SYNOPSIS

Name of Sponsor/Company: Ortho-McNeil Pharmaceutical Inc.	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: CR005491

Title of Study: A Multicenter, Active-Controlled, Randomized Study to Evaluate the Safety and Efficacy of Levofloxacin Versus Ceftriaxone Sodium or Cefuroxime Axetil in the Treatment of Community-Acquired Pneumonia in Adults

Investigators: 47 principal investigators; 6 investigators did not enroll subjects

Study Centres: 40 centers

Publications (Reference): None

Studied Period: 11 November 1992 - 25 January 1995	**Phase of development:** 2/3

Objectives:
The primary objective of this study was to compare the safety and efficacy of levofloxacin administered orally or intravenously with that of ceftriaxone sodium administered intravenously or intramuscularly or cefuroxime axetil administered orally in the treatment of community-acquired pneumonia in adult outpatients.

Methodology:
This was a randomized, open-label, active-control, multicenter study conducted in the United States and Canada. 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 medication) 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) based on changes in signs and symptoms and chest x-ray findings. The secondary efficacy variable was the microbiologic response to treatment. 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: 528 subjects for a minimum of 183 clinically and microbiologically evaluable subjects in each treatment group. Enrolled: 590 subjects evaluable for efficacy and safety: 295 subjects received levofloxacin and 295 subjects received ceftriaxone/cefuroxime.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older with a diagnosis of community-acquired pneumonia based upon clinical signs and symptoms of a lower respiratory tract infection, including at least two of the following: fever (oral temperature ≥38°C/100.4°F or rectal temperature ≥39°C/102.2°F), cough, production of purulent sputum (<10 epithelial cells and >25 WBC per low power field), chest pain, shortness of breath, or evidence of pulmonary consolidation or physical examination (rales on auscultation, dullness to percussion, or egophony), chest x-ray infiltrate compatible with acute infection; received previous antimicrobial therapy if previous therapy duration was 24 hours or less or if previous therapy duration was greater than 24 hours but no improvement or stabilization on that therapy; subjects who developed bacterial pneumonia while receiving an antifungal or antiviral agent were eligible for study entry.

Test Product, Dose and Mode of Administration:
Levofloxacin 488 mg PO or 500 mg IV q24h

Duration of Treatment: 7 to 14 days

Reference Therapy, Dose and Mode of Administration:
Ceftriaxone sodium 1-2 grams IV or IM q24h or in divided doses q12h for 7-14 days or cefuroxime axetil 500 mg PO q12h for 7-14 days)

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.

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 the clinical response to treatment measured by reduction of pretreatment signs and symptoms (defined as cured, improved, or failed) and improvement of infiltrate on radiography. The secondary efficacy parameter was the microbiologic response to treatment (defined as the eradication rate). Efficacy parameters were summarized by severity.

The safety variables included incidence, severity, and type of adverse events during the study and changes in physical findings and laboratory measurements from pretherapy to posttherapy. Ninety-five percent confidence intervals about the difference in success rates (cured and improved) between levofloxacin and the comparative therapy groups will be used to evaluate clinical equivalence.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Among all clinically evaluable subjects in the levofloxacin treatment group, 72.1% were cured, 24.3% were improved, and 3.5% failed at the posttherapy visit, compared with 69.1%, 21.3% and 9.6%, respectively in the ceftriaxone/cefuroxime treatment group. Clinical response rates were 72.3% cured, 24.4% improved, and 3.3% failed for the subset of 213 clinically evaluable subjects who received levofloxacin at q24h or q48h intervals. The data indicate that levofloxacin treatment was comparable in efficacy among subjects with severe infections and those with mild/moderate infections.

When the clinical response categories "cured" and "improved" were combined into a single category of "clinical success" for clinically evaluable subjects, levofloxacin treatment resulted in 96.5% clinical success and ceftriaxone/cefuroxime treatment resulted in 90.4% clinical success, with a 95% confidence interval of [-10.7, -1.3] for the difference (ceftriaxone/cefuroxime minus levofloxacin) in success rates. The confidence interval, the upper limit of which lies below the upper bound of 10%, establishes that levofloxacin treatment is at least equivalent to ceftriaxone/cefuroxime in terms of achieving clinical success. Clinical response rates were generally comparable across efficacy analysis groups and study centers.

Of the 205 clinically evaluable subjects in the levofloxacin treatment group who had a poststudy clinical evaluation and had a posttherapy clinical response of cured or improved, poststudy clinical responses were cure for 90.2%, improved for 5.9%, and relapse for 2.9% of subjects. Of the 193 subjects in the ceftriaxone/cefuroxime group who met the aforementioned criteria, 92.2% had a poststudy response of cure, 5.7% improved, and 2.1% relapse. Poststudy clinical response ratings for the microbiologically evaluable and intent-to-treat subjects were consistent with the results of the clinically evaluable group.

Microbiologic Results: Among subjects evaluable for microbiologic efficacy, the overall microbiologic eradication rates by subject in the levofloxacin and ceftriaxone/cefuroxime treatment groups were 98.4% and 87.5%, respectively, with a 95% confidence interval of [-17.1, -4.7], for the difference between treatments (ceftriaxone/cefuroxime minus levofloxacin). This confidence interval establishes that levofloxacin is at least equivalent to ceftriaxone/cefuroxime in terms of achieving microbiologic eradication.

The microbiologic eradication rate was 100% for the most prevalent pathogens detected in respiratory secretion cultures for all microbiologically evaluable subjects in the levofloxacin group, with the exception of *H. parainfluenzae,* which had an eradication rate of 87.5%. In the ceftriaxone/cefuroxime group, eradication rates for these pathogens ranged from 71.4% to 100%. Both levofloxacin and ceftriaxone/cefuroxime eradicated 100% of *S. pneumoniae* detected in blood culture. Levofloxacin eradicated 97.9% to 100% of atypical pathogens detected by serology, as compared with eradication rates of 75.0% to 100% among ceftriaxone/cefuroxime-treated subjects.

The posttherapy microbiologic eradication rates for *C. pneumoniae*, *H. influenzae*, *S. pneumoniae* (detected in respiratory specimens), *M. pneumoniae*, and *H. parainfluenzae*, the most prevalent pathogens, were 97.9%, 100%,

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100%, 100%, and 87.5%,, respectively, for all microbiologically evaluable subjects treated with levofloxacin as compared with 92.5%, 79.2%, 96.9%, 100%, and 71.4%, respectively, among microbiologically evaluable subjects in the ceftriaxone/cefuroxime group. Posttherapy microbiologic eradication rates were similar for clinically evaluable subjects and were somewhat lower in the intent-to-treat group, as would be expected. The microbiologic eradication rate among the 118 subjects evaluable for microbiologic efficacy who received levofloxacin at q24h or q48h intervals throughout their entire course of therapy was 99.2%.

Microbiologic eradication rates, by subject and pathogen for microbiologically evaluable subjects, were 98.1% for subjects with mild/moderate infections and 100% for subjects with severe infections in the levofloxacin group; in the ceftriaxone/cefuroxime group, these rates were 87.9% for subjects with mild/moderate infections and 85.7% for subjects with severe infections. The data indicate that levofloxacin treatment, as assessed by subject or pathogen, was comparable in efficacy among subjects with severe infections as among those with mild/moderate infections and produced eradication rates as high or higher than ceftriaxone/cefuroxime treatment.

For all efficacy analyses, groups, microbiologic eradication rates poststudy were similar to, or lower than, the corresponding posttherapy rates, with a larger number of subjects having a response of "unknown" at the poststudy time point.

The clinical response rates are comparable among the efficacy analysis groups within treatment groups. Higher clinical response and microbiologic eradication rates were observed in the levofloxacin group than in the ceftriaxone/cefuroxime group. The clinical response rates in the levofloxacin group exceeded 90.0% for all analysis groups, as did the microbiologic eradication rate in the subjects evaluable for microbiologic efficacy; the microbiologic eradication rate for intent-to-treat subjects with an admission pathogen was 88.0%. 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 and reliability of these response measures.

SAFETY RESULTS:

Five hundred eighty-four subjects of the 590 enrolled were evaluated for safety. Of the 584 evaluable subjects, 291 received levofloxacin and 293 received ceftriaxone/cefuroxime. Four levofloxacin-treated and two ceftriaxone/cefuroxime-treated subjects who were lost to follow-up with no postadmission data available were excluded from the safety analysis.

One hundred forty-six (50.2%) of 291 subjects evaluable for safety in the levofloxacin treatment group and 146 (49.8%) of 293 subjects evaluable for safety in the ceftriaxone/cefuroxime 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. All body systems had confidence intervals that included zero (indicating no statistically significant difference between treatments) with two exceptions: heart rate and rhythm disorders (reported by five levofloxacin-treated subjects and none of the ceftriaxone/ cefuroxime-treated subjects) and urinary system disorders (reported by five ceftriaxone/cefuroxime-treated subjects and none of the levofloxacin-treated subjects).

Gastrointestinal adverse events were the most common adverse events in both treatment groups (22.3% for levofloxacin and 25.9% for ceftriaxone/cefuroxime). The body system with the second highest reported incidence of adverse events for both treatment groups was the central and peripheral nervous system; the incidence of adverse events in this body system was approximately one-half that observed for the gastrointestinal system. The nature and frequency of adverse events was generally comparable across the two treatment groups with the following exceptions: a higher incidence of headache and diarrhea was noted in the ceftriaxone/cefuroxime group (10.6% and 11.3%, respectively) than in the levofloxacin group (6.5% and 5.8%, respectively) and small differences in other GI events were found between groups. In addition, chest pain occurred in 3.8% of levofloxacin-treated subjects; none of the ceftriaxone/cefuroxime-treated subjects reported chest pain. A higher percentage of levofloxacin-treated subjects (4.6%) compared with ceftriaxone/cefuroxime-treated subjects (1.5%) reported adverse events of the female reproductive system (primarily vaginitis). Also, as noted above, urinary system disorders were reported by 1.7% of ceftriaxone/cefuroxime-treated subjects while no levofloxacin-treated subject experienced an adverse event of this body system. Adverse events of the central and peripheral nervous system were reported by 14.7% of ceftriaxone/cefuroxime-treated subjects and 10.7% of levofloxacin-treated subjects; for both treatment groups, reports in this body system consisted mainly of headache.

Seventeen (5.8%) subjects in the levofloxacin treatment group and 25 (8.5%) subjects in the ceftriaxone/ cefuroxime 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 nausea (1.7%),

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diarrhea (1.4%) and injection site pain (1.0%). Drug-related adverse events reported by ≥1.0% of ceftriaxone/cefuroxime-treated subjects were diarrhea (3.8%), nausea (2.0%), dyspepsia (1.0%), and vomiting (1.0%).

The majority of adverse events were assessed as mild in severity. Twenty subjects in each of the levofloxacin and ceftriaxone/cefuroxime groups reported one or more events of marked severity. In the levofloxacin group, the most common of these events consisted of respiratory disorders (five subjects) and cardiac events (four subjects). In the ceftriaxone/cefuroxime group, the most common marked events consisted of respiratory disorders (eight subjects) and disorders of the body as a whole (four subjects).

Twenty-five subjects discontinued the study drug due to adverse events, including 13 in the levofloxacin treatment group and 12 in the ceftriaxone/cefuroxime treatment group. In the levofloxacin group, all of the adverse events (with the exception of one case of diarrhea that occurred on Day 12) leading to discontinuation emerged within the first five days of therapy; these adverse events included primarily gastrointestinal complaints or central and peripheral nervous system-related symptoms. Treatment-limiting adverse events in the ceftriaxone/cefuroxime group most frequently consisted of gastrointestinal complaints.

Twenty-three subjects in the levofloxacin treatment group and 24 subjects in the ceftriaxone/cefuroxime treatment group reported a serious or potentially serious adverse event during or up to approximately four weeks after completing study therapy, including two deaths in the levofloxacin group and eight deaths in the ceftriaxone/cefuroxime group. Of the 47 subjects with serious or potentially serious adverse events, five withdrew from the study because of the adverse event. In the majority of 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 many cases, appeared to be related to the subject's underlying physical 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 (≤4.7%) and comparable across treatment groups, with the exception of SGPT and SGOT which were elevated in a greater proportion of ceftriaxone/cefuroxime-treated subjects than levofloxacin-treated subjects. Seventy-five subjects (34 in the levofloxacin group and 41 in the ceftriaxone/cefuroxime group) had a total of 99 markedly abnormal test results after therapy start. Seven subjects in the levofloxacin group and 11 in the ceftriaxone/cefuroxime group had markedly decreased lymphocytes. Twenty-five subjects had markedly abnormal glucose levels: three levofloxacin-treated and three ceftriaxone/cefuroxime-treated subjects had increased glucose levels and 11 levofloxacin-treated and eight ceftriaxone/cefuroxime-treated subjects had decreased glucose levels. Four subjects in the levofloxacin group and 15 subjects in the ceftriaxone/ cefuroxime treatment group had markedly abnormal liver function tests (elevations in SGOT, SGPT, or alkaline phosphatase).

There were no clinically significant changes from admission to posttherapy in levofloxacin-treated or ceftriaxone/cefuroxime-treated subjects, with comparable results in the two groups.

CONCLUSIONS:

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with community-acquired pneumonia. The clinical success rate and the microbiologic eradication rates in the levofloxacin treatment group were at least therapeutically equivalent to those observed in the ceftriaxone/cefuroxime group. These data support the efficacy of levofloxacin for community-acquired pneumonia due to *S. pneumoniae*, *H. influenzae*, *C. pneumoniae*, *M. pneumoniae*, *K. pneumoniae*, *L. pneumophila*, *M. (Branhamella) catarrhalis*, and *S. aureus*.

Date of Report: 13 Sep 1995

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