Name of Company: Peninsula Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier:**	*(For National Authority Use Only)*
Name of Finished Product: Doripenem for Injection	**Volume:**	
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Title of Study: A Multicenter, Phase 3 Study to Confirm the Safety and Efficacy of Intravenous Doripenem in Complicated Lower Urinary Tract Infection or Pyelonephritis (JNJ-38 174942 DORI-06 CR005398)

Number of Investigator(s) and Number of Study Center(s): A total of 30 centers (11 in the United States, 9 in Argentina; 6 in Brazil, 3 in Austria, and 1 in Canada) enrolled 426 patients in this study.

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

Study Initiation/Completion Dates: Date study initiated: 01 May 2004
Date study completed: 03 April 2006

Phase of Development: 3

Primary Objective:

To determine the microbiological response at the test-of-cure (TOC) visit (6 to 9 days after the completion of study drug therapy) in patients with complicated lower urinary tract infections (cLUTI) and pyelonephritis* following a 10-day treatment regimen.

Secondary Objectives:

To determine the clinical response at the TOC visit (6 to 9 days after completion of study drug therapy) in patients with cUTI following a 10-day treatment regimen.

To evaluate the safety of doripenem in patients with cUTI.

Methods: This was a Phase 3, multicenter, prospective, open-label, single arm study of doripenem, administered as a 1-hour intravenous (IV) infusion (500 mg every 8 hours [q8h]) in the treatment of cUTI in adults. Urine specimens for culture were collected at Screening (within 48 hours prior to administration of the first dose of study drug therapy). Catheterized patients from whom the urine specimen was obtained through the catheter, patients who presented with pyelonephritis, and patients who were suspected to have bacteremia had blood samples drawn for culture. After at least 6 doses (approximately 48 hours) of IV study drug therapy had been administered while patients were hospitalized, the patients could have been discharged from the hospital if arrangements were made for continued IV administration of study drug therapy and the collection of all required study assessments. After 9 or more doses of IV study drug therapy, patients could have switched to levofloxacin tablets 250 mg orally q24h if no fever (oral temperature less than 37.8°C) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved relative to those before the start of IV study drug therapy; and at least 1 urine culture had been reported with no growth at 24 hours or growth with a colony count of less than 10^4 colony-forming units (CFU)/mL and no known subsequent cultures with a colony count of greater than or equal to 10^4 CFU/mL were observed.

Number of Patients (planned and analyzed): 450 planned; 426 enrolled, 423 received at least 1 dose of IV study drug therapy (Intent-to-Treat [ITT]); 250 were microbiologically evaluable (ME) at TOC, 337 were part of the microbiological modified ITT (mMITT) analysis set.

Diagnosis and Main Criteria for Inclusion: Male or female patients aged 18 years or older with clinical signs and/or symptoms of cUTI and with a pre-treatment baseline urine culture obtained within 48 hours prior to the start of administration of the first dose of study drug therapy from which a bacterial uropathogen was isolated with a growth of greater than or equal to 10^5 CFU/mL were eligible.

* Throughout this report, "cUTI" refers to both complicated lower urinary tract infection (cLUTI) and pyelonephritis.

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

Duration of Treatment: 10 days (IV and oral)

Reference Therapy, Dose, and Mode of Administration, Batch Number: None

Criteria for Evaluation:
Efficacy:
Primary Efficacy Endpoint: Per-patient microbiological cure (i.e., eradication of all baseline pathogens) rates at the TOC (6-9 days post-therapy) in the ME at TOC and mMITT analysis sets.
Secondary Efficacy Endpoints included the clinical cure rates at the TOC visit and the per baseline uropathogen microbiological outcomes (eradicated or not eradicated) at the TOC visit.
Safety was assessed through monitoring of adverse events (AEs), physical examination, vital sign measurements, and laboratory data (serum chemistries, hematology, and urinalysis).

Statistical Methods: The primary study objective was to establish non-inferiority of doripenem in this study compared to the levofloxacin arm in study DORI-05 with respect to the microbiological response (cure or failure) at TOC in the ME at TOC and mMITT analysis sets. Non-inferior efficacy of doripenem to levofloxacin was to be concluded if the lower 2-sided 95% confidence limit for the difference (doripenem minus levofloxacin) in the proportion of patients who were classified as a microbiological cure, was ≥-10%. This difference and the corresponding CI were obtained using the normal approximation to the difference between 2 binomial proportions (Wald method).
For each of the 2 efficacy endpoints described above, a sensitivity analysis was performed by adjusting for the effects of the baseline cUTI diagnosis (cLUTI or pyelonephritis) using a continuity-adjusted Cochran-Mantel-Haenszel (CMH)-type method, weighted by the number of patients in each disease category.
Safety endpoints included the proportion of patients with any treatment-emergent adverse event (TEAE), the proportion who experienced any TEAE that resulted in discontinuation of study drug therapy, and the proportion of serious adverse events (SAEs) observed during study drug therapy and up to 30 days after therapy.

Summary and Conclusions:
Disposition, Demographics, and Baseline Characteristics:
Overall, the ME at TOC analysis set was predominantly female (55%) and Caucasian (48%) with a median age of 52 years, with 32% of patients greater than or equal to 65 years of age and 15% greater than or equal to 75 years of age. Similar demographic and baseline characteristics were seen in the ITT and mMITT analysis sets. Comparability between doripenem-treated patients in DORI-06 and the levofloxacin treatment arm of DORI-05 was evaluated in terms of patient demographics, baseline characteristics, disease severity, and evaluability rates. The 2 treatment arms were judged to be comparable with a few exceptions that were considered to have no significant impact on outcome.

Efficacy Results:
Primary and Co-Primary Doripenem was microbiologically and clinically effective in the treatment of cUTI including pyelonephritis and, when compared with the levofloxacin group of DORI-05. The microbiological cure rates among patients in the ME at TOC analysis set were 83.6% and 83.4% in the doripenem group from this study and DORI-05 levofloxacin group, respectively. The corresponding treatment difference was 0.2% and the 95% CI was –6.6% to 7.0% which demonstrated that doripenem was non-inferior in efficacy to the levofloxacin arm of DORI-05 in the treatment of cUTIs for the pre-defined non-inferiority margin of -10%. The microbiological cure rates among patients in the mMITT analysis set were 82.5% versus 78.2% in the doripenem and the DORI-05 levofloxacin groups, respectively. The corresponding treatment difference was 4.3%. The 95% CI for the treatment difference from the mMITT analysis set (-2.1%, 10.7%) was consistent with the results obtained in the ME at TOC analysis set.

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Efficacy Results:

Secondary

The clinical cure rates among patients in the clinically evaluable at test-of-cure (CE at TOC) were 93.0% and 90.2% in the doripenem group in this study and the DORI-05 levofloxacin group, respectively (treatment difference: 2.8%; 95% CI: -2.4%, 7.9%). This analysis established that doripenem was not inferior to levofloxacin for the treatment of clinical symptoms of cUTI and supports the primary microbiological outcome of this study. The microbiological cure rates by baseline diagnosis for patients in the ME at TOC analysis were similar between the doripenem-treated patients in DORI-06 and the levofloxacin-treated patients in DORI-05: 74% for patients in DORI-06 and 76% for levofloxacin-treated patients in DORI-05 with cLUTI, 95% for patients in DORI-06 and 91% for levofloxacin-treated patients in DORI-05 with pyelonephritis, and 96% in both groups for patients who concurrent bacteremia at baseline. The most common uropathogen at baseline was *Escherichia coli.* Eradication rates in the ME at TOC analysis sets were similar between the treatment arms for *E. coli:* 92% for doripenem patients in this study and 87% for DORI-05 levofloxacin patients. Doripenem was microbiologically effective against the major causative pathogens of cUTI as shown by the high eradication rate of *E. coli, K. pneumoniae, P. aeruginosa,* and *A. baumannii.*

Safety Results:

Doripenem (500 mg administered by IV infusion over 1 hour q8h) was generally safe and well tolerated by patients aged 18 years or older with cUTI including pyelonephritis. Three hundred and twenty-four (77%) patients reported at least 1 treatment-emergent adverse event; 124 (29%) patients reported at least 1 study drug-related adverse event. Adverse events that occurred with the greatest frequency included headache and phlebitis, reported by 80 (19%) and 39 (9%), respectively, of patients overall. Seizures are currently a carbapenem class label warning but no seizures were reported for patients receiving doripenem in this DORI-06 trial. Thirty-nine (9%) patients had a serious adverse event. Most serious adverse events were reported as sporadic, single events. Urinary tract infection was the most common serious adverse event, reported in 1.4% of doripenem-treated patients. The rate of this particular event (i.e., indication related event) is probably more accurately assessed as outcome measure than by the frequency at which it was reported as adverse events. Four patients died during this DORI-06 study, but 1 of these deaths (from sepsis) occurred before the patient received any study drug therapy treatment. The other causes of death were worsening of bladder tumor, ventricular arrhythmia, and respiratory insufficiency. In the opinion of the investigator, all the deaths were unrelated to study drug therapy.

Liver enzyme elevations have been associated with -lactam antibiotics, but in this study the frequency of this laboratory finding was uncommon.

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Conclusions:

- Doripenem was microbiologically and clinically effective in this study and was therapeutically non-inferior to levofloxacin IV administration in DORI-05 in the treatment of patients with cUTI, including pyelonephritis.
- Doripenem was effective in patients with cLUTI, pyelonephritis, including complicated pyelonephritis, and those who had concurrent bacteremia at study entry.
- High microbiological cure rates of 99% and clinical improvement rates of 99% at the end of IV therapy suggest that the overall response at TOC could be attributed to the doripenem IV portion of the therapeutic regimen and not the oral levofloxacin switch portion.
- Common uropathogens against which doripenem was effective included *E. coli, K. pneumoniae, P. aeruginosa, and P. mirabilis.*
- Doripenem was shown to be generally safe and well tolerated.

Date of the Report: 06 November 2006

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