SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: LEVAQUIN® NAME OF ACTIVE INGREDIENT: RWJ-25213-097 (levofloxacin)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: LEVO-INI-1001 (CR004174)

Title of Study: An Open-Label Randomized Multiple-Dose Study to Evaluate Levofloxacin Steady-State Pharmacokinetics and Safety in Subjects With Varying Degrees of Renal Function

Coordinating Investigator: William Smith, M.D. New Orleans Center for Clinical Research, New Orleans, LA; USA

Publication (Reference): None

Studied Period (years): Clinical Conduct: 04 January 2004 to 26 April 2006 Sample Analysis in Plasma: 28 June 2005 to 19 May 2006 Sample Analysis in Urine: 26 January to 20 May 2006 Sample Analysis in Dialysate: 13 to 14 April 2006	**Phase of Development:** 1

Objectives: The primary objective of this study was to evaluate the clinical comparability of levofloxacin pharmacokinetics, safety, and tolerability in subjects with varying degrees of renal function under the currently recommended dosing regimen (every 24 hours [q24h] for subjects with creatinine clearance [CL_{CR}] ≥50 mL/min, and every 48 hours [q48h] for subjects with CL_{CR} <50 mL/min, or those requiring hemodialysis (HD) or continuous ambulatory peritoneal dialysis [CAPD]) and the newly proposed alternative regimen (q24h for all subjects).

Methodology: This was an open-label, randomized, parallel-group, multiple-dose, multicenter study, consisting of a 21-day pretreatment screening phase, a 7-day open-label treatment phase, and a 7-day posttreatment phase (or follow-up phase for subjects with early study withdrawal). Subjects who met the prestudy eligibility criteria were randomized to 1 of 10 treatment groups based on degree of renal function or method of dialysis. The randomization also included stratification by renal status. All subjects received a single 750-mg dose of levofloxacin on Day 1. Subsequent doses of either 250, 500, or 750 mg of levofloxacin (q24h or q48h) were based on renal function. Serial blood samples were collected from each subject before dosing and at specified times for up to 24 h (Day 1) and 168 h (Day 7) after dosing for pharmacokinetic evaluations. Pharmacokinetic blood samples were also collected predose on Days 3 to 6. Urine was collected on Days 1 and 7 before dosing and over specific time intervals up to 48 hours postdosing depending on dose regimen. Dialysate fluid samples were collected on Day 7 from HD subjects immediately before dosing (as dialysis began) and at the end of the dialysis treatment. Subjects were confined overnight at the study unit on Days 0, 1, 6, and 7 until the 24-hour blood samples were collected on Days 2 and 8. Safety was based on the incidence, relationship to therapy, and severity of treatment-emergent adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital sign measurements, electrocardiograms (ECGs), and physical examination findings.

Number of Subjects (planned and analyzed): 60 planned (approximately 6 subjects per treatment group), 59 enrolled, 59 randomized; 56 evaluable for pharmacokinetics; 59 evaluable for safety

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 to 65 years inclusive, with varying degrees of renal function and foreseeable stable renal function for the duration of the trial were enrolled in this study. Subjects receiving HD or CAPD received the same dialysis treatment for at least 6 months before screening.

Test Product, Dose and Mode of Administration, NDC No. and Batch Nos.: Levofloxacin was administered orally as a 250-mg, 500-mg, or 750-mg tablets.

Dose	NDC No.	Batch Nos.
250-mg	0045-1520-50	4CG927, 4KG406
500-mg	0045-1525-50	4EG093, 4LG556
750-mg	0045-1530-20	4AG703

Reference Therapy, Dose and Mode of Administration, NDC No.: None

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Duration of Treatment: Levofloxacin was administered for up to 7 days depending on the treatment group.

Criteria for Evaluation:

Pharmacokinetics: Mean concentrations of levofloxacin were determined in plasma, urine, and/or dialysate fluid samples collected predose and up to 24 h (Day 1) and 168 h (Day 7) postdose. In addition, samples were collected predose on Days 3 to 6. Pharmacokinetic parameters included C_{min}, C_{max}, $C_{avg,}$, C_{trough}, t_{max}, $t_{½}$, AUC_{24}, AUC_{48}, AUC_{24-48}, AUC_{∞}, CL/F, CL_R, Vd/F, Ae_{0-24}, and Ae (% Dose).

Safety: Safety was evaluated by monitoring treatment-emergent adverse events and changes in clinical laboratory values, vital sign measurements, electrocardiograms (ECGs), and physical examination findings.

Statistical Methods:

Pharmacokinetics: Plasma levofloxacin concentration versus time profiles were plotted for each subject and for each treatment group. Predose levofloxacin plasma concentrations on Days 5, 6, and 7 (q24h), and on Days 3, 5, and 7 (q48h) were graphically displayed to assess steady-state attainment. Plasma, urine, and dialysate fluid levofloxacin concentration data and pharmacokinetic parameter estimates were summarized by treatment group using descriptive statistics (e.g., N, arithmetic mean, geometric mean, median, minimum, maximum, standard deviation, and coefficient of variation [CV]) for those subjects with evaluable pharmacokinetic data under single- (Day 1) and multiple-dose (Day 7) conditions, respectively.

Safety: The incidence, relationship to therapy, and severity of treatment-emergent adverse events were summarized for each treatment group using a standard adverse event dictionary based on World Health Organization Adverse Reaction Terminology (WHOART). Changes from baseline in clinical laboratory values were assessed by descriptive statistics and summarized for pre- versus posttreatment cross tabulations (with classes for below, within, and above normal ranges). Laboratory abnormalities were listed. Changes in vital sign measurements, ECGs, and physical examination findings were summarized by descriptive statistics.

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SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Mean (standard deviation [SD]) plasma levofloxacin pharmacokinetic parameters following the last dose (Day 7) of a multiple dose regimen in healthy and renally impaired subjects are shown in the table below.

Treatment (Dose Regimen)	t_{max} (h)	C_{max} (µg/mL)	AUC_{24} (µg*h/mL)	AUC_{24-48} (µg*h/mL)	AUC_{48} (µg*h/mL)	CL_{ss}/F (L/h)	$t_{1/2}$ (h)
Trt A (CL_{CR}>80; 750 mg, q24h)	2.50 (0.55)	8.27 (1.28)	82.9 (9.93)	--	96.7 (16.5)	9.15 (1.04)	8.3 (2.9)
Trt B (CL_{CR} 50 to <=80; 750 mg q24h)	3.00 (1.10)	9.49 (1.92)	158 (50.1)	--	232 (95.3)	5.18 (1.68)	18.4 (8.0)
Trt C (CL_{CR} 20 to 49; 750 mg, 750 mg q48h)	4.83 (2.56)	9.58 (2.43)	179 (48.4)	103 (35.3)	282 (80.2)	2.79 (0.561)	32.1 (4.1)
Trt D[b] (CL_{CR} 10 to 19; 750 mg, 500 mg q48h)	2.25 (1.50)	12.4 (0.191)	215 (17.2)	146 (20.3)	362 (36.6)	1.39 (0.132)	41.5 (7.3)
Trt G (CL_{CR} 30 to 49; 750 mg, 500 mg q24h)	4.67 (1.63)	9.54 (1.55)	171 (43.7)	--	264 (83.4)	3.06 (0.694)	24.0 (5.6)
Trt H (CL_{CR} 10 to 29; 750 mg, 250 mg q24h)	1.80 (0.84)	6.71 (1.62)	122 (44.2)	--	203 (82.4)	2.33 (1.02)	33.3 (8.0)

n=6 [a] n=5; [b] n=4

For the healthy subjects (Group A), mean exposure parameters were generally similar (C_{max}) or lower (AUC) than in all groups of renally impaired subjects. With successively increasing degrees of renal impairment, parameters of overall exposure (AUC_{24} and AUC_{48}) increased. Apparent clearance decreased with increasing renal impairment, resulting in prolonged elimination, as shown by a successively increasing mean half-life with increasing impairment.

The 2 groups of moderately impaired subjects (Groups C and G) were generally consistent in their pharmacokinetic parameters. Similarly, the 2 groups of severely impaired subjects (Groups D and H) were generally consistent in their pharmacokinetic parameters, although exposure parameters in Group D (12.4 µg/mL and 215 µg•h/mL for C_{max} and AUC, respectively) were somewhat higher than in Group H (6.71 µg/mL and 122 µg•h/mL for C_{max} and AUC_{24}, respectively). These differences were most likely due to differences in maintenance dose regimen or to inter-subject variability in these small groups.

Mean (SD) plasma levofloxacin pharmacokinetic parameters following the last dose (Day 7) of a multiple dose regimen in HD and CAPD subjects are shown in the table below.

Treatment (Dose Regimen)	t_{max} (h)	C_{max} (µg/mL)	AUC_{24} (µg*h/mL)	AUC_{24-48} (µg*h/mL)	AUC_{48} (µg*h/mL)	CL_{ss}/F (L/h)	$t_{1/2}$ (h)
Hemodialysis (Trt E; 750 mg, 500 mg q48h)	2.85 (4.56)	7.92 (1.34)	135 (45.8)	96.2 (39.1)	231 (83.9)	2.34 (0.604)	68.6 (45.1)
Hemodialysis[a] (Trt I; 750 mg, 250 mg q24h)	0.92 (0.58)	7.70 (1.31)	117 (23.0)	--	207 (50.1)	2.20 (0.370)	55.0 (11.2)
CAPD (Trt F; 750 mg, 500 mg q48h)	6.33 (8.71)	9.02 (1.61)	173 (42.6)	136 (28.9)	309 (70.6)	1.68 (0.323)	59.0 (19.8)
CAPD[a] (Trt J; 750 mg, 250 mg q24h)	2.50 (1.32)	9.43 (2.56)	196 (53.4)	--	346 (92.9)	1.34 (0.294)	61.8 (13.2)

n=6 [a] n=5

Mean maximal plasma concentrations were similar in both groups of HD subjects (7.92 and 7.70 µg/mL in Groups E and I, respectively) and in both groups of CAPD subjects (9.02 and 9.43 µg/mL, respectively); t_{max} was highly variable, with group means ranging from 0.92 to 6.33 hours. Other pharmacokinetic parameters (AUC_{24}, AUC_{48}, CL/F, Vd/F, and $t_{1/2}$) were also similar in the 2 groups of HD and in the 2 groups of CAPD subjects.

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In all but one subject, C_{max} and AUC_{24} values were higher than the therapeutic reference value for antibacterial efficacy. Regardless of renal impairment status, AUC_{24-48} values were similar or higher for the q24h regimens compared to the q48h regimens. These values were also generally higher than those of the healthy normal subjects. Based on these data, the lower dose given more frequently with the q24h regimen yields equal or higher exposure to levofloxacin during the 24- to 48-hour post-dose period than the q48h dose regimen.

Mean pharmacokinetic parameters from the present study (dose normalized to 750 mg, as appropriate) in healthy subjects, in each group of renally impaired subjects and in HD subjects and CAPD were generally comparable to the parameters from the corresponding renal impairment group reported in the current levofloxacin label.

SAFETY RESULTS: Levofloxacin (up to 750 mg/day) for 7 days was well tolerated in renal-impaired adult subjects with stable renal disease. There were no deaths or serious adverse events. One subject had an adverse event (elevated liver function tests) leading to premature treatment discontinuation. For serum chemistry, hematology, and urinalysis laboratory tests, there were no clinically relevant changes in mean values. There were no treatment-related trends or clinically relevant changes in mean vital sign values, ECG assessments, or physical examination findings.

CONCLUSION: The proposed levofloxacin q24h dosing regimens in renally impaired and dialysis subjects provided comparable parameters of exposure (C_{max} and AUC) as the currently recommended dosing regimens (q24h for subjects with CL_{CR} >50 mL/min and q48h for subjects with CL_{CR} <50 mL/min). Both the q24h and the q48h regimens provided steady-state daily exposure that is associated with efficacy in subjects with normal renal function receiving a 750 mg q24h regimen. Treatment with levofloxacin was safe and well tolerated. No deaths or serious adverse events occurred during the study, and only 1 subject discontinued treatment because of an adverse event (elevated liver function tests).

Date of the report: 22 December 2006

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