CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-6906000:2.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	Ceftobiprole medocaril	
Name of Active Ingredient(s)	Ceftobiprole	

Protocol No.: 30982081-CAP-3001, CR011407

Title of Study: Randomized, Double-Blind, Multicenter Study of Ceftobiprole Medocaril Versus Ceftriaxone with/without Linezolid in Treatment of Subjects Hospitalized With Community-Acquired Pneumonia

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Publication (Reference): Not applicable

Study Period: 5 June 2006 to 19 July 2007 | **Phase of Development:** 3

Objectives: The primary objective of this study was to demonstrate the noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid with respect to the clinical cure rate at the test-of-cure (TOC) visit in subjects hospitalized with community-acquired pneumonia (CAP). The secondary objectives outlined in the protocol for this study were to compare the following in hospitalized CAP subjects after treatment with ceftobiprole versus treatment with ceftriaxone with or without linezolid: 1) the microbiological eradication rate at the TOC visit, 2) the clinical cure rate and the microbiological eradication rate at the TOC visit of subjects who required mechanical ventilation within the first 48 hours of enrollment, 3) the clinical and microbiological relapse rates at the late follow-up (LFU) visit, and 4) the 30-day pneumonia-specific mortality rates. Other objectives were to assess the pharmacokinetics and the safety and tolerability of ceftobiprole in subjects hospitalized with CAP.

Methodology: This was a randomized, double-blind, multicenter study of ceftobiprole versus ceftriaxone with or without linezolid designed to assess the efficacy and safety of ceftobiprole in adult subjects with CAP requiring hospitalization. Subjects were assigned to treatment with either ceftobiprole or ceftriaxone with or without linezolid in a 1:1 ratio using a randomization schedule that was balanced using randomly permuted blocks. Subjects were stratified by the Pneumonia Outcomes Research Team (PORT) Severity Index (PSI) score at randomization (PSI ≤90 versus PSI ≥91), and by the need for anti-staphylococcal therapy (linezolid or placebo). After 3 days (72 hours), all subjects were evaluated daily to determine if they met the criteria for optional switch to oral cefuroxime axetil. The study consisted of 5 phases: a baseline/pretreatment phase, an on-treatment phase, an end of therapy (EOT) phase (within 48 hours after completion of treatment), a TOC phase (7 to 14 days after EOT), and an LFU phase (28 to 35 days after EOT).

Number of Subjects (planned and analyzed): Planned: 670 subjects were planned to achieve 532 (266 in each treatment group) clinically evaluable subjects. Randomly assigned to treatment (Intent-to-treat [ITT] analysis set): 638 subjects (314 in the ceftobiprole group and 324 in the ceftriaxone with or without linezolid group) at 103 sites worldwide. Other analysis sets: 632 subjects were included in the safety, 469 in the clinically evaluable, 184 in the microbiological intent-to-treat (mITT), and 144 in the microbiologically evaluable analysis sets.

Diagnosis and Main Criteria for Inclusion: Subjects who were at least 18 years of age or older who were hospitalized with CAP severe enough to require treatment with intravenous antibiotics for at least 3 days were eligible for this study. The inclusion and exclusion criteria were designed to exclude subjects likely to be infected with atypical bacterial pathogens and non-bacterial CAP pathogens such as viruses.

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 10-5EXP and I060607. Ceftobiprole was reconstituted with reconstitution solution, supplied in 10 mL vials; bulk batch number PD05081.

Reference Therapy, Dose and Mode of Administration, Batch No.: Ceftriaxone, 2 g administered once daily as a 30-minute intravenous infusion, bulk batch numbers X-10, Z-11, and Z-21. Linezolid, 600 mg administered every 12 hours as a 60-minute intravenous infusion to subjects with suspected or confirmed methicillin-resistant *Staphylococcus aureus* (MRSA); bulk batch numbers 05L20Z34 and 05I02Z97.

Oral Therapy, Dose and Mode of Administration, Batch No.: Subjects who were switched to oral therapy received cefuroxime axetil, 500 mg every 12 hours; bulk batch numbers C108705, C274633, and C279773.

Duration of Treatment: The total duration of therapy (intravenous plus oral) was 5 to 14 days.

SYNOPSIS (CONTINUED)

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 (minimum inhibitory concentration) was estimated for each individual and summarized descriptively. Pharmacokinetic parameter estimates for ceftobiprole were compared qualitatively between healthy volunteers and subjects with CAP with normal renal function and CAP subjects with varying degrees of renal impairment. In addition, the pharmacokinetic parameters for ceftobiprole were assessed by degrees of renal impairment.

Efficacy:

Clinical outcomes:

- 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 outcomes:

- Microbiological outcome was assessed at the TOC visit and categorized as Eradication, Presumed Eradication, Colonization, Persistence, Presumed Persistence, Superinfection, or Not Evaluable.
- Microbiologic 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.

Safety: Safety assessments included the incidence, type, severity, and relationship to study medication of treatment-emergent adverse events during the study; and changes in pretreatment to post-treatment in clinical laboratory test results, vital sign measurements, and physical examination findings.

Statistical Methods: This was a noninferiority study to compare ceftobiprole with ceftriaxone with or without linezolid. The primary efficacy endpoint was the clinical cure rate at the TOC visit performed on the clinically evaluable analysis set, and the ITT analysis set served as the co-primary population. The secondary efficacy endpoints were tested using a step down hierarchical procedure in the following order: 1) microbiological eradication rate at the TOC visit, 2) clinical cure rate at the TOC visit for subjects who had a PSI score ≥91, 3) the 30-day pneumonia-specific mortality rates. Other objectives of interest were also defined in the Statistical Analysis Plan.

A 2-sided 95% confidence interval was calculated for the between-treatment difference (ceftobiprole minus ceftriaxone with or without linezolid) in the clinical cure rates at the TOC visit. Noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid was concluded if the lower limit of this confidence interval was greater than or equal to –10%. The secondary efficacy endpoints were analyzed by presenting 2-sided 95% confidence intervals for the between-treatment difference (ceftobiprole minus ceftriaxone with or without linezolid) at the TOC visit. All secondary hypotheses were tested at the 15% margin of noninferiority. For the microbiological eradication rate and the clinical cure rate for subjects who had a PSI score ≥91, noninferiority of ceftobiprole compared to ceftriaxone with or without linezolid was concluded if the lower limit of the confidence interval was greater than or equal to the non-inferiority margin. For the 30-day pneumonia-specific mortality rate, noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid was concluded if the upper limit of the confidence interval was less than or equal to the non-inferiority margin.

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

All subjects who were exposed to study medication were evaluated for safety. 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.

After database lock, the Sponsor reassessed available information on study site performance at all sites that participated in this study. Significant compliance issues were identified at one site. Based on these findings, the Sponsor excluded all data generated from this site from all analyses.

SYNOPSIS (CONTINUED)

SUMMARY - CONCLUSIONS

PHARMACOKINETICS: Based on the limited number of subjects with rich pharmacokinetic assessments (N=4), no pharmacokinetic conclusions could be made. For the majority of subjects with sparse pharmacokinetic samples, plasma ceftobiprole concentrations were above the MIC of 4 µg/mL during the dosing interval.

EFFICACY RESULTS: Noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid was demonstrated within the 10% noninferiority margin for the primary efficacy endpoint, clinical cure rate at the TOC visit (7 to 14 days after the EOT visit) in subjects with CAP requiring hospitalization, for both the clinically evaluable and ITT co-primary analysis sets. Clinical cure rates at the TOC visit were 86.6% and 87.4% in the ceftobiprole and the ceftriaxone with or without linezolid groups, respectively, in the clinically evaluable analysis set, and 76.4% and 79.3%, respectively, in the ITT the analysis set (Table 1).

Table 1: Clinical Cure Rates at the TOC Visit
(Study CR011407: Clinically Evaluable and Intent-to-Treat Analysis Sets)

	-- Ceftobiprole --			--- Ceftriaxone --				
	N	n	%	N	n	%	Diff (%)[a]	95% CI[b]
Clinically Evaluable								
All subjects	231	200	86.6	238	208	87.4	-0.8	(-6.9; 5.3)
Intent-to-Treat								
All subjects	314	240	76.4	324	257	79.3	-2.9	(-9.3; 3.6)

Note: n is the number of subjects with a clinical outcome of cure.
[a] Ceftobiprole minus ceftriaxone with/without linezolid.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
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A 15% noninferiority margin was used to test all secondary hypotheses. Noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid within the 15% margin was demonstrated for all of the secondary efficacy endpoints (microbiological eradication at the TOC visit, clinical cure rate at the TOC visit in subjects with a PSI score ≥91, and 30-day pneumonia-specific mortality rate) (Tables 2, 3, and 4).

Table 2: Microbiological Eradication Rates at the TOC Visit
(StudyCR011407: Microbiologically Evaluable and Microbiological Intent-to-Treat Analysis Sets)

	-- Ceftobiprole --			--- Ceftriaxone --				
	N	n	%	N	n	%	Diff (%)[a]	95% CI[b]
Microbiologically Evaluable								
All subjects	68	60	88.2	76	69	90.8	-2.6	(-12.6; 7.5)
Microbiological Intent-to-Treat								
All subjects	87	70	80.5	97	79	81.4	-1.0	(-12.4; 10.4)

Note: n is the number of subjects with a microbiological outcome of eradication or presumed eradication.
[a] Ceftobiprole minus ceftriaxone with/without linezolid.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
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Table 3: Clinical Cure Rates at the TOC Visit for Subjects With a PSI Score of at Least 91
(Study CR011407: Clinically Evaluable and Intent-to-Treat Analysis Sets)

	-- Ceftobiprole --			--- Ceftriaxone --				
	N	n	%	N	n	%	Diff (%)[a]	95% CI[b]
Clinically Evaluable								
All subjects	51	46	90.2	58	49	84.5	5.7	(-6.7; 18.1)
Intent-to-Treat								
All subjects	69	56	81.2	72	56	77.8	3.4	(-9.9; 16.7)

Note: PSI score of at least 91 corresponds to PORT IV and V.
[a] Ceftobiprole minus ceftriaxone with/without linezolid.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
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SYNOPSIS (CONTINUED)

Table 4: Analysis of 30-Day Pneumonia Specific Mortality Rates
(Study CR011407: Clinically Evaluable and Intent-to-Treat Analysis Sets)

	-- Ceftobiprole --			--- Ceftriaxone --				
	N	n	%	N	n	%	Diff (%)[a]	95% CI[b]
Clinically Evaluable								
All subjects	231	0	0.0	238	2	0.8	-0.8	(-2.0; 0.3)
Intent-to-Treat								
All subjects	314	1	0.3	324	3	0.9	-0.6	(-1.8; 0.6)

Note: n is the number of subjects who died of pneumonia.
[a] Ceftobiprole minus ceftriaxone with/without linezolid.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
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In addition, results were similar between the treatment groups for all other efficacy assessments, including 30-day all-cause mortality rates, clinical cure rate by oral switch status, duration of therapy, and clinical and microbiological outcomes at the LFU visit.

Clinical cures were observed for 26 (93%) of 28 microbiologically evaluable subjects in the ceftobiprole group who had *S. pneumoniae* detected at baseline, including cures for both subjects with MDRSP. Clinical cures were observed for all 7 subjects in the ceftobiprole group who had *S. aureus* at baseline, including 1 subject with MRSA, and for all subjects who had *H. influenzae*, *E. coli*, *M. catarrhalis*, or *K. oxytoca* isolated at baseline. Clinical cures were observed for 6 (67%) of 9 subjects with *H. parainfluenzae* and 4 (80%) of 5 subjects with *K. pneumoniae*. The microbiological eradication rates for these pathogens were similar to the clinical cure rates for subjects with these pathogens.

SAFETY RESULTS: Ceftobiprole administered at 500 mg using a 120-minute intravenous infusion every 8 hours was safe and well tolerated in this study. No statistically significant differences were observed between the treatment groups in the overall incidence of adverse events, deaths, serious adverse events, or discontinuations due to adverse events. The incidence of treatment-related adverse events was higher in the ceftobiprole group than the ceftriaxone with or without linezolid group, largely due to higher rates of treatment-related nausea (7% versus 2%, respectively) and vomiting (5% versus 2%, respectively). The incidence of treatment-related adverse events that were considered serious or that led to treatment discontinuation were not significantly different between the 2 treatment groups.

Eighteen subjects, 9 subjects in each treatment group, died during the study. One of the deaths in the ceftriaxone with or without linezolid group was considered by the investigator to be probably related to the study treatment. None of the deaths in the ceftobiprole group were considered related to treatment by the investigator. Adverse events reported in 5% or more of subjects in the ceftobiprole group were nausea (10%), vomiting (9%), diarrhea (7%), headache (7%), and insomnia (5%). Adverse events reported in 5% or more of subjects in the ceftriaxone with or without linezolid group were diarrhea (9%), headache (7%), and hypokalemia (6%).

A total of 72 (11%) subjects, 35 (11%) in the ceftobiprole group and 37 (11%) in the ceftriaxone with or without linezolid group, reported at least 1 serious adverse event during the study. The most frequently reported serious adverse event in both treatment groups was pneumonia, occurring in 5 (2%) subjects in the ceftobiprole group and 10 (3%) subjects in the ceftriaxone with or without linezolid group. Adverse events that resulted in discontinuation from study medication were reported for 18 (6%) subjects in the ceftobiprole group and 12 (4%) subjects in the ceftriaxone with or without linezolid group.

Among adverse drug reactions that occurred in more than 1 subject in the ceftobiprole group, the incidences of nausea, vomiting, rash, and dysgeusia were ≥2-fold higher in the ceftobiprole group compared with the ceftriaxone with or without linezolid group, and the difference in the incidence (ceftobiprole minus ceftriaxone with or without linezolid) of infusion site reactions was more than 2%. There were no clinically significant changes after baseline in clinical laboratory values, vital signs, or physical examinations. The incidence of markedly abnormal test results for individual hematology and chemistry analytes was comparable across the treatment groups.

CONCLUSION: The results of this study demonstrate that 1) ceftobiprole is as effective as ceftriaxone with or without linezolid for subjects with CAP requiring hospitalization due to gram-positive and gram-negative pathogens, and 2) ceftobiprole administered at 500 mg using a 120-minute intravenous infusion every 8 hours is well tolerated with an acceptable safety profile.

Issue Date of the Clinical Study Report: 03 November 2009

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