SYNOPSIS

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

Protocol No.: 30982081CSI1002

Title of Study: An Exploratory Study to Evaluate the Penetration of Ceftobiprole Into Soft Tissue Determined by In Vivo Microdialysis in Healthy Volunteers

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Publication (Reference): none

Study Period: 20 June 2007- 18 September 2007

Phase of Development: 1

Objectives: The primary objectives of the pilot study were to investigate the feasibility of using the microdialysis technique to measure ceftobiprole by determining its recovery by the microdialysis probe and to determine the necessary washout period needed to ensure all of the calibration solution was cleared from the tissues and microdialysis probes before dosing.

The primary objective of the main study was to measure the penetration of ceftobiprole into subcutaneous (s.c.) adipose tissue and skeletal muscle and to determine the concentration-versus-time profiles of ceftobiprole in these tissues using the microdialysis technique and in plasma after administration of a single intravenous (i.v.) infusion of ceftobiprole 500 mg administered over 2 hours.

The secondary objective was to further assess the safety and tolerability of ceftobiprole after a single i.v. infusion.

Methods This was a single center, open-label, one-arm, nonrandomized study in healthy men and women. This study consisted of 2 parts: a pilot study and the main study. A pilot study with 3 subjects was conducted first to validate the microdialysis method with ceftobiprole. At least 10% recovery must have been achieved in order to quantify ceftobiprole in the dialysate. If the pilot study demonstrated a ≥10% recovery, it was followed by the main study, which enrolled 12 subjects. Pilot study subjects were admitted to and discharged from the study unit on Day 1 after completion of the microdialysis procedure and safety assessments. One week after discharge subjects returned for a follow-up visit to assess ongoing or new adverse events. The main study consisted of a screening examination, a 2-day open-label treatment phase, end-of-study procedures on Day 2, and a follow-up visit or telephone contact 1 to 2 weeks later. Including the 21-day-screening phase, the expected duration of the main study was approximately 5 weeks. Subjects enrolled in the main study underwent the microdialysis procedure as performed in the pilot study for 60 minutes. After the microdialysis procedure, subjects received a single 2-hour infusion of ceftobiprole 500 mg. Serial blood and dialysate samples were collected at specified time points from predose through 24 hours after the start of the infusion for estimation of ceftobiprole and ceftobiprole medocaril concentrations. Additional samples were collected for measurement of protein binding.

Number of Subjects (planned and analyzed): The analysis population consisted of healthy men and women, aged 18 to 55 years, inclusive, who successfully completed screening evaluations, received the ceftobiprole infusion, and had all plasma and microdialysis samples collected. Three control subjects were enrolled for the pilot study only and 12 subjects were enrolled in the main study. Subjects in the

main study who withdrew before the 24-hour pharmacokinetic (PK) blood sample and microdialysis sample on Day 2 were replaced so that an analysis population of 12 healthy adults was achieved.

Test Product, Dose and Mode of Administration, Batch No.: Ceftobiprole medocaril was provided in vials as 500 mg freeze-dried powder.

Pilot Study

Ceftobiprole (BAL9141) was locally administered via the microdialysis probe at a concentration of approximately 30 μg/mL at a flow rate of 1.5 μl/minute for 60 minutes.

Main Study

Each subject received ceftobiprole (BAL9141) locally via the microdialysis probe, as in the in vivo recovery experiment, for in vivo calibration of the dialysis probe. After the washout period determined by the pilot study, each subject received a single 2-hour i.v. infusion of ceftobiprole medocaril (BAL5788, JNJ-30982081) 500 mg. The i.v. kit and bag was weighed before and after each infusion. Immediately after the end of the infusion (and after the i.v. bag had been weighed), an aliquot of the infusion solution (approximately 1 mL) was obtained.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Criteria for Evaluation:

PHARMACOKINETIC EVALUATIONS:

Venous blood and dialysate samples were collected. Ceftobiprole medocaril and ceftobiprole plasma and ceftobiprole dialysate concentrations were assayed using validated liquid-chromatography methodology, with tandem mass spectrometric detection. Plasma protein binding for ceftobiprole medocaril and ceftobiprole were measured from plasma samples using a qualified assay.

Based on the individual plasma concentration-time data, given actual sampling times, the following PK parameters of ceftobiprole in plasma and dialysate were estimated: $C_{max,}$ $t_{max,}$ $AUC_{last,}$ $AUC_{\infty,}$ $\lambda_{z,}$ $t_{1/2,}$ CL (for plasma only), and V_d (for plasma only). As a measure of tissue penetration, $AUC_{tissue}/AUC_{plasma}$ concentration ratios were determined for s.c. adipose and skeletal muscle tissues. The plasma concentration was corrected to account for plasma protein binding.

If deemed necessary, additional PK data analyses were performed.

PHARMACODYNAMIC EVALUATIONS/CRITERIA:

The time above a concentration of 4 μg/mL, a presumable MIC for relevant organisms, was estimated for ceftobiprole in both plasma (corrected for the free fraction) and s.c. adipose and skeletal muscle tissues.

SAFETY EVALUATIONS:

The study included the following evaluations of safety and tolerability: adverse events, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), electrocardiogram (ECG), vital signs, physical examination, serology, pregnancy tests, urine drug screen, and alcohol breath test.

Any clinically significant abnormalities persisting at the end of the study were followed by the investigator until resolution or until a clinically stable endpoint was reached.

Statistical Methods

Sample Size Determination

As this was an exploratory study, the sample sizes of approximately 3 subjects for the pilot study and 12 subjects for the main study were based upon empiric considerations.

The intersubject coefficient of variation for AUC and C_{max} from plasma after a single dose and multiple doses was estimated to be less than or equal to 20%; with a sample size of 12 subjects the point estimate of PK parameters of ceftobiprole in plasma will fall within 88% to 114% of the true value with 95% confidence.

Pharmacokinetics

Plasma concentration-versus-time profiles for each subject were plotted, mean plasma concentration-time profiles were plotted, and plasma and tissue concentration data at each time point were summarized by descriptive statistics. Pharmacokinetic parameters, pharmacodynamic (PD) estimates, and protein binding information was summarized with mean, median, minimum, maximum, standard deviation, and coefficient of variation.

Safety Analyses

Safety from Day -1 through poststudy follow-up were evaluated by examining incidence, severity, relationship to study drug, and type of adverse events; changes in clinical laboratory results; physical examination; vital signs measurements; and concomitant medication/therapy. Data from the main study was summarized using descriptive statistics and data from the pilot study were listed only.

RESULTS:

In the Pilot study, 3 men were enrolled and completed the study. In the Main study, 12 subjects were enrolled (6 men and 6 women) (Table 3). All subjects completed the study.

Study Completion/ Early Withdrawal Information
(Study 30982081-CSI-1002: Safety Analysis Set)

Subject Completed Treatment/trial Reason for Withdrawal/termination	Total (N=12) n (%)
Total no. subjects	12 (100)
Completed	12 (100)

Note: Percentages calculated with the number of subjects in each group as denominator.
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The subjects enrolled in the pilot study were all men and had a median age of 26. The subjects enrolled in the main part of the study were half men and half women. The majority of subjects enrolled in the main study were white and the median age was 22 years. Men and women were similar in demographic characteristics, although height, weight and age were higher for men. The BMI was similar for men and women.

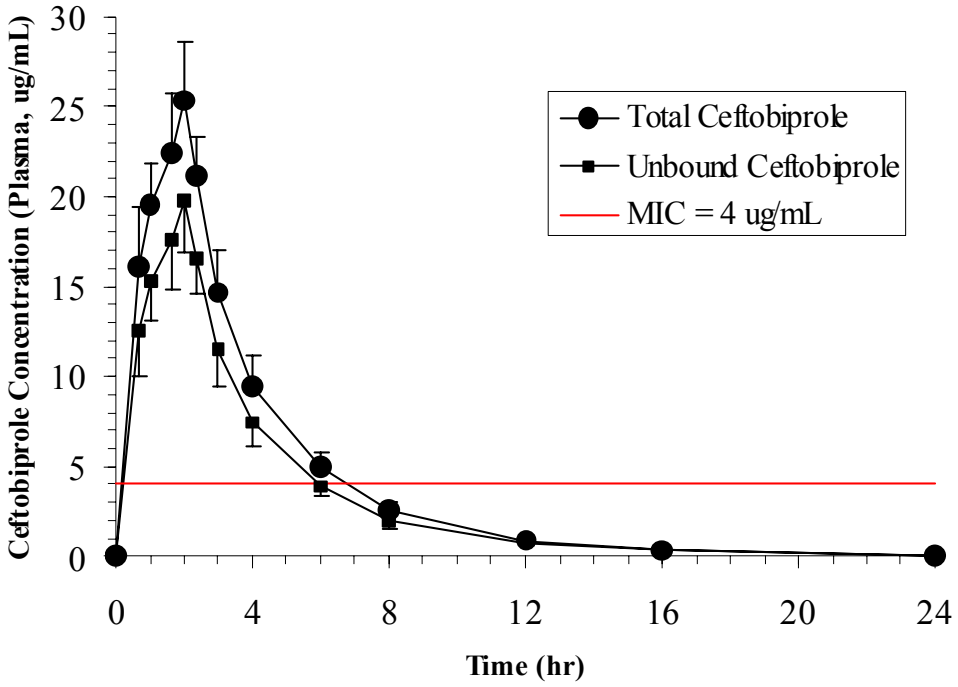
PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Mean ceftobiprole medocaril concentrations in plasma were below quantitation limit (BQL) in most subjects across the sampling period and therefore, pharmacokinetic analysis of ceftobiprole medocaril concentrations was not performed.

No subject withdrew from the main study and all data points were included in the analysis of the pharmacokinetics of ceftobiprole in plasma and dialysate. Ceftobiprole exposure (C_{max} and AUC) is greater in plasma than in skeletal muscle, followed by adipose tissue. Estimates of plasma CL, V, and elimination t1/2 were comparable to that observed in previous studies.

Overall tissue penetration as determined by the ratio of $AUC_{tissue}/AUC_{plasma}$ was 0.69 and 0.49, in skeletal muscle and adipose tissue respectively. Assuming an MIC of 4 μg/mL, the unbound %T>MIC exceeded 30% in all tissues studied.

Mean Ceftobiprole Concentration Time Profiles in Unbound Plasma



Mean Ceftobiprole Pharmacokinetic Parameters in Plasma, Skeletal Muscle, and Adipose Tissue

Parameter	Plasma	Skeletal Muscle	Adipose Tissue
C_{max} (µg/mL)	25.8 (2.96)	14.0 (3.22)	9.61 (4.74)
t_{max} (h)	1.92 (0.15)	2.25 (0.14)	2.25 (0.21)
AUC_{last} (h.µg/mL)	97.1 (10.3)	50.6 (10.9)	34.3 (19.0)
$AUC_{last\ unbound}$ (h.µg/mL)	76.0 (8.81)	NA	NA
AUC_{∞} (h.µg/mL)	98.0 (10.5)	53.2 (11.5)	36.5 (19.4)
$AUC_{\infty\ unbound}$ (h.µg/mL)	76.9 (8.94)	NA	NA
$t_{1/2}$ (h)	2.61 (0.33)	2.61 (0.52)	2.56 (0.39)
Vd_z (L)	19.4 (3.61)	NA	NA
CL (L/h)	5.15 (0.53)	NA	NA
%T>MIC*	71.6 (5.63)	53.6 (9.62)	35.1 (22.2)

NA = Not Assessed

* this value represents unbound ceftobiprole concentrations, corrected for individual protein binding

SAFETY RESULTS: No deaths or other serious adverse events were reported, and no one discontinued treatment because of an adverse event. The most commonly reported adverse events among subjects were dysgeusia (5 subjects), nasopharyngitis (3 subjects). The cases of dysgeusia were considered by the investigator to be probably related to study drug, and those of nasopharyngitis were to be of doubtful relationship to study drug. One case each of insomnia and headache were classified as persistent by the investigator, and were considered mild and possibly related to study drug. No adverse event was considered severe.

Changes in clinical laboratory values were not considered clinically significant. One subject experienced both increased platelet volume and decreased platelet count, which were persistent and considered by the investigator as mild in severity and to be possibly related to study drug. Changes in vital sign measurements were not clinically significant.

CONCLUSION:

The results of this study demonstrate that ceftobiprole penetrates into skin and the surrounding soft tissue. The penetration of ceftobiprole as determined by *in vivo* microdialysis into skeletal muscle and adipose tissue was 0.69 and 0.49, respectively. Overall, the observed ceftobiprole penetration into skeletal muscle and subcutaneous adipose tissue as determined by *in vivo* microdialysis was comparable to what has been reported with other cephalosporins. Ceftobiprole was well tolerated and no subject discontinued study drug due to an adverse event.

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