SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Zevtera™, Zeftera™
Name of Active Ingredient(s)	ceftobiprole medocaril

Protocol No.: BAP00248/307

Title of Study: A Phase 3, Randomized, Double-Blind Study of Ceftobiprole Medocaril Versus Linezolid Plus Ceftazidime in the Treatment of Nosocomial Pneumonia

NCT No.: NCT00210964 and NCT00229008

Clinical Registry No.: CR005032 and CR005140

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Publication (Reference): not applicable

Study Period: 06 April 2005 to 22 May 2007

Phase of Development: 3

Objectives: The primary objective of the study was to demonstrate the noninferiority of ceftobiprole compared with linezolid plus ceftazidime with respect to the clinical cure rate at the Test of Cure (TOC) visit in subjects with nosocomial pneumonia (NP). The secondary objectives outlined in the study protocol were to compare ceftobiprole versus linezolid plus ceftazidime in the treatment of subjects with NP with regard to the following: microbiological eradication rate at the TOC visit, clinical cure and microbiological eradication rates at the late follow-up (LFU) visit, and 30-day pneumonia-specific mortality rates. Other objectives outlined in the study protocol were to assess the pharmacokinetics of ceftobiprole in NP subjects and to compare the following between the treatment groups: the 30-day all-cause mortality rates, the duration of therapy in subjects with NP, and the clinical cure rate and microbiological eradication rates at the TOC visit in subjects with ventilator-associated pneumonia (VAP). These objectives were further clarified and expanded in the Statistical Analysis Plan prior to database lock (see Statistical Methods section below).

Methods: This was a randomized, double-blind, multicenter study of ceftobiprole versus linezolid plus ceftazidime, designed to assess the efficacy and safety of ceftobiprole in subjects with NP including VAP. This study was initiated as 2 separate regional studies, with one study enrolling subjects in North and South America and the other study enrolling subjects outside North and South America. With the exception of the difference in regions, the 2 protocols were identical. With Amendment INT-5, the 2 studies were combined into a single study with a single protocol. Subjects who met all of the inclusion criteria and none of the exclusion criteria were randomly assigned to treatment centrally in a 1:1 ratio to ceftobiprole (500 mg every 8 hours as a 120-minute intravenous infusion) or linezolid (600 mg every 12 hours as a 60-minute intravenous infusion) plus ceftazidime (2 g every 8 hours as a 120-minute intravenous infusion). The scheduled duration of the study treatment was 7 to 14 days. If more than 14 days of treatment were necessary, the subject was to have been discontinued. Subject randomization was stratified by infection type (NP and VAP) and by the Acute Physiology and Chronic Health Evaluation (APACHE II) score (according to scores of 8 to 19 and 20 to 25, respectively). Subjects who had VAP were further stratified by time to randomization after onset of mechanical ventilation (<5 or ≥5 days of ventilation). Subjects were evaluated before the start of therapy (screening/predose), during therapy visits on Day 4±1, Day 8±1, Day 14±1 (prior to treatment prolongation), and at an end of therapy (EOT) visit, performed within 24 hours after last administration

of study drug. A TOC evaluation was done 7 to 14 days after the EOT visit. Subjects were also evaluated for relapse at the LFU visit, which occurred 28 to 35 days after the EOT visit.

Number of Subjects (planned and analyzed): Planned: 770 subjects were planned to achieve 462 (231 in each treatment group) clinically evaluable subjects. Consented: 795 subjects. Screen Failures: 14 subjects. Randomly assigned to treatment (Intent-to-Treat [ITT]): 781 subjects (391 in the ceftobiprole group and 390 in the linezolid/ceftazidime group) at 157 sites worldwide. Other analysis sets: 772 subjects were included in the safety, 495 subjects in the clinically evaluable (CE), 536 subjects in the microbiological ITT (mITT), and 332 in the microbiologically evaluable (ME).

Diagnosis and Main Criteria for Inclusion: men or women aged ≥18 years suffering from nosocomial pneumonia (NP) or ventilator-associated pneumonia (VAP) after a minimum of 72 hours of hospitalization or stay in a chronic care facility who had microbiological samples (respiratory secretions) suitable for culture and microscopy and had an APACHE II score ≥8 and ≤25. Subjects with NP were further defined as having all of the following: 1) Clinical signs or symptoms of pneumonia with at least 2 of the following criteria: a) a new onset of purulent sputum production or respiratory secretions or a worsening in character of sputum; b) tachypnea (respiratory rate ≥20 per minute), particularly if progressive in nature, or c) hypoxemia or respiratory failure requiring mechanical ventilation; 2) new or persistent (persistence was defined as the infiltrate being radiographically visible for at least 72 hours) radiographic infiltrates (not related to another disease process); and 3) fever or leukocytosis/leukopenia consistent with a diagnosis of pneumonia. VAP was defined as nosocomial pneumonia that developed more than 48 hours after onset of mechanical ventilation.

Test Product, Dose and Mode of Administration, Batch No.: Ceftobiprole, 500 mg administered every 8 hours as a 120-minute intravenous infusion; bulk batch numbers 30-4EXP, 10-5EXP, and 9-5EXP. Ceftobiprole was reconstituted with reconstitution solution, supplied in 10 mL vials; bulk batch numbers PD04032, PD04033, PD04034, PD04050, PD04051, and PD04080.

Reference Therapy, Dose and Mode of Administration, Batch No.: Linezolid, 600 mg administered every 12 hours as a 60-minute infusion; bulk batch numbers 04H24Z29, 04E12Z21, 04E12Z23, 04E27Z42, and 05I02Z97. Ceftazidime, 2 g administered every 8 hours as a 120-minute infusion; bulk batch numbers 5020604, 5003, 5007, X003, X004, and X006.

Duration of Treatment: The scheduled duration of therapy was 7 to 14 days.

Criteria for Evaluation: Pharmacokinetics: Plasma concentrations at each time point of measurement from the rich and sparse pharmacokinetic assessments were evaluated by descriptive statistics. Time above MIC was estimated for each individual and summarized descriptively.

Efficacy: Clinical outcome was assessed at the TOC visit, 7 to 14 days after EOT, and was categorized as Cure, Failure, or Not Evaluable. Clinical outcome was assessed at the LFU visit, 28 to 35 days after the EOT, for evaluable subjects with a clinical outcome of Cure at the TOC visit and who were evaluable at the LFU visit, and was categorized as Cure, Relapse, or Not Evaluable.

Microbiological outcome was assessed at the TOC visit and categorized as Eradication, Presumed Eradication, Colonization, Persistence, Presumed Persistence, Superinfection, or Not Evaluable. Microbiological outcome was assessed at the LFU visit for evaluable subjects with a microbiological outcome of Eradication or Presumed Eradication at the TOC visit and who were evaluable at the LFU visit, and was categorized as Eradication, Presumed Eradication, Relapse, or Not Evaluable.

Statistical Methods: This was a noninferiority study to compare ceftobiprole with linezolid plus ceftazidime. The primary objective of this study was to demonstrate the noninferiority of ceftobiprole versus linezolid plus ceftazidime (comparator), with respect to the clinical cure rate at the TOC visit, in subjects with NP (including VAP). This objective was to be demonstrated in the CE and ITT co-primary analysis sets. The secondary objectives were to demonstrate the noninferiority of ceftobiprole versus linezolid plus ceftazidime with respect to the following outcomes using a

hierarchical testing procedure in the following order: 1) microbiological eradication rate at the TOC visit; 2) clinical cure rate at the TOC visit in subjects with NP caused by *S. aureus* (including MRSA); 3) clinical cure rate at the TOC visit in subjects with VAP; 4) clinical relapse rate at the LFU visit in subjects with NP, and 5) 30-day pneumonia-specific mortality rates in subjects with NP. Other objectives of interest were defined in the Statistical Analysis Plan.

A 2-sided confidence interval was calculated for the difference (ceftobiprole minus linezolid plus ceftazidime) in the clinical cure rate at the TOC visit. Noninferiority of ceftobiprole compared with linezolid plus ceftazidime was concluded if the lower limit of this CI was greater than or equal to -15%. The secondary efficacy endpoints were analyzed by presenting 2-sided 95% confidence intervals for the between-treatment differences (ceftobiprole minus linezolid plus ceftazidime) at the TOC visit. For the microbiological eradication rate and the clinical cure rate, noninferiority of ceftobiprole compared to linezolid plus ceftazidime was concluded if the lower limit of this interval was greater than or equal to the non-inferiority margin. All secondary hypotheses were tested at the 15% margin of noninferiority.

Analyses of the primary efficacy endpoint and select secondary parameters were performed in the CE and ITT analysis sets to examine the consistency of treatment effects across subgroups. Differences in clinical outcomes and/or microbiological outcomes between the treatment groups were presented along with their 2-sided 95% CI when there were a sufficient number of subjects in each treatment group. The Breslow-Day test was performed to assess the homogeneity of the cure rates in each strata within each subgroup. Clinical cure rates and microbiological eradication rates were also summarized for each isolated pathogen by MIC values in both microbiologically evaluable and mITT populations.

Safety data were summarized using descriptive statistics for treatment-emergent adverse events reported during the study and for pretherapy to posttherapy changes in clinical laboratory test results, vital sign measurements, and physical examination findings.

RESULTS:

STUDY POPULATION: Similar percentages of subjects did not complete the study in each treatment group: 32% of ceftobiprole subjects and 31% of linezolid plus ceftazidime subjects. The distribution of subjects by reasons for discontinuation was similar between the treatment groups. The most common reason for discontinuation was death (20% of ceftobiprole subjects and 19% of linezolid plus ceftazidime subjects) (Table 1).

Table 1: Study Completion and Discontinuation Information for All Subjects
(Study BAP00248/307: Intent-to-Treat Analysis Set)

Completion Status Reason for Discontinuation	Ceftobiprole (N=391) n (%)	Linezolid/Ceftazidime (N=390) n (%)	Total (N=781) n (%)
Completed	265 (68)	269 (69)	534 (68)
Discontinued	126 (32)	121 (31)	247 (32)
Death	77 (20)	74 (19)	151 (19)
Adverse event	14 (4)	6 (2)	20 (3)
Lost to follow-up	6 (2)	12 (3)	18 (2)
Resistant organism at baseline	6 (2)	5 (1)	11 (1)
Subject choice (subject withdrew consent)	7 (2)	2 (1)	9 (1)
Lack of efficacy	3 (1)	6 (2)	9 (1)
Other	13 (3)	16 (4)	29 (4)

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A total of 140 (36%) subjects in the ceftobiprole group and 146 (37%) subjects in the linezolid plus ceftazidime group were considered not clinically evaluable at the TOC visit. The primary reasons that subjects were not clinically evaluable at the TOC visit were absence of a TOC visit (11% of

ceftobiprole subjects and 12% of linezolid plus ceftazidime subjects) and use of effective concomitant therapy (10% of ceftobiprole subjects and 11% of linezolid plus ceftazidime subjects).

Demographic and baseline characteristics for subjects in the ITT analysis set were generally similar between the 2 treatment groups except that there was a baseline imbalance with respect to sex between the 2 treatment groups (p value = 0.009). The percentage of male subjects in the ceftobiprole group (71%) was greater than in the linezolid plus ceftazidime group (62%). Analysis of clinical cure rates by sex showed that the treatment effect was consistent for both sexes, indicating that the imbalance did not affect the clinical outcome at TOC.

EFFICACY RESULTS: Noninferiority of ceftobiprole compared with linezolid plus ceftazidime was demonstrated within the 15% noninferiority margin for the primary efficacy endpoint, clinical cure rate at the TOC visit, for both the CE and ITT co-primary analysis sets. Clinical cure rates at the TOC visit were 69.3% and 71.3% in the ceftobiprole and linezolid plus ceftazidime groups, respectively, in the CE analysis set, and 49.9% and 52.8%, respectively, in the ITT analysis set (Table 2).

Table 2: Clinical Cure Rates at the TOC Visit for All Subjects
(Study BAP00248/307: Clinically Evaluable and Intent-to-Treat Analysis Sets)

	Ceftobiprole			Linezolid/ Ceftazidime				
	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Clinically Evaluable								
All subjects	251	174	69.3	244	174	71.3	-2.0	(-10.0; 6.1)
Intent-to-Treat								
All subjects	391	195	49.9	390	206	52.8	-2.9	(-10.0; 4.1)

Note: n is the number of subjects with a clinical outcome of Cure.
[a] Ceftobiprole minus linezolid/ceftazidime.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions. A lower limit greater than or equal to -15% indicates that ceftobiprole is not inferior to linezolid/ceftazidime.
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Subgroup analyses showed a significant difference in the clinical cure rates between the 2 treatment groups with respect to the non-VAP and VAP subject stratum. Using the Breslow-Day test, the treatment by ventilation status interaction p-value was 0.069. For non-VAP subjects in the CE analysis set, the clinical cure rates were 77.8% (154/198) in the ceftobiprole group and 76.2% (141/185) in the linezolid plus ceftazidime group (Table 3). In VAP subjects, the clinical cure rates were 37.7% (20/32) in the ceftobiprole group and 55.9% (33/59) in the linezolid plus ceftazidime group (Table 3). A similar trend was observed in the ITT analysis set.

Table 3: Clinical Cure Rates at the TOC Visit for All Subjects by Infection Type
(Study BAP00248/307: Clinically Evaluable Analysis Set)

	Ceftobiprole			Linezolid/ Ceftazidime				
	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Infection type								
Non-VAP	198	154	77.8	185	141	76.2	1.6	(-6.9; 10.0)
VAP	53	20	37.7	59	33	55.9	-18.2	(-36.4; -0.0)

Note: n is the number of subjects with a clinical outcome of Cure.
[a] Ceftobiprole minus linezolid/ceftazidime.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
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Noninferiority was not demonstrated between the 2 treatments within the 15% noninferiority margin for the first secondary endpoint, microbiological eradication at the TOC visit for all subjects. Microbiological eradication (including presumed eradication) rates at the TOC visit were 53.7% and

62.4% in the ceftobiprole and linezolid plus ceftazidime groups, respectively, in the ME analysis set, and 39.0% and 47.2%, respectively, in the ITT analysis set (Table 4).

Table 4: Microbiological Eradication Rates at the TOC Visit for All Subjects
(Study BAP00248/307: Microbiologically Evaluable and Microbiological Intent-to-Treat Analysis Sets)

	Ceftobiprole			Linezolid/ Ceftazidime				
	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Microbiologically Evaluable								
All subjects	162	87	53.7	170	106	62.4	-8.6	(-19.2; 1.9)
Microbiological Intent-to-Treat								
All subjects	269	105	39.0	267	126	47.2	-8.2	(-16.5; 0.2)

Note: n is the number of subjects with microbiological eradication.
[a] Ceftobiprole minus linezolid/ceftazidime.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
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Since the null hypothesis for microbiological eradication at the TOC visit was not rejected at the 2-sided 5% level of significance, further inferential testing of the secondary objectives was not carried out, consistent with the step-down hierarchical testing process. Further efficacy analyses are provided below for informational purposes.

Clinical relapse rates for all subjects in the CE analysis set at the LFU visit were 4.6% (7/152) in the ceftobiprole group and 4.5% (7/156) in the linezolid plus ceftazidime group. Clinical relapse rates for non-VAP subjects in the CE analysis set at the LFU visit were 3.7% (5/135) in the ceftobiprole group and 3.1% (4/128) in the linezolid plus ceftazidime group. Relapse rates for VAP subjects in the CE analysis set at the LFU visit were 11.8% (2/17) in the ceftobiprole group and 10.7% (3/28) in the linezolid plus ceftazidime group.

For all subjects, the 30-day pneumonia-specific mortality rates were 5.6% (14/251) in the ceftobiprole group and 7.0% (17/244) in the linezolid plus ceftazidime group in the CE analysis set, and 6.6% (26/391) in the ceftobiprole group and 6.2% (24/390) in the linezolid plus ceftazidime group in the ITT analysis set. For non-VAP subjects, the 30-day pneumonia-specific mortality rates were 4.5% (9/198) in the ceftobiprole group and 5.9% (11/185) in the linezolid plus ceftazidime group in the CE analysis set, and 5.9% (17/287) in the ceftobiprole group and 5.6% (16/284) in the linezolid plus ceftazidime group in the ITT analysis set. For VAP subjects, the 30-day pneumonia-specific mortality rates were 9.4% (5/53) in the ceftobiprole group and 10.2% (6/59) in the linezolid plus ceftazidime group in the CE analysis set and 8.7% (9/104) in the ceftobiprole group and 7.5% (8/106) in the linezolid plus ceftazidime group in the ITT analysis set.

For all subjects in the ME analysis set, the following cure rates by baseline pathogen were observed: For subjects with *S. aureus*, the clinical cure rates were 57.8% (37/64) in the ceftobiprole group and 67.5% (52/77) in the linezolid plus ceftazidime group. The clinical cure rates in subjects with MSSA were 54.1% (20/37) in the ceftobiprole group and 69.4% (34/49) in the linezolid plus ceftazidime group. The clinical cure rates for subjects with MRSA were 63.0% (17/27) in the ceftobiprole group and 64.3% (18/28) in the linezolid plus ceftazidime group. For subjects with *Streptococcus pneumoniae,* the clinical cure rates were 63.6% (7/11) in the ceftobiprole group and 93.3% (14/15) in the linezolid plus ceftazidime group. The clinical cure rates in subjects with *Pseudomonas aeruginosa* at baseline were 63% (17/27) in the ceftobiprole group and 71% (24/34) in the linezolid plus ceftazidime group. The clinical cure rates in subjects with non-ESBL producing Enterobacteriaceae were 57.6% (19/33) in both treatment groups. The clinical cure rates in subjects with *Klebsiella pneumoniae* were 69% (11/16) in the ceftobiprole group and 70% (16/23) in the linezolid plus ceftazidime group.

PHARMACOKINETIC RESULTS: Considering the limitation in the sample size in both non-VAP and VAP subjects, it appears that the pharmacokinetics of ceftobiprole were different in VAP subjects

compared with non-VAP subjects, characterized by higher clearance and higher volume of distribution. Increases in clearance and volume of distribution in ICU patients have been described for other β-lactam antibiotics, as was recently described for ertapenem, where the distribution volume and clearance nearly doubled in VAP patients. In addition, plots of ceftobiprole and ceftazidime concentrations from sparse sampling against the predicted profiles indicated that many VAP subjects treated with ceftazidime were above the predicted profile, while most VAP subjects treated with ceftobiprole had concentrations below the range typically observed in healthy volunteers.

SAFETY RESULTS: The overall incidences of adverse events, serious adverse events, adverse events that led to discontinuation, and treatment-related adverse events were similar between the 2 treatment groups. The adverse events reported in 5% or more subjects in the ceftobiprole group were: diarrhea (11%), hypokalemia (10%), hyponatremia (10%), pyrexia (9%), vomiting (7%), and anemia (5%). The adverse events reported in 5% or more subjects in the linezolid plus ceftazidime group were: diarrhea (15%), hypokalemia (8%), pyrexia (8%), hyponatremia (6%), constipation (6%), and anemia (5%). The incidence of serious adverse events and discontinuations due to adverse events was higher in the ceftobiprole group, as indicated by 4.4% and 3.6% differences, respectively, when compared with the linezolid plus ceftazidime group.

Among all subjects, a similar percentage of subjects (23% of subjects in the ceftobiprole group and 22% of subjects in the linezolid plus ceftazidime group) died during the course of the study. However, the percentage of VAP subjects who died was higher in the ceftobiprole treatment group (34%) compared with the linezolid plus ceftazidime treatment group (24%). Among non-VAP subjects, 19% of ceftobiprole-treated and 21% of linezolid plus ceftazidime-treated subjects died during the study. Kaplan-Meier estimates of time to death for VAP subjects showed that the difference between the 2 treatment groups was observed early in the study, during the treatment phase.

The incidences of vomiting, dysgeusia, hyponatremia, and seizures were higher in ceftobiprole-treated subjects. The incidence of nausea was similar between the 2 treatment groups, and the incidence was low (3-4%) and at levels that were expected, given the study population. Two subjects in the ceftobiprole treatment group had an ALT level ≥3 times the ULN plus a bilirubin level ≥2 times the ULN after baseline, but neither subject met the criteria as defined by Hy's law in the U.S. FDA draft guidance on drug-induced liver injury because both had evidence of significant baseline cholestasis prior to the initiation of study drug. Seizures were reported in 14 ceftobiprole-treated subjects compared with 5 comparator treated subjects. Of the 14 ceftobiprole-treated subjects with seizures, 10 had a history of severe intracranial trauma/hemorrhage or a history of seizures. Of the remaining 4 subjects, 1 subject had a seizure after therapy was stopped and 1 had severe electrolyte abnormalities that likely predisposed him to having a seizure.

There were no clinically significant changes in laboratory parameters, vital sign measurements or physical examinations. Mean changes from baseline to the EOT visit for the hematology and chemistry parameters were similar between the 2 treatment groups and no remarkable changes were apparent.

The actual mortality rates in this study were compared with predicted mortality rates, which were derived as the average over all subjects within each subgroup of the predicted mortality rate for each subject based on the APACHE II score using a published formula. As shown in Table 5, the observed mortality rates in non-VAP subjects in both treatment groups and in VAP subjects in the linezolid plus ceftazidime group were similar to the predicted rates. However, the mortality rate in VAP subjects in the ceftobiprole group was higher than the predicted rate. Thus, the observed difference in mortality between the treatment groups in the VAP subjects likely reflects a higher than expected mortality in the ceftobiprole group rather than lower than expected mortality in the linezolid plus ceftazidime group.

Table 5 Mortality Predicted by Baseline APACHE II Score
(Study BAP00248/307: Intent-to-Treat Analysis Set)

Infection Type	Treatment Group	Predicted Mortality[a]	Actual Mortality
Non-VAP	Ceftobiprole	18.5 %	18.8 %
Non-VAP	Linezolid/Ceftazidime	19.0 %	21.2 %
VAP	Ceftobiprole	24.2 %	33.7 %
VAP	Linezolid/Ceftazidime	24.2 %	22.6 %

[a] Based on Knaus WA. Critical Care Medicine. 13: 818, 1985.
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STUDY LIMITATIONS: There were no notable limitations in the study design or the population enrolled. However, although noninferiority was demonstrated in the primary endpoint of clinical cure in all subjects, the generalizability of the results to the target patient population is limited because noninferiority was not demonstrated in the subset of subjects with VAP.

CONCLUSION: The results of this study demonstrate that ceftobiprole administered as 500 mg using a 120-minute intravenous infusion every 8 hours was 1) as effective as linezolid plus ceftazidime in treating non-ventilator-associated nosocomial pneumonia (non-VAP), and 2) well tolerated with an acceptable safety profile in non-VAP subjects. However, the dosing regimen of ceftobiprole used in this study was less effective than linezolid plus ceftazidime in treating subjects with VAP, and further work is required to better understand the use of ceftobiprole in these subjects.

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