SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: LEVAQUIN® NAME OF ACTIVE INGREDIENT(S): RWJ-25213-097 (levofloxacin)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR002389

Title of Study: An Open-Label Study of Levofloxacin to Evaluate Bacteriologic Outcome in the Treatment of Children Who are at Risk for Acute Otitis Media That is Difficult to Treat

Coordinating Investigator: Ron Dagan, M.D. – Soroka Medical Center, Beer Sheva; Israel

Publication (Reference): None

Study Initiation/Completion Dates:

Clinical Conduct:	19 November 2002 – 15 July 2003
Sample Analysis in Plasma:	23 April 2003 – 18 July 2003
Sample Analysis in Middle Ear Fluid:	5 May 2003 – 24 July 2003

Phase of development: 3

Objectives: The primary objective of this study was to assess the rate of eradication of bacteria from the middle ear fluid (MEF) at Visit 2 (Study Days 4 to 6) in infants and children who had acute otitis media (AOM) and were at high risk for difficult-to-treat infections caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*. Secondary objectives were to assess the efficacy of levofloxacin based on clinical cure rate, clinical success (cured plus improved) rate, and microbiologic responses at 2 to 5 and 10 to 17 days after the last dose; and the clinical failure rate at Visit 2. Safety was also assessed. Per Amendment ISR-1, supplemental secondary objectives were evaluated at 1 study center: assessment of the relationship between plasma and MEF concentrations of levofloxacin, occurrence of subjects colonized with *S. pneumoniae,* and the relationship of *S. pneumoniae* isolates from the nasopharynx to those from MEF.

Methodology: This was a multicenter, nonrandomized, open-label study conducted in the United States, Argentina, Costa Rica, and Israel. Pediatric subjects (≥6 months to <5 years of age) with clinical signs and symptoms of AOM who were at high risk for difficult-to-treat AOM, and who met the prestudy eligibility criteria were enrolled and received levofloxacin 10 mg/kg oral suspension twice daily for 10 days followed by posttreatment assessment. A combination of clinical assessment and microbiologic assessment of MEF and blood was used to evaluate efficacy. MEF samples were collected at screening for determination of levofloxacin susceptibility. Per Amendment ISR-1, additional MEF samples and plasma samples were collected at Visit 2 from subjects at 1 center for further microbiologic and pharmacokinetic (PK) analyses. Safety was based on the incidence, relationship to therapy, and severity of treatment-emergent adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, and physical examination findings. Supplementary safety evaluations for musculoskeletal (MS) adverse events were performed throughout the study, as needed. An independent expert advisory group, Data Safety Monitoring Committee (DSMC), evaluated the safety data on an ongoing basis with emphasis on serious and MS adverse events. Immediately following this study, subjects who received at least 1 dose of levofloxacin were eligible to continue in a long-term (1-year) surveillance study (in which no study drug was to be administered) to further assess MS adverse events. The surveillance study is ongoing, and the results will be summarized in a separate report.

Number of Subjects (planned and analyzed): 186 planned; 205 enrolled; 42 evaluable for PK; 93 evaluable for microbiologic efficacy at Visit 2 (37 evaluable for *S. pneumoniae,* and 54 evaluable for *H. influenzae)*; 163 evaluable for clinical efficacy; 204 evaluable for safety.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥6 months to <5 years who had signs and symptoms of AOM (middle ear effusion, acute inflammation of the ear, acute purulent otorrhea) and who were at high risk for difficult-to-treat AOM (recurrent or persistent AOM).

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Test Product, Dose and Mode of Administration, Batch No.: Levofloxacin 10 mg/kg oral suspension b.i.d. (up to 500 mg/day), Batch: R11715, R11832, R12031, and R12116 (GFI# 25213-097-FB-030); V02PF8084 (D02PF7170/PE1767)

Reference Therapy, Dose and Mode of Administration, Batch No.: None.

Duration of Treatment: Levofloxacin was to be administered for 10 consecutive days.

Criteria for Evaluation:

Pharmacokinetics: Steady-state levofloxacin exposure (C_{ss}) was estimated from plasma and MEF. The levofloxacin exposure ratio between MEF and plasma was also calculated.

Efficacy: The primary endpoint was the eradication rate of the admission pathogens (isolated from MEF) at Visit 2 (Study Day 4 to 6), with special emphasis on pathogens of interest: *S. pneumoniae* and *H. influenzae*. Secondary endpoints included posttreatment (Visits 3 and 4 [2 to 5 and 10 to 17 days after the last dose, respectively]) clinical cure and clinical success rates, Visit 2 clinical failure rates, and posttreatment microbiologic response rates.

Safety: Safety was evaluated by monitoring treatment-emergent adverse events (with special emphasis on MS adverse events) and changes in clinical laboratories, vital signs, and physical examination findings.

Statistical Methods:

Pharmacokinetics: Steady-state levofloxacin exposure (C_{ss}) and the exposure ratio between MEF and plasma were tabulated and summarized by postdose time, sex, and age group (≤2 years, >2 years).

Efficacy: The primary efficacy endpoint was the eradication (documented or presumed) rate of the admission pathogens at Visit 2 with special emphasis on the pathogens of interest, *S. pneumoniae* and *H. influenzae*. The eradication rates were expressed as the percent of the Microbiologically Evaluable Analysis Set at Visit 2 showing documented or presumed eradication of the admission pathogens. Eradication rates were also summarized by age group (≤2 years, >2 years), race, sex, country, and study center (primary analysis only). Subgroup analyses by country used Israel versus non-Israel due to high enrollment at the Israeli center. Descriptive statistics were used to summarize clinical cure and clinical success rates at Visits 3 and 4 and clinical failure rate at Visit 2. The clinical cure, success, and failure rates were expressed as percentages and analyzed by age group. The clinical response rates at Visits 2, 3, and 4 were summarized by country (Israel versus non-Israel). Ninety-five percent CIs were constructed for the clinical and microbiologic response rates. The relationship between microbiologic and clinical responses was also assessed, but without formal statistical analysis. Except for the assessment of the relationship between plasma and MEF concentrations of levofloxacin, the results of the supplemental secondary assessments performed at the Israeli center are not presented in this report.

Safety: The incidence of treatment-emergent adverse events was summarized by severity, relationship to study drug, and age group (≤2 years, >2 years) using a standard adverse event dictionary based on WHOART. MS adverse events were described. Changes in clinical laboratory tests and vital signs were summarized using descriptive statistics. Physical examination abnormalities were listed.

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SUMMARY - CONCLUSIONS

PHARMACOKINETICS: At Visit 2 (Study Day 4 to 6), the mean levofloxacin MEF and plasma concentrations for subjects ≤ 2 years of age with measurable MEF/plasma concentration ratios were 2.85 and 3.26 µg/mL, respectively, during the approximate 12-hour postdosing interval. Levofloxacin MEF/plasma concentration ratios within 12 hours after dosing ranged from 0.48 to 1.54. Compatible MEF/plasma concentration ratios were observed in males (mean 0.96) and females (mean 0.83). Subjects who had MEF samples collected during the first 2 hours after dosing (Visit 2) had quantifiable concentrations of levofloxacin in MEF, indicating that levofloxacin rapidly reached the MEF.

EFFICACY RESULTS: Pathogens isolated from MEF at admission (subject's infection) were eradicated in 89% of subject infections at the primary efficacy endpoint (Visit 2, Study Day 4 to 6). At this same visit, all (100%) *H. influenzae* infections and 84% of *S. pneumoniae* infections were eradicated. Three (2%) subjects were clinical failures at Visit 2.

SAFETY RESULTS: Levofloxacin was well tolerated in infants and children ≥6 months to <5 years of age with clinical signs and symptoms of AOM who were at high risk for difficult-to-treat AOM. Of the 204 subjects evaluable for safety, 122 experienced 1 or more adverse events. Most adverse events (95%) were mild to moderate in severity. Twelve were marked in severity: vomiting (2 events), otitis media (1), abdominal pain (1), fever (1), palmar-plantar erythrodysaesthia (1), rash (1), heat rash (1), maculo-papular rash (1), anorexia (1), increased alkaline phosphatase (1), varicella (1). Most of the marked events (75%) were considered doubtfully related or not related to study drug. Twelve subjects (6%) discontinued study drug due to an adverse event. Vomiting was the most common treatment-limiting adverse event and occurred in 4% of subjects. Six subjects experienced a MS adverse event. All of the MS events were considered doubtfully related or not related to study drug.

There were no deaths. Seven subjects (3%) experienced 8 serious adverse events. Most of the serious adverse events were considered doubtfully related or not related to study.

CONCLUSIONS:

The results of this study suggest that levofloxacin is likely to be as effective as first-line therapies (e.g., amoxicillin) for the treatment of AOM and that levofloxacin would be considered an effective therapy in treating children with recurrent and/or persistent AOM.

Levofloxacin 10 mg/kg twice daily for 10 days was well tolerated in infants and children ≥6 months to <5 years of age. There were no significant safety findings. Subjects who participated in this study are currently being followed in a safety surveillance study to collect long-term data on MS events.

Date of the report: 30 JUNE 2004

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