SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: LEVAQUIN® NAME OF ACTIVE INGREDIENT(S): Levofloxacin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: LOFBO-PHI-116 **Title of Study:** An Open-Label, Randomized, 3-Way Crossover Study to Evaluate the Bioequivalence of an Oral Suspension Formulation, an Oral Solution Formulation, and the Marketed Tablet Formulation of Levofloxacin in Healthy Subjects.		
Principal Investigator: Irving E. Weston, MD, MDS Pharma Services, Phoenix, AZ; USA		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: First Cohort: 02 November 2002 to 04 November 2002; Second Cohort: 15 November 2002 to 25 November 2002. Sample Analysis: 4 December 2002 to 17 December 2002.		**Phase of development:** 1
Objectives: The primary objective of this study was to assess the bioequivalence of an oral suspension formulation of levofloxacin, an oral solution formulation of levofloxacin, and the 500 mg marketed LEVAQUIN® (levofloxacin) tablet, with the tablet formulation as the reference. The secondary objective of the study was to assess the bioequivalence of the oral suspension and the solution formulations, with the suspension formulation as the reference. Safety was also assessed.		
Methodology: This was a randomized, open-label, single-center, single-dose, 3-way crossover, definitive bioequivalence study of 3 oral formulations of levofloxacin (tablet, suspension, and solution) in healthy men and women. It was planned to enroll 36 subjects and to randomly assign each to 1 of 6 treatment-sequence groups (6 subjects in each, 3 men and 3 women). The study comprised a screening period, 3 open-label treatment periods (Periods I, II, and III) separated by washout periods of at least 4 days between doses, and a posttreatment (or early withdrawal) period. The subjects who completed the study received a single dose of all 3 study drug formulations, 1 formulation on Day 1 of each of Periods I, II, and III. Blood samples were collected on Days 1, 2, and 3 of each treatment period immediately before dose administration (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 10, 14, 24, 30, 36, and 48 hours after for measurement of levofloxacin concentration. For all treatment periods, subjects were sequestered at the study site from 6:00 p.m. on Day 0 through the collection of the 48-hour blood sample on Day 3. The posttreatment period consisted of procedures, such as a physical examination and clinical laboratory testing, to ensure the safety of the subjects before they were discharged from the study. Safety was monitored throughout the study.		
Number of Subjects (planned and analyzed): Planned: 36; Analyzed for safety: 72; Analyzed for Pharmacokinetics: 34 Two cohorts of 36 subjects each were enrolled in this study. The first cohort received 1 dose of study drug and completed Period 1. Because many errors occurred in the handling of study procedures by the study site, the study was stopped and reinitiated. The subjects completed early termination procedures. Their data were included in safety analyses; however, no blood samples collected to measure levofloxacin concentrations were analyzed, and no data were included in pharmacokinetic analyses. Thirty-four subjects of the second cohort completed all study procedures.		
Diagnosis and Main Criteria for Inclusion: Men and women aged 18 to 55 years who were considered to be healthy based on a detailed medical history, physical examination, 12-lead electrocardiogram, toxicology screen, specific antigen and antibody screens, and clinical laboratory evaluations.		
Test Product, Dose and Mode of Administration, Batch No.: Levofloxacin 125 mg/5 mL oral suspension GFI 25213-097-FB-030, Bulk Lot: D01LL0856. Levofloxacin 125 mg/5 mL oral solution GFI 25213-097-EA-006, Bulk lot: D02LK0977. Levofloxacin 500-mg tablets, commercial product, NDC 0045-1525-50, Bulk lot: D00LK0530.		

SYNOPSIS (CONTINUED)

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Duration of Treatment: First cohort: 1 dose of study drug; Second cohort: 3 doses of study drug.

Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters were estimated by model independent methods and summarized: C_{max}, t_{max}, $t_{½}$, AUC_{∞}, CL/F, and Vd/F.

Safety: Safety evaluations included adverse event monitoring, standard clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs measurements, physical examinations, and pregnancy tests for women of childbearing potential.

Statistical Methods:

Pharmacokinetics: For each subject, plasma concentration-time profiles were plotted for all treatments received. Mean plasma concentration-time profiles were plotted for each treatment. Plasma concentration data at each time point were summarized with mean, standard deviation and coefficient of variation for each treatment. All estimated pharmacokinetic parameters were summarized with mean, median, geometric mean, minimum, maximum, standard deviation, and coefficient of variation for each treatment.

The primary pharmacokinetic parameters of interest for the statistical analysis were AUC_{∞} and C_{max}. The analysis was performed on log-transformed estimated pharmacokinetic parameters. Only data from subjects who completed the 3 treatment periods were included in the statistical analysis. Analysis of variance (ANOVA) models were fit to the data with 1 of the parameters of interest (AUC_{∞} or C_{max}) as the dependent variable and the effects due to treatment-sequence group, treatment, and period as fixed effects, and subjects nested within the treatment-sequence groups as a random effect.

Testing for the treatment-sequence group and period effects was carried out at the 10% and 5% levels of significance, respectively, using the appropriate error terms. The estimated least square means and intrasubject variability from the above model were used to construct 90% confidence intervals (CIs) for the difference in means on the logarithmic scale between the following pairs of treatments:

1. Oral suspension formulation (Test) to marketed tablet (Reference)
2. Oral solution formulation (Test) to marketed tablet (Reference)
3. Oral solution formulation (Test) to oral suspension formulation (Reference).

The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratio of the mean pharmacokinetic parameters for the above pairs of treatments.

In the treatment pairs listed above, a test formulation was considered to be bioequivalent to the reference formulation if the corresponding 90% CIs fell within the 80% to 125% limits of bioequivalence.

Safety: The number of subjects with treatment-emergent adverse events was summarized for each treatment by body system and preferred term, severity, and relationship to study drug. Laboratory data were summarized by the type of laboratory test. The data collected at each scheduled time point and the changes in values from baseline in each treatment period were summarized using descriptive statistics. Vital signs data collected at each scheduled time point, and the changes from baseline for each treatment were summarized using descriptive statistics. Physical examination results were listed.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

The mean plasma concentration-time profiles for the 3 treatments were nearly superimposable.

At the 10% level of significance, the sequence group effect was not significant for either of the log-transformed pharmacokinetic parameters AUC_{∞} and C_{max}. At the 5% level of significance, the period effect for $AUC_{\infty}$was not significant while that for C_{max} was significant.

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Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: LEVAQUIN® NAME OF ACTIVE INGREDIENT(S): Levofloxacin	Volume: Page:	

SUMMARY – CONCLUSIONS (Continued)

PHARMACOKINETIC RESULTS: (Continued)

For both AUC and C_{max}, the 90% confidence intervals for the ratios of the means comparing the levofloxacin suspension formulation with the marketed tablet fell within the 80% to 125% limits of bioequivalence.

	Geometric Mean			90% Confidence Interval	
Parameter	Suspension	Tablet	Ratio (%)	Lower limit (%)	Upper limit (%)
AUC_{∞}, µg•h/mL	47.33	46.89	100.93	98.57	103.34
C_{max}, µg/mL	5.12	4.97	103.04	98.18	108.15

Similar findings were observed when the levofloxacin solution was compared to the tablet formulation.

	Geometric Mean			90% Confidence Intervals	
Parameter	Solution	Tablet	Ratio (%)	Lower Limit (%)	Upper Limit (%)
AUC_{∞}, µg•h/mL	46.57	46.89	99.31	96.99	101.69
C_{max}, µg/mL	5.46	4.97	109.91	104.73	115.36

Additionally, the results for the solution formulation compared with the suspension formulation fell within the 80% to 125% limits of bioequivalence.

	Geometric Mean			90% Confidence Intervals	
Parameter	Solution	Suspension	Ratio (%)	Lower limit (%)	Upper limit (%)
AUC_{∞}, µg•h/mL	46.57	47.33	98.40	96.10	100.75
C_{max}, µg/mL	5.46	5.12	106.67	101.63	111.95

SAFETY RESULTS: No death or other serious adverse event occurred during this study. Twenty subjects (28%) experienced adverse events: 10 (21%) after receiving the solution, 10 (21%) after the suspension, and 8 (17%) after the tablet. All events, except 1 moderately severe event, were mild. Twenty were possibly related to study drug, 19 doubtfully related, and 7 not related. One subject withdrew from the study because of the adverse events of mildly severe chest pain and moderately severe syncope after receiving the suspension. The number of incidents and the types of adverse events were about equally distributed among the 3 treatments. All adverse events were resolved. No clinically significant trends in changes in clinical laboratory results, vital signs measurements, or physical examinations were seen, and all pregnancy tests were negative.

CONCLUSION: The levofloxacin oral solution and the levofloxacin oral suspension formulations were bioequivalent to the tablet formulation for both total exposure (AUC_{∞}) and peak exposure (C_{max}). The oral solution formulation was also bioequivalent to the suspension formulation for both total exposure (AUC_{∞}) and peak exposure (C_{max}). The 3 single 500-mg doses of levofloxacin administered orally in this study as a solution, suspension, and tablet were well-tolerated by the healthy adult subjects.

Date of the report: 20 June 2003