

SYNOPSIS

Name of Sponsor/Company: R.W. Johnson Pharmaceutical Research Institute	Individual Trial Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use only):</i>
Name of Finished Product: Levaquin [®]		
Name of Active Ingredient: levofloxacin		
Protocol No: CR005479		
Title of Study: A Multicenter, Double-Blind, Randomized Study to Compare the Safety and Efficacy of Oral Levofloxacin with that of Ciprofloxacin HCl in the Treatment of Uncomplicated Skin and Skin Structure Infections in Adults		
Investigators: 15 principal investigators; all investigators enrolled subjects		
Study Centres: 15 centers		
Publications (Reference): None		
Studied Period: 22 January 1993 - 27 December 1994		Phase of development: 3
Objectives: The primary objective of this study was to compare the safety and efficacy of levofloxacin administered orally with that of ciprofloxacin administered orally in the treatment of uncomplicated skin and skin structure infection in adult outpatients.		
Methodology: This was a randomized, double-blind, active-control, multicenter study conducted in Argentina, Brazil, Columbia, and Mexico. Subjects were assigned to one of two treatment groups (levofloxacin or comparator) in a 1:1 ratio according to a computer-generated randomization schedule. Efficacy evaluations included assessments of posttherapy (2-7 days following last dose of study drug) clinical response rates and posttherapy microbiologic response rates by pathogen and by subject in those subjects with a response of cured or improved posttherapy. The primary variables for this study were clinical response to treatment (defined as cured, improved, or failed) and microbiologic response to treatment (eradicated, partially eradication, persisted). Safety evaluations included incidence of treatment-emergent adverse events, and changes from admission to posttherapy in clinical laboratory test results and in physical examination.		
Number of Subjects (planned and analyzed): Planned enrollment: 400 subjects. Enrolled: 361 subjects evaluable for safety; 180 subjects received levofloxacin treatment and 181 received ciprofloxacin. Data for 89 subjects enrolled at 3 Mexican study centers not evaluable for efficacy; accordingly, 272 subjects evaluable for efficacy, 136 subjects received levofloxacin and 136 subjects received ciprofloxacin.		
Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older with a diagnosis of skin and/or skin structure infection as evidenced by: localized pain, erythema, swelling, drainage, or other clinical signs and symptoms. Additional inclusions: multiple sites of infection were allowed; culture from infected area must have been available. Subjects with any of the following were excluded: condition that required parenteral antimicrobial therapy; osteomyelitis; severe infection; an infection due to an organism known prior to study entry to be resistant to either study drug; signs and symptoms of septic shock; requirement of debridement at the site of infection; previous allergic or serious adverse reaction to quinolones; severe lactose intolerance; calculated creatinine clearance less than 30 mL/min; grossly underweight (40 kg or less); history of effective systemic antimicrobial therapy within 48 hours prior to admission; requirement of a second systemic antimicrobial regimen or use of a topical antimicrobial at the site of infection; seizure disorder; requirement of major tranquilizers.		
Test Product, Dose and Mode of Administration: Levofloxacin 500 mg PO q24h		
Duration of Treatment: 7 days for levofloxacin plus 3 days for matching placebo and 10 days for ciprofloxacin		
Reference Therapy, Dose and Mode of Administration Ciprofloxacin 500 mg PO q12h		

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Criteria for Evaluation: Efficacy: <ul style="list-style-type: none"> Clinical response assessed posttherapy 2 to 7 days following last dose of therapy. Posttherapy clinical response categorized as cured, improved, failed, or unable to evaluate. Microbiologic outcomes: <ul style="list-style-type: none"> Microbiologic response assessed posttherapy by pathogen and by subject categorized as eradicated, partially eradicated, or persisted. Safety: <ul style="list-style-type: none"> Occurrence of treatment-emergent adverse events during the study; changes from admission to posttherapy in clinical laboratory test results and in physical examination. 		
Statistical Methods: The primary efficacy variables were the clinical response to treatment (defined as cured, improved, or failed) and the microbiologic response to treatment (defined as eradicated, partially eradicated, or persisted). The safety analyses involved the examination of the incidence, severity, and type of adverse events reported during the study and by changes in physical findings and clinical laboratory tests from pre- to posttherapy. Adverse events were summarized for each treatment group by body system and primary term. The proportions of subjects in each treatment group reporting an adverse event were compared using Fisher's exact two-sided test, if appropriate. Mean changes in laboratory tests from baseline to posttherapy for each treatment group were compared using a two-sided t-test for two independent samples. Vital signs were summarized to facilitate identification of clinically significant changes. The clinical response rates based on the resolution of signs and symptoms at posttherapy for levofloxacin and ciprofloxacin were compared using the Wilcoxon rank sum test with one degree of freedom. The proportions of subjects with a clinical success (cured or improved) for each treatment group were compared using Fisher's exact two-sided test and 95% confidence intervals were computed around the difference in success rates to claim equivalence. The microbiological eradication rates for levofloxacin and ciprofloxacin HCl were compared using Fisher's exact two-sided test. A 95% confidence interval around the difference in eradication rates was computed. The microbiological eradication rates for infections were compared using the Wilcoxon rank sum test with one degree of freedom. All statistical inferences were based on a Type I error rate of 0.05.		
SUMMARY – CONCLUSIONS EFFICACY RESULTS: Clinical Results: Among clinically evaluable subjects in the levofloxacin treatment group, 80.6% were cured and 15.5% were improved, compared with 75.0% and 18.5% in the ciprofloxacin treatment group, respectively. Five (3.9%) subjects in the levofloxacin treatment group and eight (6.5%) subjects in the ciprofloxacin treatment group failed treatment. In the intent-to-treat group, levofloxacin treatment resulted in 77.9% cure, 16.2% improvement, and 4.4% failure; 1.5% of subjects could not be evaluated; ciprofloxacin treatment resulted in 72.8% cure, 18.4% improvement, and 5.9% failure; 2.9% of subjects could not be evaluated. For clinically evaluable subjects, when the clinical response categories “cured” and “improved” were combined into a single category of “clinical success,” levofloxacin treatment resulted in 96.1% clinical success and ciprofloxacin treatment resulted in 93.5% clinical success, with a confidence interval of [-8.4, 3.3] for the difference (ciprofloxacin minus levofloxacin) in success rates. The upper limit of this confidence interval lies below the upper bound of 10%, thereby supporting the therapeutic equivalence of the two treatments. Ninety-five percent confidence intervals were computed for each study center with 10 or more clinically evaluable subjects in each treatment group and for all other centers combined; the confidence intervals demonstrate the consistency of results across centers. In the intent-to-treat group, the clinical success rates for treatment with levofloxacin and ciprofloxacin were 94.1% and 91.2%, respectively. The individual 95% confidence intervals for all of the analysis groups support the therapeutic equivalence of the two treatments. MICROBIOLOGIC RESULTS: The overall microbiologic eradication rates by pathogen in the levofloxacin and ciprofloxacin treatment groups were 93.2% and 91.7%, respectively, with a 95% confidence interval of [-8.3, 5.2] for the difference between treatments (ciprofloxacin minus levofloxacin). The eradication rates in the levofloxacin and ciprofloxacin treatment groups by subject were 93.0%		

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and 89.7%, with a 95% confidence interval of [-11.7, 5.1] for the difference between treatments. Microbiologic results were generally comparable across analysis groups and centers.

The microbiologic eradication rates for gram-positive and gram-negative aerobes in the levofloxacin treatment group were 93.1% and 100%, respectively, and in the ciprofloxacin treatment groups were 91.0% and 92.6%, respectively. There was a 94.3% eradication rate for the most common pathogen (*S. aureus*) and a 94.4% eradication rate for the second most common pathogen (*S. pyogenes*) in the levofloxacin group. The corresponding eradication rates in the ciprofloxacin treatment group were 93.3% and 92.3%, respectively.

Comparable results were seen across analysis groups for both clinical and microbiologic endpoints. There was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency and reliability of these response measures. In addition, the clinical and microbiologic responses for all subjects were comparable to those described here.

SAFETY RESULTS:

Three hundred fifty-seven (98.9%) of 361 subjects enrolled were evaluated for safety. Of the 357 evaluable subjects, 179 received levofloxacin and 178 received ciprofloxacin. Four subjects (one in the levofloxacin group and three in the ciprofloxacin group) were lost to follow-up with no postadmission safety data available and were therefore excluded from the safety analysis.

Thirty-nine (21.8%) of 179 evaluable subjects in the levofloxacin treatment group and 29 (16.3%) of 178 evaluable subjects in the ciprofloxacin treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator to be related or unrelated to study drug.

Adverse events were most common in the gastrointestinal system with similar incidence rates in the levofloxacin (12.3%) and ciprofloxacin (10.7%) groups. For the remaining body systems, the frequency of adverse events was similar in both treatment groups except for a slightly higher incidence of central and peripheral nervous system disorders (mostly dizziness) in the levofloxacin group than in the ciprofloxacin group. The most frequently reported adverse events were nausea (5.6% incidence rate for levofloxacin-treated subjects versus 3.4% for ciprofloxacin-treated subjects), diarrhea (5.0% versus 2.2%), dizziness (4.5% versus 1.7%), and somnolence (3.4% versus 2.8%). The two treatment groups were generally comparable with respect to the type and incidence of adverse events. Two subjects in each of the levofloxacin and ciprofloxacin groups reported adverse events of marked severity. Three of these markedly severe adverse events were considered probably related to study drug administration, one in the levofloxacin group (diarrhea) and two in the ciprofloxacin group (nausea and abdominal pain). Drug-related adverse events reported by $\geq 1.0\%$ of levofloxacin-treated subjects were nausea (2.2%), diarrhea (1.7%), and somnolence (1.7%). Drug-related adverse events reported by $\geq 1.0\%$ of ciprofloxacin-treated subjects were nausea (2.2%), abdominal pain (1.7%), insomnia (1.7%), diarrhea (1.1%), and vomiting (1.1%).

Seven (2.0%) subjects discontinued the study drug due to adverse events, including five (2.8%) in the levofloxacin treatment group and two (1.1%) in the ciprofloxacin treatment group. The treatment-limiting adverse events in both groups were predominantly gastrointestinal complaints (abdominal pain, vomiting, diarrhea, and nausea).

Two subjects in the levofloxacin treatment group and one subject in the ciprofloxacin treatment group reported a serious or potentially serious adverse event during or approximately two weeks after completing study therapy. The subject in the ciprofloxacin treatment group died 13 days after receiving the last dose of study drug; the events (cardiac failure, sudden death) were considered remotely related to study drug administration. Both events reported by the subjects in the levofloxacin treatment group (malignant lymphoma and accidental injury) were considered unrelated to study drug administration.

There were no clinically significant mean changes from admission to posttherapy for any laboratory analyte in the levofloxacin-treated or ciprofloxacin-treated group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group for subjects who had both admission and posttherapy data available was low ($\leq 5.0\%$) and generally comparable across treatment groups for all analytes. Twenty-eight subjects (14 in the levofloxacin group and 14 in the ciprofloxacin group) had a total of 36 markedly abnormal test results after therapy start. Twelve subjects had elevated blood urea nitrogen levels: seven (5.0%) in the levofloxacin group and five (3.5%) in the ciprofloxacin-treated group. Three subjects in the levofloxacin-treated group and one subject in the ciprofloxacin-treated group had elevated phosphorus levels.

There were no clinically significant changes in vital signs from admission to posttherapy in levofloxacin-treated or

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<p>ciprofloxacin-treated subjects, with comparable results in the two groups. Similarly, there were no clinically significant treatment-emergent physical examination abnormalities.</p> <p>CONCLUSIONS:</p> <p>Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with uncomplicated skin and skin structure infections. The clinical success and microbiologic eradication rates in the levofloxacin treatment group were therapeutically equivalent to those observed in the ciprofloxacin group. Data from this trial support the effectiveness of levofloxacin for uncomplicated skin and skin structure infections due to <i>S. aureus</i> and <i>S. pyogenes</i>.</p>		
Date of Report: 08 December 1995		

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