SYNOPSIS CR005029

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Ceftobiprole medocaril NAME OF ACTIVE INGREDIENT(S): Ceftobiprole	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR005029 **Title of Study:** A Phase 3, Randomized, Double-Blind Study Of Ceftobiprole Medocaril versus Vancomycin with Ceftazidime in the Treatment of Complicated Skin and Skin Structure Infections		
Investigator: Multicenter, 129 sites		
Publication (Reference): Not applicable		
Study Initiation/Completion Dates: 30 September 2005 to 13 October 2006		**Phase of development:** 3
Objectives: The primary objective of this study was to demonstrate the noninferiority of ceftobiprole compared with vancomycin plus ceftazidime, with respect to the clinical cure rate at the test-of-cure (TOC) visit, in subjects with complicated skin and skin structure infections (cSSSI) due to suspected or proven gram-positive and/or gram-negative infection. Secondary objectives were to assess the differences between subjects treated with ceftobiprole or vancomycin plus ceftazidime in the following order: 1) clinical relapse rate at the late follow-up (LFU) visit, 2) microbiological eradication rate at the TOC visit, 3) microbiological relapse rate at the LFU visit. Other objectives were to assess the differences between subjects treated with ceftobiprole or vancomycin plus ceftazidime with respect to time to clinical cure; time to microbiological eradication; time to defervescence; duration of treatment for clinically cured subjects; pharmacokinetics parameters; and safety and tolerability of treatment with ceftobiprole		
Methodology: This was a randomized, double-blind, multicenter, comparative study. Subjects were assigned to 1 of 2 treatment regimens (ceftobiprole or vancomycin plus ceftobiprole) in a 2:1 ratio according to a randomization schedule, which was balanced using randomly permuted blocks and stratified by infection type (diabetic foot infection, wound or abscess infection site within 30 days of surgery or trauma, or cellulitis). The primary efficacy parameter was clinical outcome (cure, failure, not evaluable) at the TOC visit (7 to 14 days following completion of study medication). Secondary efficacy parameters included the following: microbiological outcome ([presumed] eradication, colonization, [presumed] persistence, superinfection, not evaluable) at the TOC visit; clinical and microbiological outcomes at the LFU visit (28 to 35 days following completion of study medication); evolution of signs and symptoms of disease (e.g., time to defervescence); time to clinical cure; and time to microbiological eradication. Safety evaluations included type, incidence, severity, and relationship to study drug of treatment-emergent adverse events and changes from admission to posttherapy in clinical laboratory test results, vital signs, and physical examination findings.		
Number of Subjects (planned and analyzed): Planned: 816 subjects to achieve 570 (380 in ceftobiprole group and 190 in vancomycin plus ceftazidime group) clinically evaluable subjects. Randomly assigned to treatment (Intent-to-treat [ITT] analysis set): 828 subjects, 547(66%) in the ceftobiprole group and 281(34%) in the vancomycin plus ceftazidime group. Other analysis sets: 822 subjects were included in the safety, 729 in the clinically evaluable, 658 in the mITT, and 590 in the microbiologically evaluable analysis sets. A total of 66 subjects were evaluable for rich pharmacokinetic analysis		
Diagnosis and Main Criteria for Inclusion Subjects who were at least 18 years of age or older with signs of infection consistent with a diagnosis of cSSSI, including diabetic foot infection, were eligible for this study. Subjects with infection caused by gram-positive or gram-negative pathogen(s) or had a mixed infection, and with a severity of infection requiring intravenous therapy were enrolled in the study.		
Test Product, Dose and Mode of Administration, Batch No.: Ceftobiprole at 500 mg administered as a 120-minute intravenous infusion 3 times daily (every 8 hours); bulk batch numbers 30-4EXP, 09-5EXP, and 10-5EXP. Ceftobiprole was reconstituted with reconstitution solution, supplied as 10 mL vials, bulk batch numbers PD04033, PD04034 and PD05050, respectively.		

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Reference Therapy, Dose and Mode of Administration, Batch No.: Reference Therapy, Dose and Mode of Administration, Batch No.: Vancomycin 1 g, twice daily (administered as a 60-minute intravenous infusion every 12 hours); bulk batch numbers 3964911F, 3965011F, and 3969112F. Ceftazidime 1 g, 3 times daily (administered as a 120-minute intravenous infusion every 8 hours); bulk batch numbers 5020604, X003, and X004.

Duration of Treatment: 7 to 14 days for both study medications

Criteria for Evaluation:

Pharmacokinetics: Based on the individual plasma concentration-time data from the rich pharmacokinetic sampling, given actual sampling times, the following pharmacokinetic parameters of ceftobiprole were estimated on Day 4±1: maximum concentration (C_{max}), time to reach maximum concentration (t_{max}), Area under the plasma concentration-time curve from 0 to the last measurable time point (AUC_{last}), Area under the plasma concentration-time curve over the 8 hour dosing interval (AUC_{τ}) and from 0 to the time of the last measurable concentration (AUC_{last}), half-life ($t_{½}$), amount excreted (A_e), %T>MIC (percent of time that the unbound drug was above the minimum inhibitory concentration of 4 μg/mL).

Assessment of the pharmacokinetic parameters of the prodrug ceftobiprole medocaril depended on whether there were sufficient samples with measurable plasma concentrations. Urine concentrations of ceftobiprole were used to determine urinary excretion. Pharmacokinetic parameter estimates for ceftobiprole were compared qualitatively with the same regimen between healthy volunteers and subjects with cSSSI. In addition, the pharmacokinetic parameters for ceftobiprole were assessed by degrees of renal impairment.

Efficacy:

Clinical outcomes:

- Clinical outcome was assessed posttherapy at the TOC visit, 7 to 14 days following the end of therapy (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 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 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.

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Statistical Methods: This was a noninferiority study to compare ceftobiprole with vancomycin plus ceftazidime. The primary efficacy endpoint was the clinical cure rate at the TOC visit, with the clinical outcome assessed as Cure, Failure, or Not Evaluable. The secondary efficacy endpoints were: 1) clinical relapse rate at the LFU visit, 2) microbiological outcome (assessed as [Presumed] Eradication, Colonization, [Presumed] Persistence, Superinfection, or Not Evaluable) at the TOC visit, and 3) microbiological relapse rate at the LFU visit. Other efficacy assessments were: 1) time to clinical cure, 2) time to microbiological eradication, 3) time to defervescence, 4) duration of treatment, and 5) collection of medical resource utilization (MRU) data.

Clinical outcome was analyzed by presenting the 2-sided 95% confidence intervals for the between-treatment difference (ceftobiprole minus vancomycin plus ceftazidime) in the clinical cure rate at the TOC visit. Noninferiority of ceftobiprole compared with vancomycin plus ceftazidime could be concluded if, for the clinical cure rate at the TOC visit, the lower limit of the 2-sided 95% confidence intervals of the between-treatment difference was more than or equal to –10%. Microbiological eradication rate at the TOC visit was analyzed in a manner similar to the clinical cure rate at the TOC visit.

Analyses of the clinical cure rates and microbiological eradication rates were performed for subgroups. The Breslow-Day test was performed to test for the homogeneity of treatment differences among strata of each subgroup variable.

The association between clinical outcome and microbiological outcome was tested using the Cochran-Mantel-Haenszel (CMH) test for general association

Clinical relapse rate and microbiological relapse rate were analyzed by presenting a 2-sided 95% confidence interval for the between-treatment difference (ceftobiprole minus vancomycin plus ceftazidime) at the LFU visit. Noninferiority of ceftobiprole compared with vancomycin plus ceftazidime was concluded if the upper limit of this interval was less than or equal to 10%.

Time to defervescence, time to clinical cure, and time to microbiological eradication were analyzed using a 2-sided log-rank test based on the Kaplan-Meier method at the 5% significance level. The duration of treatment was summarized descriptively (i.e., the number of observations, mean, standard deviation, median and range) for each treatment group.

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

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SUMMARY - CONCLUSIONS

PHARMACOKINETICS: Systemic exposure was lower in cSSSI subjects with normal renal function, 33% for C_{max} and 18% for AUC_{τ}, compared with healthy volunteers (Study CSI-1004). Half-life was similar between healthy volunteers and cSSSI subjects with normal renal function. Total systemic clearance was 30% higher in subjects with cSSSI compared to healthy volunteers. The %T>MIC for the unbound ceftobiprole concentrations was also similar in cSSSI subjects with normal renal function compared to healthy volunteers. Compared to cSSSI subjects with normal renal function and the same dosing regimen, cSSSI subjects with mild renal impairment had higher systemic exposure (51% for C_{max}, 45% for AUC_{τ}), similar half-life, and lower (33%) CL_s. Compared to cSSSI subjects with normal renal function, cSSSI subjects with moderate renal impairment and dosage adjustment to 500 mg twice a day, had similar C_{max}, lower (35%) AUC_{last}, and lower (24%) CL_s. Half-life increased to 7 hours, indicating slower elimination. The significance of these results is limited based on the small number of subjects with renal impairment.

Parameter	BAP00414			CSI-1004
	Normal Renal Function N=56	Mild Renal Impairment N=8	Moderate Renal Impairment [a] N=2	Normal Renal Function N=27
C_{max} (μg/mL)	22.2 (6.62)	33.5 (14.3)	24.8 (7.99)	33.0 (4.83)
t_{max} (h)[b]	2.00 (0.25–4.67)	1.99 (1.00-2.08)	1.92 (1.00-2.83)	1.97 (1.67-1.98)
AUC_{0-8} (μg•h/mL	83.6 (21.8)	124 (33.5)	NC	102 (11.9)
AUC_{last} (μg•h/mL	82.4 (22.0)	120 (36.7)	111 (33.0)	117 (14.5)
CL_s (L/h)	6.38 (1.67)	4.27 (1.08)	4.85 (1.61)	4.89 (0.69)
$t_{1/2}$ (h)	4.00 (6.46)	3.01 (0.962)	7.01 (3.25)	3.3 (0.3)
A_e (mg)	361 (262)	230 (126)	365 (9.33)	494 (28.8)
%T>MIC (total)	84.0 (13.0)	100	100	91.3 (7.90)
%T>MIC (unbound)	77.1 (13.2)	NC	NC	84.3 (8.64)

[a] dosing interval was 12 hours but samples were only collected for 8 hours

[b] Median (range)

NC = not calculated.

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EFFICACY RESULTS: The noninferiority of ceftobiprole compared with vancomycin plus ceftazidime was demonstrated for the primary efficacy endpoint, clinical cure rate at the TOC visit (7 to 14 days after the EOT visit) in subjects with cSSSI, for both the clinically evaluable and ITT co-primary analysis sets. Clinical cure rates at the TOC visit were 90.5% and 90.2% in the ceftobiprole and the vancomycin plus ceftazidime groups, respectively, in the clinically evaluable analysis set and 81.9% and 80.8%, respectively, in the ITT the analysis set.

Table 1: Clinical Cure Rate at the TOC Visit
(Study BAP00414: Clinically Evaluable and Intent-to-Treat Analysis Sets)

	Ceftobiprole			Vancomycin/Ceftazidime				
	N	n	%	N	n	%	Diff (%)[a]	95% CI[b]
Clinically Evaluable								
All Subjects	485	439	90.5	244	220	90.2	0.4	(-4.2; 4.9)
Intent-to-Treat								
All Subjects	547	448	81.9	281	227	80.8	1.1	(-4.5; 6.7)

[a] Ceftobiprole minus vancomycin/ceftazidime.
[b] 2-sided 95% confidence interval is based on the Normal approximation to the difference of the 2 proportions.
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The noninferiority of ceftobiprole compared with vancomycin plus ceftazidime was demonstrated for 2 of the secondary efficacy endpoints (i.e., clinical relapse rate at the LFU visit [Table 2], and microbiological eradication at the TOC visit) [Table 3].

Table 2: Clinical Relapse Rate at the LFU Visit
(Study BAP00414: Clinically Evaluable at the LFU Visit Analysis Set)

Clinical outcome at LFU	Ceftobiprole (N=419) n (%)	Vancomycin/ Ceftazidime (N=208) n (%)	Ceftobiprole Minus Vancomycin/ Ceftazidime Diff (%)[a]	C.I.[b]
Cure	410 (97.9)	207 (99.5		
Relapse	9 (2.1)	1 (0.5)	1.7	(-0.0; 3.3)

Note: The clinically evaluable analysis set at the LFU visit included all clinically evaluable subjects who had a derived clinical outcome of Cure at the TOC visit and were clinically evaluable at the LFU visit.
[a] Ceftobiprole minus vancomycin/ceftazidime.
[b] 2-sided 95% confidence interval for the difference of the clinical relapse rates. An upper limit less than or equal to 10% indicates that ceftobiprole is not inferior to vancomycin/ceftazidime.
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Table 3: Microbiological Eradication Rates at the TOC Visit
(Study BAP00414: Microbiologically Evaluable and Microbiological Intent-to-Treat Analysis Sets)

	Ceftobiprole			Vancomycin/Ceftazidime				
	N	n	%	N	n	%	Difference (%)[a]	C.I.[b]
Microbiologically Evaluable								
All Subjects	391	344	88.0	199	177	88.9	-1.0	(-6.4; 4.5)
Modified Intent-to-Treat								
All Subjects	434	344	79.3	224	177	79.0	0.2	(-6.3; 6.8)

Note: n is the number of subjects with a microbiological outcome of eradication or presumed eradication
[a] Ceftobiprole minus vancomycin/ceftazidime.
[b] 2-sided 95% CI is based on the Normal approximation to the difference of the 2 proportions.
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The microbiological relapse rate at the LFU visit was higher in the ceftobiprole treatment group compared with the vancomycin plus ceftazidime group, however, the difference between the treatment groups stayed within the noninferiority margin of 10% [Table 4].

Table 4: Microbiological Relapse Rates at the LFU Visit
(Study BAP00414: Microbiologically Evaluable at LFU Visit Analysis Set)

	Ceftobiprole (N=325)	Vancomycin/Ceftazidime (N=167)	Diff (%)[a]	C.I.[b]
Microbiological Outcome at LFU	n (%)	n (%)		
Eradication/Presumed eradication	317 (97.5)	167 (100)		
Relapse[c]	8 (2.5)	0	2.5	(0.8; 4.1)

Note: The Microbiologically Evaluable analysis set at LFU included all microbiologically evaluable subjects who had a microbiological outcome of Eradication or Presumed Eradication at the TOC visit and were microbiologically evaluable at the LFU visit.

[a] Ceftobiprole minus vancomycin/ceftazidime.

[b] 2-sided 95% confidence interval for the difference of the microbiological relapse rates, an upper limit less than or equal to 10% indicates that ceftobiprole is not inferior to vancomycin/ceftazidime.

[c] Relapse included Colonization, Persistence, or Superinfection, but not [Presumed] Eradication or Not Evaluable (which included missing LFU visit).

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The clinical cure rates at the TOC visit in the subset of subjects with diabetic foot infections, which are considered more difficult to treat as they are caused by a broader spectrum of pathogens, were comparable between the treatment groups for both the clinically evaluable and ITT analysis sets. The clinical cure rate in these subjects was 86.2% in the ceftobiprole group and 81.8% in the vancomycin plus ceftazidime group for the clinically evaluable analysis set

The clinical cure rates at the TOC visit in subjects with *S. aureus* (MRSA and MSSA) isolated from the infection site at baseline were comparable: 90% and 94% for MRSA and MSSA, respectively, in the ceftobiprole group compared with 86% and 93%, respectively, in the vancomycin plus ceftazidime group for the microbiologically evaluable analysis set.

SAFETY RESULTS:

Ceftobiprole was well tolerated in this study; the majority of adverse events were mild and not treatment related. The incidences of adverse events, treatment-limiting adverse events, and serious adverse events in ceftobiprole-treated subjects were similar to the incidences that were observed in the vancomycin plus ceftazidime-treated subjects.

Four subjects, 3 in the ceftobiprole group and 1 in the vancomycin plus ceftazidime treatment group, died. All of the deaths were considered unrelated to study medication

The most frequently-reported adverse events (i.e., those reported by 2% or more of subjects) in the ceftobiprole group were: nausea (11%), headache and diarrhea (8% each), vomiting (6%), and rash and insomnia (5% each). The most frequently reported adverse events in the vancomycin plus ceftazidime group were: nausea (7%), pruritus and diarrhea (6% each), headache, insomnia, and constipation (5% each), vomiting, rash, and anemia (4% each).

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A total of 39 (7%) subjects in the ceftobiprole group and 24 (9%) in the vancomycin plus ceftazidime group reported at least 1 serious adverse event during the course of the study. Serious adverse events reported in at least 2 ceftobiprole-treated subjects were: cellulitis, skin infection, and hyponatremia (3 subjects each), and osteomyelitis, amputation, necrosis, femur fracture, nausea, and anemia (2 subjects each). Serious adverse events reported in at least 2 vancomycin plus ceftazidime-treated subject were: cellulitis (3 subjects) and pneumonia, pleural effusion and amputation (2 subjects each).

A total of 26 (5%) subjects in the ceftobiprole group and 16 (6%) in the vancomycin plus ceftazidime group discontinued study medication due to an adverse event. Adverse events reported in at least 2 subjects that resulted in discontinuation of ceftobiprole treatment were: hyponatremia (3 subjects), and hypersensitivity, rash, maculo-papular rash, peripheral edema, and dyspnea (2 subjects each). Adverse events reported in at least 2 subjects that resulted in discontinuation of vancomycin plus ceftazidime treatment were: rash (3 subjects), and drug hypersensitivity, nausea, catheter site phlebitis, pyrexia, and osteomyelitis (2 subjects each).

There were no clinically significant changes postbaseline in clinical laboratory values, vital signs, or physical examinations. The incidence of markedly abnormal test results for individual hematology and chemistry analytes within a given treatment group was low (≤10%) and comparable across the treatment groups.

CONCLUSION:

The results of this study demonstrate that 1) ceftobiprole is as effective as vancomycin plus ceftazidime for subjects with cSSSI due to gram-positive and gram-negative pathogens, including subjects with diabetic foot infections, and 2) ceftobiprole administered at 500 mg using a 120-minute intravenous infusion 3 times daily is safe and well tolerated. Overall systemic exposure of ceftobiprole appears to be lower in cSSSI subjects with normal renal function compared with healthy volunteers; however, %T>MIC was similar in both populations. The pharmacokinetics of ceftobiprole in subjects with cSSSI will be further evaluated in a population pharmacokinetic analysis.

Date of the report: 24 April 2007

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