 233 meropenem); 315 were microbiologically evaluable (ME) at TOC (162 doripenem, 153 meropenem); and 385 were included in the microbiological modified ITT (mMITT) analysis set (200 doripenem, 185 meropenem).

Diagnosis and Main Criteria for Inclusion: Male and female patients ≥18 years with clinical evidence of IAI, and with planned/recent (within 24 hours) operative/percutaneous drainage of an infection focus, confirming the presence of cIAI.

Test Product, Dose, and Mode of Administration, Batch Numbers: Doripenem for Injection 500 mg given by IV infusion over 1 hour q8h.

Duration of Treatment: 5 to 14 days (IV only or IV plus oral)

Reference Therapy, Dose, and Mode of Administration, Batch Number: Meropenem 1 g given by IV bolus over 3-5 min q8h.

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Criteria for Evaluation:
Efficacy: Primary efficacy endpoints included clinical cure rate at TOC (21-60 days post-therapy) in the ME at TOC analysis set and the clinical cure rate at any time up to 60 days after the last dose of study drug therapy in the mMITT analysis set. Secondary efficacy endpoints included clinical cure rates at the EFU visit (6-20 days post-therapy), and per-patient microbiological cure rates (i.e., eradication or presumed eradication of all baseline pathogens) at the EFU and TOC visits.
Safety: Safety was assessed through monitoring of adverse events, including possible allergic reactions and study drug intolerability, physical examinations, vital sign measurements, and clinical laboratory data (serum chemistry, hematology, and urinalysis).

Statistical Methods: The primary efficacy analysis was to establish non-inferiority of doripenem to meropenem at TOC in the ME at TOC and mMITT analysis sets. Non-inferior efficacy of doripenem was concluded if the lower limit of the 2-sided 95% CI around the treatment difference (doripenem minus meropenem) in the proportion of patients who were classified as a clinical cure was ≥ -15%. This difference and the corresponding CI were obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method). Safety analyses were conducted on the ITT analysis set. Safety endpoints included the proportion of patients with any treatment-emergent adverse event (TEAE), the proportion with any TEAE resulting in discontinuation of study drug therapy, and the proportion with serious adverse events (SAEs) during study drug therapy and up to 30 days after the last dose of study drug therapy.

Summary and Conclusions:
Disposition, Demographics, and Baseline Characteristics: The most common baseline intra-abdominal pathogens (in mMITT patients) included *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus intermedius, Enterococcus faecalis, Bacteroides caccae, Bacteroides thetaiotaomicron, Bacteroides fragilis,* and *Bacteroides uniformis,* with similar proportions in the 2 treatment arms. Overall, patients in the ME at TOC analysis set were predominantly male (64.2%, doripenem; 64.1%, meropenem), and Caucasian (79.0%, doripenem; 86.3%, meropenem) with a mean age of 45 years (44.7 years, doripenem; 44.8 years, meropenem); 16% of patients were 65 years of age or older and 4% were 75 years of age or older.
There were no notable differences between the 2 treatment arms with respect to demographic and baseline characteristics in the ME at TOC analysis set. Similar demographic and baseline characteristics were seen in the 2 treatment arms in the ITT and mMITT analysis sets.
Efficacy Results: For the primary efficacy analysis, the clinical cure rates at TOC (21-60 days post-therapy) and at any time up to 60 days after the last dose of study drug therapy were similar in both treatment arms in both the ME at TOC and mMITT analysis sets, respectively. In the ME at TOC analysis set, the lower bound of the 2-sided 95% CI around the treatment difference was > -15%, confirming that doripenem therapy was non-inferior to meropenem. Results from the mMITT analysis set were consistent with those of the ME at TOC analysis set. Results of the sensitivity analyses on the primary endpoint were consistent with those of the primary analyses.

Analysis Set	Doripenem	Meropenem	Difference (2-sided 95% CI)
Microbiologically Evaluable at TOC	135/162 (83.3%)	127/153 (83.0%)	0.3% (-8.6%, 9.2%)
mMITT (CR_1_mMITT)	149/200 (74.5%)	140/185 (75.7%)	-1.2% (-10.3%, 8.0%)

The secondary efficacy analysis results support those of the primary analyses.

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Clinical cure rates at the EFU visit were comparable between the 2 treatment arms for both the CE/ME at EFU analysis sets. Doripenem therapy was effective against major causative pathogens of cIAI, including *E. coli, K. pneumoniae, P. aeruginosa, S. intermedius, B. caccae, B. thetaiotaomicron, B. fragilis,* and *B. uniformis.* For anaerobic pathogens, including both gram-positive and gram-negative isolates, favorable per pathogen microbiological outcomes (eradication or presumed eradication) of 84% and 79% at TOC were seen in the doripenem and meropenem treatment arms, respectively. Per-patient microbiological cure rates at TOC were similar for both treatment arms.

Safety Results: Doripenem (500 mg administered by IV infusion over 1 hour q8h) was generally safe and well tolerated by patients ≥18 years with cIAI. Overall, the type and incidence of TEAEs were similar in both treatment arms, and no unexpected safety signals were found. Most events were mild or moderate in severity. Similar proportions of patients in both treatment arms reported allergic reactions, possible study drug intolerability, and phlebitis. No seizures were reported. Nausea was the most frequently reported TEAE (10% of patients per treatment arm), and also the most frequently reported study drug related AE (4%, doripenem; 3%, meropenem). Most cases of nausea were mild or moderate in severity, and resulted in study drug therapy discontinuation in 1 doripenem-treated patient.

Treatment-emergent SAEs were reported in 17% and 19% of doripenem- and meropenem-treated patients, respectively; 19 patients died (8, doripenem; 11, meropenem), and no reported SAEs were related to study drug therapy.

Treatment-emergent adverse events leading to study drug therapy discontinuation were reported in 4% of patients in each treatment arm. Elevated ALT and AST values above 3xULN were uncommon during this study. One doripenem-treated patient and 2 meropenem-treated patients met the definition of Hy's High Risk classification (i.e., ALT > 3xULN and bilirubin > 1.5xULN); these patients did not have any evidence of drug-induced liver disease.

Overall, no unexpected clinically significant changes in vital sign measurements were observed.

Conclusions:

Doripenem was clinically effective in the treatment of patients with cIAI and therapeutically non-inferior to meropenem.

Doripenem was microbiologically effective against major causative pathogens of cIAI at the TOC visit including *E. coli, K. pneumoniae, P. aeruginosa, S. intermedius, B. fragilis, B. caccae, B. thetaiotaomicron,* and *B. uniformis* with similar per-patient microbiological cure rates in both treatment arms and high per-patient microbiological cure rates at the TOC visit.

Doripenem was clinically effective at the EOT(IV) with clinical cure/improvement rates greater than 90%.

Doripenem was clinically and microbiologically effective at the EFU visit.

Doripenem was generally safe and well tolerated with a safety profile similar to that of meropenem.

Date of the Report: 02 November 2006

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