SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho-McNeil Pharmaceutical, Inc. 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.: CR002809

Title of Study: A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Levofloxacin 750 mg Once Daily for 5 Days Versus Levofloxacin 500 mg Once Daily for 10 days in the Treatment of Acute Bacterial Sinusitis in Adults

Principal Investigator: Fifty-eight principal investigators enrolled subjects.

Publication (Reference): None

Study Initiation/Completion Dates: 18 October 2002 - 23 April 2004 **Phase of development:** 3B

Objectives: The primary objective of this study was to show that a five-day course of levofloxacin, 750 mg, orally (p.o.) once daily (q.d.) was at least as effective as a 10-day course of levofloxacin, 500 mg, p.o. q.d. for the treatment of acute bacterial sinusitis. Secondary objectives included the eradication or presumed eradication of admission pathogens and the collection of additional safety information.

Methodology: This was a multicenter, randomized, double-blind, Phase 3B non-inferiority study conducted in the United States involving outpatient adults with acute bacterial maxillary sinusitis. Subjects were randomized 1:1 to receive either levofloxacin 750 mg p.o. q.d. for five days or levofloxacin 500 mg p.o. q.d. for 10 days. All subjects received study medication for 10 days. Subjects in the 750 mg group received levofloxacin for the first five days and placebo for the last five days, whereas subjects in the 500 mg group received levofloxacin for 10 days. The subjects were assessed clinically at four visits: Visit 1 Admission (Study Day 1), Visit 2 On-Therapy (Study Day 3-5), Visit 3 Test-of-Cure (Study Day 17-22), and Visit 4 Poststudy (Study Day 35-45). Efficacy evaluations included clinical and microbiologic responses to treatment. Safety evaluations included incidence of treatment-emergent adverse events (beginning on-therapy or anytime up to 24 days after the first dose of active study drug) and changes from admission to posttherapy in clinical laboratory test results, physical examination findings, and vital signs. Data were pooled across investigational sites for analysis.

Number of Subjects (planned and analyzed): Planned enrollment: approximately 530 subjects, to provide at least 182 microbiologically evaluable subjects. Enrolled and randomized: 784 subjects. Received at least one dose of study medication (Intent-to-Treat [ITT] population): 780 subjects, including 389 in the 750 mg group and 391 in the 500 mg group.

Diagnosis and Main Criteria for Inclusion: Adult (18 years of age or older) male and female outpatients were eligible for enrollment if they had a clinical diagnosis of acute bacterial sinusitis, defined by the presence of clinical signs and symptoms lasting for less than 28 days, the presence of visible nasal purulence, computed tomography (CT) or standard sinus x-rays showing total sinus opacification or an air fluid level, and two or fewer episodes of bacterial sinusitis within the preceding 12 months. Subjects must have agreed to undergo maxillary sinus puncture or endoscopy at Visit 1 for collection of a sinus specimen. Subjects were excluded from study entry if they had a diagnosis of chronic sinusitis; had previous systemic antimicrobial therapy within 72 hours of study entry (exceptions being ≤24 hours of antimicrobial therapy or clinical failure on previous therapy); had presence or history of serious complications of sinusitis or required surgery for the treatment of sinusitis; required chronic use of >20 mg/day of prednisone or equivalent dose of other corticosteroids; had cystic fibrosis; had infection caused by a pathogen resistant to levofloxacin; had neutropenia; had calculated creatinine clearance <50 mL/min; had documented infection with HIV with CD4 counts <200 cells/mm^3; were pregnant or nursing; or had seizure disorder or a psychiatric condition requiring use of major tranquilizers.

Test Product, Dose and Mode of Administration, Batch No.: Levofloxacin 750 mg capsules (R11836, R11996, R12090) were supplied as over-encapsulated 750 mg LEVAQUIN® commercial tablets.

Reference Therapy, Dose and Mode of Administration, Batch No.: Levofloxacin 500 mg capsules (R11838, R11998, R12092) were supplied as over-encapsulated 500 mg LEVAQUIN commercial tablets.

Placebo capsules, which were identical to the levofloxacin capsules but contained cornstarch filler, were included in the medication kits with the levofloxacin 750 mg capsules.

Duration of Treatment: 10 days for all subjects. Subjects in the 750 mg group received levofloxacin for the first five days followed by placebo for the last five days. Subjects in the 500 mg group received levofloxacin for 10 days.

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Criteria for Evaluation:

Clinical Outcomes:

- Clinical response at the Test-of-Cure Visit, based on resolution of signs and symptoms observed on admission. Posttherapy clinical response was categorized as cure, improvement, failure, or unable to evaluate.
- Clinical response at the Poststudy Visit in subjects who completed therapy and were cured or improved at the Test-of-Cure Visit. Poststudy clinical response was categorized as long-term cure, long-term improvement, relapse, or unable to evaluate.
- Resolution of signs and symptoms at the Test-of-Cure Visit, changes in CT, and x-ray findings, and changes in the Sino-Nasal Outcome Test 16 (SNOT-16) questionnaire, which lists symptoms and social/emotional consequences of having acute bacterial sinusitis.

Microbiologic Outcomes:

- Microbiologic response at the Test-of-Cure Visit. Responses were assessed by subject's infection (categorized as eradicated/presumed eradicated, persisted/presumed persisted, or unknown) and by pathogen (categorized as eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, or unknown).
- Microbiologic response at the Poststudy Visit for subjects who completed therapy and were cured or improved at the Test-of-Cure Visit. Responses were assessed by subject's infection (categorized as eradicated/presumed eradicated, relapse/presumed relapse, new infection, or unknown) and by pathogen (categorized as eradicated, microbiologic relapse, presumed microbiologic relapse, new infection, or unknown).

Safety: Occurrence of treatment-emergent adverse events during the study; changes from admission to posttherapy in clinical laboratory test results, physical examination findings, and vital signs.

Statistical Methods: The primary efficacy variable was the clinical success rate (proportion cured or improved) at the Test-of-Cure Visit in subjects evaluable for microbiologic efficacy. A two-sided 95% confidence interval (CI) around the difference between treatment groups (levofloxacin 500 mg regimen minus levofloxacin 750 mg regimen) was computed. To conclude that a five-day course of levofloxacin 750 mg/day was at least as efficacious as a 10-day course of levofloxacin 500 mg/day, the upper bound of the 95% CI had to be less than 15%.

Secondary efficacy variables were: 1) microbiologic response by subject's infection at the Test-of-Cure Visit; 2) microbiologic response by admission pathogen at the Test-of-Cure Visit; 3) changes in signs and symptoms, including radiographic findings, from admission to posttherapy; 4) changes in the SNOT-16 results from admission to posttherapy; and 5) poststudy clinical and microbiologic responses of subjects who completed therapy and were cured or improved at the Test-of-Cure Visit. Two-sided 95% CIs around the treatment differences in posttherapy infection eradication rates overall and for the most prevalent pathogens were computed.

Descriptive statistics were used to summarize treatment-emergent adverse events and pretherapy to posttherapy changes in laboratory test results and vital signs. Two-sided 95% CIs were calculated for the differences between the treatment groups in the rates of treatment-emergent adverse events overall and within each body system, and for the most commonly occurring treatment-emergent adverse events.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Clinical Results: For the microbiologically evaluable subjects, the clinical success rates at the Test-of-Cure Visit were 91.4% in the levofloxacin 750 mg group and 88.6% in the levofloxacin 500 mg group; the 95% CI around the difference was (-10.0, 4.2). For subjects who underwent maxillary sinus puncture, the clinical success rates were similar in the 750 mg group (90.0%) and the 500 mg group (93.7%), with a 95% CI of (-4.8, 12.1). For those who underwent an endoscopic procedure, the rate was higher in the 750 mg group (93.5%) than in the 500 mg group (79.6%), with a 95% CI of (-27.2, -0.6).

Thus, in the overall microbiologically evaluable population, an upper limit of the 95% CI of 4.2% was realized. In subsets of the overall microbiologically evaluable population, this limit of -0.6% was realized for subjects who underwent endoscopy and of 12.1% for subjects who underwent maxillary sinus puncture. For each of these comparisons, the upper bound of the 95% CI was below 15% as originally planned. These results indicate that levofloxacin 750 mg for five days is at least as efficacious as levofloxacin 500 mg for 10 days not only for the total microbiologically evaluable population but also for subsets of subjects categorized by the specimen collection procedure.

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EFFICACY RESULTS (Continued):

The clinical success rates were 89.6% for the levofloxacin 750 mg group and 85.6% for the levofloxacin 500 mg group in subjects with histories of allergy, with a 95% CI of (-15.1, 7.1). The rates were 92.9% and 93.2%, respectively, in subjects with no history of allergies, with a 95% CI of (-9.0, 9.5).

At poststudy, eight (5.8%) subjects in the 750 mg group and nine (6.8%) subjects in the 500 mg group had experienced clinical relapses.

The clinical results were similar for each treatment group in the ITT, modified ITT, and clinically evaluable populations.

Microbiologic Results: For microbiologically evaluable subjects, the microbiologic eradication rates by infection (eradication/presumed eradication of all admission pathogens for a subject) based on results obtained at the Test-of-Cure Visit were 92.1% in the levofloxacin 750 mg group and 89.3% in the levofloxacin 500 mg group, with a 95% CI of (-9.7, 4.1). The eradication rates with the two regimens were similar for gram-positive aerobic pathogens (90.1% versus 90.6%, respectively, with a 95% CI of [-9.9, 10.9]) and gram-negative aerobic pathogens (93.0% versus 88.2%, respectively, with a 95% CI of [-13.2, 3.5]). The statistical results indicate that levofloxacin 750 mg/day for five days was at least as effective as levofloxacin 500 mg/day for 10 days in eradicating infections in subjects with acute bacterial sinusitis.

SAFETY RESULTS: Levofloxacin 750 mg q.d. for five days was safe and well-tolerated in subjects with acute bacterial sinusitis. Overall, 39.8% of subjects in the 750 mg group and 34.5% of subjects in the 500 mg group reported at least one treatment-emergent adverse event (beginning on-therapy or anytime up to 24 days after the first dose of active study drug.) The 95% CI around the difference was (-12.2, 1.6), indicating that the overall rates of treatment-emergent adverse events were comparable between the two treatment groups. The most commonly reported adverse events in the 750 mg group were nausea (8.2%), diarrhea (5.1%), and headache (4.6%). The most commonly reported adverse events in the 500 mg group were diarrhea (4.9%) and nausea (4.3%). The 95% CIs around the differences in rates of adverse events indicated no statistically significant difference between the two treatment groups for any frequently reported (≥2%) events except nausea (8.2% in the 750 mg group and 4.3% in the 500 mg group; 95% CI [-7.4, -0.4]) and vomiting (3.6% and 1.3%, respectively; 95% CI [-4.6, -0.0]). The types and rates of treatment-emergent adverse events observed with both levofloxacin regimens evaluated in this study are consistent with the known safety profile of levofloxacin.

The rates of all treatment-emergent adverse events, adverse events in individual body systems, markedly severe adverse events, serious adverse events, events resulting in discontinuation of treatment, and markedly abnormal laboratory findings were not notably different between the two levofloxacin treatment groups. Mean changes in vital signs from admission to posttherapy were not clinically significant. There were no deaths during the study period, and no unusual or unexpected treatment-emergent safety problems.

CONCLUSION: Levofloxacin 750 mg administered p.o. once daily for five days was as well-tolerated and at least as effective as the levofloxacin regimen (500 mg administered p.o. once daily for 10 days) currently approved for the treatment of acute bacterial sinusitis. The 750 mg dose was at least as effective as the 500 mg dose in subgroups of the subjects categorized by the type of procedure used for obtaining a sinus specimen and by the presence or absence of allergy histories. The results of this study support the efficacy of levofloxacin 750 mg/day for five days in the treatment of subjects with acute bacterial sinusitis associated with the following pathogens: *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.

Date of the report: 07 OCTOBER 2004

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