SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 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.: CR004171

Title of Study: A Multicenter, Long-Term, Active-Surveillance Study of Musculoskeletal Disorders That Occur After Initiating a Course of Levofloxacin or Non-fluoroquinolone Therapy for Acute Infectious Diseases in Children Who Were Enrolled in Phase 3 Clinical Trials Involving Levofloxacin Therapy

Coordinating Investigator: John Bradley, M.D. - Children's Hospital and Health Center, San Diego, CA; USA

Publication (Reference): Noel GJ, Bradley, JS, Kauffman RE. Comparative Safety Profile of Levofloxacin in 2523 Children With a Focus on Four Specific Musculoskeletal Disorders. Pediatr Infect Dis J 2007;26: 879–891.

Study Initiation - Completion Date: 27 August 2002 - 28 April 2010 | **Phase of development: 3**

Objectives: The primary objective of this study was to evaluate and compare the overall incidence of musculoskeletal (MS) disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) in pediatric subjects that occurred during the 60-day period after the first dose of levofloxacin with that of 'standard' non-fluoroquinolone therapy (comparator) for an acute bacterial infection. Secondary objectives included assessment of 1) overall incidence of MS disorders including impaired growth in the 1-year period after the first dose, 2) incidence of each MS disorder that occurred at weight- and nonweight-bearing joints in the 30-day, 60-day and 1-year periods after the first dose, and 3) incidence of each MS disorder including impaired growth (1-year only) in the 30-day, 60-day and 1-year periods after the first dose.

Methodology: This was a prospective, long-term, comparative, multicenter, observational study conducted in the United States, Argentina, Brazil, Chile, Costa Rica, Israel, Mexico, and Panama. Pediatric subjects who took at least 1 dose of levofloxacin or comparator as part of a prior Phase 3 levofloxacin study to treat an acute bacterial infection (Studies CR002392, CR002389, and CR004168) were eligible to participate in this long-term surveillance study. A comparator treatment was not included in the design of Study CR002389. No study drugs were administered during the current study. Safety was based on the incidence of MS disorders (tendinopathy, arthritis, arthralgia, gait abnormality, and impaired growth); the incidence, relationship to therapy, and severity of all serious and MS adverse events; and on changes in physical examination findings. A Data Safety Monitoring Committee (DSMC) reviewed all adverse events, including serious and MS adverse events, on an ongoing basis. Upon review of events that were reported as related to the musculoskeletal system, the DSMC categorized these as possible MS disorders. All subjects were to be evaluated for 1 year (Surveillance Phase) after the first dose of study drug (levofloxacin or comparator) in the previous study. Those children diagnosed as having persisting musculoskeletal events or disorders during the 1-year period or identified by the DSMC as requiring long-term evaluation, were to be evaluated yearly for 5 years after the first dose of study drug or until the event resolved (MS Disorder Follow-Up Phase), whichever occurred first.

Number of Subjects: 2582 were eligible; 2233 were enrolled.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 6 months to 16 years who took at least 1 dose of levofloxacin or comparator as part of a Phase 3 levofloxacin study to treat an acute bacterial infection.

Test Products, Doses and Modes of Administration, Batch Nos.: Not applicable for this observational study.

Reference Therapies, Doses and Modes of Administration, Lot Nos.: Not applicable for this observational study.

Duration of Treatment: Not applicable for this observational study.

Criteria for Evaluation: The primary endpoint was the overall incidence of MS disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) during the 60-day period after the first dose of study drug (levofloxacin or comparator). Secondary endpoints included the overall incidence of MS disorders (including impaired growth) during the 1-year period after the first dose, incidence of each MS disorder at weight- and nonweight-bearing joints (30-day, 60-day and 1-year periods), and incidence of each individual MS disorder (30-day, 60-day and 1-year periods) including impaired growth (1-year only). Safety was also evaluated by monitoring MS and serious adverse events (SAE) and changes in physical examination findings.

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Statistical Methods: The primary endpoint, overall incidence of MS disorders during the 60-day period after the first dose of study drug (levofloxacin or comparator), was summarized by sex, race, age group, pubescence stage, and country. The incidence of MS disorders was assessed for different subgroups (age, sex, country group [US vs. non-US], and pubescence stage).

Secondary endpoints were estimated by determining the proportion of subjects who had a MS disorder within the 30-day, 60-day or 1-year periods after the first dose of study drug (levofloxacin or comparator). Time to onset and cumulative incidence of MS disorders were assessed.

The incidence, severity, and relationship to study drug of MS and SAEs were summarized by treatment using a standard adverse event MedDRA dictionary. Physical examination abnormalities are available upon request.

SUMMARY – CONCLUSIONS:

PRIMARY AND SECONDARY SAFETY ANALYSIS RESULTS:

Primary analysis: A total of 36 subjects (28 levofloxacin, 8 comparator) out of 2233 (1340 levofloxacin, 893 comparator) had MS disorders as assessed by the Data Safety Monitoring Committee in the 60-day period after first dose. Levofloxacin had a significantly higher incidence of disorders than the comparator group (2.1% vs. 0.9%, p-value: 0.038). The most frequently occurring MS disorder in both groups was arthralgia (levofloxacin – 22/1340 [1.6%] subjects; comparator – 7/893 [0.8%] subjects).

Secondary analysis: Musculoskeletal disorders were reported more frequently in levofloxacin subjects than in comparator-treated subjects over the 1-year period. This difference was statistically significant (p-value: 0.025). At each of the 3 evaluation periods (30-Day, 60-Day and 1-Year) there was a greater incidence of MS disorders at weight-bearing joints than nonweight-bearing joints for both treatment groups. This difference was significant at the 60-Day period (p-value: 0.025), and the 1-Year period (p-value: 0.047).

OTHER SAFETY RESULTS: Summaries of the incidence of MS disorders from start of study drug to 35 days after the last dose of the study drug (the 35-Day visit) and from the 35-Day Visit through the 1-Year follow-up visit were conducted. At the 35-Day visit there were a total of 24 out of 1340 subjects (1.8%) in the levofloxacin group and 8 out of 893 subjects (0.9%) in the comparator group who had MS disorders. The difference between the 2 treatment groups was not significant (p-value: 0.101). At the period between 35-Day visit through the 1-Year follow-up visit there were 26 out of 1340 subjects (1.9%) in the levofloxacin group and 9 out of 893 subjects (1.0%) in the comparator group who had MS disorders. The incidence of MS disorders in this period was similar between treatment groups (p-value: 0.116).

Overall, 153 subjects (103 levofloxacin subjects, 50 comparator subjects) reported MS adverse events. The most frequently reported MS adverse events were arthralgia and myalgia (2% total each). No other event was reported by >1% of subjects.

A total of 134 subjects (90 levofloxacin, 44 comparator) reported serious adverse events. The most frequently reported event category was infections and infestations (3% in each treatment group). Only pneumonia and surgery were reported by ≥1% of subjects.

Abnormal coordination (1 levofloxacin and 1 comparator subject each) and hypotonia (1 levofloxacin subject) were the only nervous system disorders reported.

Based on the assessment of the responsible investigator, the sponsor, or the DSMC, out of the 2233 subjects who enrolled in this study, 207 subjects (124/1340 [9%] levofloxacin subjects, 83/893 [9%] comparator subjects) required yearly follow-up during the MSD Follow-Up Phase for 1 or more of the following reasons: 174 subjects (104 levofloxacin-treated subjects, 70 comparator-treated subjects) were assessed as being growth impaired or possibly growth impaired; 62 subjects (37 levofloxacin-treated subjects; 25 comparator-treated subjects) required follow-up as assessed by the investigator; 7 subjects (3 levofloxacin-treated subjects and 4 comparator-treated subjects) were assessed with persisting MS adverse events, and 5 subjects (4 levofloxacin-treated subjects and 1 comparator-treated subject) required follow-up as assessed by the DSMC.

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CONCLUSION:

- Pediatric subjects treated for an acute bacterial infection with levofloxacin showed a significantly higher incidence of MS disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) compared to 'standard' non-fluoroquinolone therapy (comparator) (p-value: 0.038) at the 60-day period after the first dose.
- Arthralgia was the most frequently-occurring MS disorder occurring at the 30-day, 60-day, and 1-year periods after the first dose for both treatment groups.
- There were more MS disorders reported in the weight-bearing joints than in the nonweight-bearing joints.
- The incidence of MS disorders that occurred at weight-bearing joints was significantly higher at 60-day (p-value: 0.025), and 1-year (p-value: 0.047) periods after the first dose. The incidences of MS disorders in the weight-bearing joints between the treatment groups was not statistically different in the 30-day period (p-value: 0.074). The incidences of MS disorders at the nonweight-bearing joints was similar between the treatment groups at all 3 evaluation periods.
- Significant differences between the treatment groups in the overall incidence of MS disorders, and the incidence of MS disorders at the weight-bearing joints in the 1-year period were primarily due to the differences that were observed in the 60-day period.
- The overall difference in the incidence of protocol-defined impaired growth for levofloxacin-treated subjects vs. comparator-treated subjects at the 1-year period after the first dose was not significant (p-value = 0.869).
- During the MSD Follow-Up Phase, there was no higher incidence of MS disorders in the levofloxacin-treated group. Independent of treatment assignment, there was no evidence for new treatment-associated MS disorders or treatment-associated growth impairment in the MSD Follow-Up Phase.

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