SYNOPSIS

Name of Sponsor/Company: R.W. Johnson Pharmaceutical Research Institute	Individual Trial Table Referring to Part of the Dossier: Volume: Page:	(*For National Authority Use only):*
Name of Finished Product: Levaquin®		
Name of Active Ingredient: levofloxacin		

Protocol No: CR005497

Title of Study: A Multicenter, Randomized Study to Compare the Safety and Efficacy of Oral Levofloxacin with that of Cefuroxime Axetil in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis in Adults

Investigators: 43 principal investigators; 9 investigators enrolled no subjects

Study Centres: 34 centers

Publications (Reference): None

Studied Period: 31 August 1993 - 16 May 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 cefuroxime axetil administered orally in the treatment of acute bacterial exacerbation of chronic bronchitis in adult outpatients.

Methodology:
This was a randomized, open-label, active-control, multicenter study conducted in the United States. 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 (5-7 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 efficacy variable for this study was clinical response to treatment (defined as cured, improved, or failed), and the secondary efficacy variable was the 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: 492 subjects evaluable for efficacy and safety; 248 subjects received levofloxacin treatment and 244 received cefuroxime axetil.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older with a diagnosis of acute bacterial exacerbation of chronic bronchitis as evidenced by: history of chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema), recent increase in cough, change in character and/or increase in production of sputum, or other clinical signs and symptoms on physical examination. Additional inclusions: appropriate candidates for oral therapy, appropriate sputum specimen available; previous antimicrobial therapy allowed if previous therapy duration was ≤24 hours or if previous therapy duration was >24 hours and there was no improvement or stabilization on that therapy. Subjects with any of the following were excluded: illness requiring parenteral antimicrobial therapy; an infection due to an organism known prior to study entry to be resistant to either study drug; previous allergic or serious adverse reaction to quinolones; calculated creatinine clearance ≤50 mL/min; acute bronchitis, pneumonia, or cystic fibrosis; required a second systemic antimicrobial agent; seizure disorder; or unstable psychiatric illness.

Test Product, Dose and Mode of Administration:
Levofloxacin 500 mg PO q24h

Duration of Treatment: 5-7 days for levofloxacin and 10 days for cefuroxime axetil

Reference Therapy, Dose and Mode of Administration:
Cefuroxime axetil 250 mg PO q12h

Criteria for Evaluation:

Efficacy:

- Clinical response assessed posttherapy 5 to 7 days following last dose of therapy. Posttherapy clinical response

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categorized as cured, improved, failed, or unable to evaluate.

Microbiologic outcomes:

- Microbiologic response assessed posttherapy by pathogen and by subject, categorized as eradicated, partially eradicated, or persisted.

Safety:

- 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 variable was clinical response to treatment (defined as cured, improved, or failed) and the secondary efficacy variable was 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.

The responses of cured and improved were combined and classified as a clinical success in order to perform interval estimation. A two-sided 95% confidence interval about the difference in clinical success rates between levofloxacin and cefuroxime axetil was provided to estimate equivalence.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

CLINICAL RESULTS: Among clinically evaluable subjects in the levofloxacin treatment group, 80.6% were cured and 14.0% were improved, compared with 75.5% and 17.0% in the cefuroxime axetil treatment group. Twelve (5.4%) subjects in the levofloxacin treatment group and 17 (7.4%) subjects in the cefuroxime axetil treatment group failed treatment. In the modified intent-to-treat group, levofloxacin treatment resulted in 75.0% cure, 15.3% improvement, and 6.0% failure; 3.6% of subjects could not be evaluated; cefuroxime axetil treatment resulted in 72.5% cure, 17.6% improvement, and 7.4% failure; 2.5% 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 94.6% clinical success and cefuroxime axetil treatment resulted in 92.6% clinical success, with a 95% confidence interval of [-6.8, 2.7] for the difference (cefuroxime axetil minus levofloxacin) in success rates. All of the treatment differences in this confidence interval lie below the upper bound of 10%, thereby establishing clinical equivalence of the two treatments. Confidence intervals computed for each study center with 10 or more clinically evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers. In the modified intent-to-treat group, the clinical success rates for treatment with levofloxacin and cefuroxime axetil were 90.3% and 90.2%, respectively. The individual confidence intervals for all of the analysis groups are centered below zero and are consistent with therapeutic equivalence of the two treatments regarding clinical success rates.

MICROBIOLOGIC RESULTS:

The overall microbiologic eradication rates by pathogen in the levofloxacin and cefuroxime axetil treatment groups were 97.4% and 94.6%, respectively, with a 95% confidence interval of [-6.8, 1.2] for the difference between treatments (cefuroxime axetil minus levofloxacin) assuming independence of multiple pathogens and multiple strains within a subject. The eradication rates in the levofloxacin and cefuroxime axetil treatment groups by subject were 96.3% and 93.2%, with a confidence interval of [-8.6, 2.5]. Using a confidence interval upper bound of 10% for eradication rates greater than 90%, this interval supports therapeutic equivalence between the two treatments. Microbiologic results were generally comparable across analysis groups and centers.

The most prevalent pathogens for both levofloxacin and cefuroxime axetil treatment groups were gram-negative aerobes (77.4% and 72.1% of pathogens for the two treatment groups); the remaining pathogens were gram-positive aerobes (22.6% and 27.9% of pathogens in the two treatment groups). The microbiologic eradication rates for gram-negative and gram-positive aerobes in the levofloxacin treatment group were 98.0% and 95.3%, and in the cefuroxime axetil treatment group were 93.8% and 96.8%. There was 95.5% eradication of the most common pathogen (*H. influenzae)* and 100.0% eradication of the second and third most common pathogens (*H. parainfluenzae* and *M. (Branhamella) catarrhallis*) in the levofloxacin treatment group versus eradication rates of 90.6% to 93.8% in the cefuroxime axetil treatment group. There

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was a 100% eradication of *S. aureus* and 87.5% eradication of *S. pneumoniae* in the levofloxacin treatment group versus 97.1% and 100.0% eradication in the cefuroxime axetil group.

Comparable results were seen across analysis groups for both clinical and microbiologic endpoints. In addition, there was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency of the clinical and microbiologic responses.

SAFETY RESULTS:

Four hundred eighty-four (98.4%) of 492 subjects enrolled were evaluated for safety. Of the 484 evaluable subjects, 243 received levofloxacin and 241 received cefuroxime axetil. Eight subjects (five in the levofloxacin treatment group and three in the cefuroxime axetil treatment group) were lost to follow-up with no postadmission data available and were therefore excluded from the safety analysis.

One-hundred twenty-seven (52.3%) of 243 evaluable subjects in the levofloxacin treatment group and 124 (51.5%) of 241 evaluable subjects in the cefuroxime axetil treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. Body systems with the highest reported incidence of adverse events were the gastrointestinal system and the central and peripheral nervous system. The most frequently reported adverse events were headache (13.2% incidence rate for levofloxacin-treated subjects versus 10.0% for cefuroxime axetil-treated subjects), diarrhea (7.4% versus 12.4%), nausea (7.4% versus 4.6%), and dizziness (7.0% versus 3.7%). The two treatment groups were generally comparable with respect to the type and incidence of adverse events. Twenty-four (9.9%) subjects in the levofloxacin treatment group and 19 (7.9%) subjects in the cefuroxime axetil treatment group had adverse events considered by the investigator to be drug-related, ie, probably or definitely related to study drug. Drug-related adverse events reported by ≥1.0% of levofloxacin-treated subjects were vaginitis (4.1%), nausea (2.5%), and diarrhea (1.6%). Drug-related adverse events reported by ≥1.0% of cefuroxime axetil-treated subjects were diarrhea (2.5%), taste perversion (1.7%), and vaginitis (2.0%). The majority of adverse events were assessed as mild in severity. Thirteen subjects in the levofloxacin treatment group reported one or more adverse events of marked severity, including marked dyspnea and headache in two subjects each. Twelve subjects in the cefuroxime axetil treatment group reported one or more adverse events of marked severity, including diarrhea and chest pain in two subjects each. Of the four subjects with marked drug-related adverse events, two were in the levofloxacin treatment group (pruritus in one subject and nausea in one subject) and two were in the cefuroxime axetil treatment group (chest pain and rhinitis in one subject and diarrhea in one subject).

Fifteen subjects discontinued the study drug due to adverse events, including seven in the levofloxacin treatment group and eight in the cefuroxime axetil treatment group. The treatment-limiting adverse event was considered serious or potentially serious in one levofloxacin-treated subject (dyspnea) and one cefuroxime-treated subject (syncope). No deaths occurred during the study.

Nine subjects in the levofloxacin treatment group and five subjects in the cefuroxime axetil treatment group reported a serious or potentially serious adverse event during or up to approximately three weeks after completing study therapy. Of the 14 subjects with serious or potentially serious adverse events, two subjects withdrew from the study because of the adverse event. In all cases, the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug, and in most cases was attributed to the subject's underlying condition.

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for any laboratory analytes in either treatment group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group was low (≤2.2%) and comparable across treatment groups. Twenty-nine subjects (12 in the levofloxacin group and 17 in the cefuroxime axetil group) had a total of 33 markedly abnormal test results after therapy start. Overall, six subjects in each treatment group had abnormal glucose levels: two levofloxacin-treated subjects and five cefuroxime axetil-treated subjects had increased glucose levels; four levofloxacin-treated subjects and one cefuroxime axetil-treated subject had decreased glucose levels. One subject in the levofloxacin group and four subjects in the cefuroxime axetil group had markedly abnormal liver function tests (elevations in SGOT or SGPT). Three subjects in the levofloxacin group and six subjects in the cefuroxime axetil group had markedly abnormal hematology tests (decreased neutrophils or lymphocytes).

There were no clinically significant changes in vital signs from admission to posttherapy in levofloxacin-treated or cefuroxime axetil-treated subjects, with comparable results in the two groups. Similarly, there were no clinically significant treatment-emergent physical examination abnormalities.

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CONCLUSIONS: Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with acute bacterial exacerbation of chronic bronchitis. The clinical responses in the levofloxacin treatment group were therapeutically equivalent to those observed in the cefuroxime axetil group, as were the microbiologic eradication rates. These data support the efficacy of levofloxacin for acute bacterial exacerbation of chronic bronchitis due to *H. influenzae*, *H. parainfluenzae*, *M. (Branhamella) catarrhalis*, *S. pneumoniae*, and *S. aureus*.		
Date of Report: 16 Jun 1995		

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