### SYNOPSIS

<u>NAME OF SPONSOR/COMPANY</u> : Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY U.S.E ONLY)		
NAME OF FINISHED PRODUCT: LEVAQUIN <sup>®</sup>	Volume:			
NAME OF ACTIVE INGREDIENT: RWJ-25213-097 (levofloxacin)	Page:			
Protocol No.: CR002392				
<b>Title of Study:</b> A Multicenter, Randomized, Open-Label, Comparative Study to Compare the Efficacy and Safety of Levofloxacin and Standard of Care Therapy in the Treatment of Children With Community-Acquired Pneumonia in the Hospitalized or Outpatient Setting				
Coordinating Investigator: John Bradley, M.E	0. – Children's Hospital and Health C	enter, San Diego, CA; U.S.A		
Publication (Reference): None				
Study Initiation/Completion Dates: Clinical Conduct: 27 August 2002 to 18 June 2004 Sample Analysis in Plasma: 05 December 2003 to 16 September 2004 Sample Analysis in Pleural Fluid: 09 September 2004 to 10 September 2004		Phase of development: 3		
<b>Objectives:</b> The primary objective of this study was to establish the efficacy (clinical response [cured vs. not cured] at the Test-of-Cure Visit) of levofloxacin to be non-inferior to "standard of care" antibiotic therapy in the treatment of community-acquired pneumonia (CAP) in children aged 6 months to 16 years, inclusive. Secondary objectives included evaluation of clinical response at the Posttherapy Visit, evaluation of Microbiologic Response at the Posttherapy Visit and Test-of-Cure Visits, evaluation of clinical and microbiologic responses by age group, and determination of steady-state levofloxacin exposure in each age group. Safety was also assessed.				
Methodology: This was an open-label, randomized, active-comparator, non-inferiority, multicenter study conducted in the United States, Mexico, and various Latin American countries (Argentina, Brazil, Costa Rica, and Panama). Subjects with CAP who met the prestudy eligibility criteria were randomized to receive either levofloxacin (intravenous [i.v.], oral suspension, or oral tablet) or a comparator antimicrobial therapy for 10 days followed by posttreatment assessment. The randomization included stratification by age and country to ensure a 3:1 levofloxacin:comparator ratio within each age group (Group I: ≥6 months to <5 years; Group II: ≥5 to 16 years) and country. Subjects were either hospitalized or outpatients. Due to differences in the microbiologic etiology of pneumonia and differences in drug clearance in children, the comparators, doses, routes of dosing, and dosing regimens differed by age group. A combination of clinical assessment, chest radiography, microbiologic assessment of sputum and blood, and serology was used to evaluate efficacy. Additionally, blood samples were collected from levofloxacin-treated subjects for determination of steady-state levofloxacin exposure. Levofloxacin levels in pleural fluid were measured to assess the concentration of the drug in subjects who had pleural effusion or empyema sampled. 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. A Data Safety Monitoring Committee (DSMC) reviewed serious and MS adverse events on an ongoing basis. Immediately following this study, subjects who took at least 1 dose of study drug (levofloxacin or comparator) were eligible to continue in a long-term (1-year) surveillance study (in which no study drug was to be administered) to further				

728 randomized (546 levofloxacin, 182 comparator); 470 evaluable for pharmacokinetics; 539 evaluable for clinical efficacy at the Test-of-Cure Visit (405 levofloxacin, 134 comparator); 208 evaluable for microbiologic efficacy (158 levofloxacin, 50 comparator); 712 evaluable for safety (533 levofloxacin, 179 comparator).

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<b>Diagnosis and Main Criteria for Inclusion:</b> Male and female subjects aged 6 months to 16 years with 2 or more clinical signs and symptoms of pneumonia (defined as: fever, shortness of breath, cough, chest pain, abnormal WBC count, and pulmonary consolidation on physical examination) and radiographic evidence of pulmonary infiltrate compatible with acute infection requiring antibiotic therapy.				
<b>Test Products, Doses and Modes of Administration, Batch Nos.:</b> Levofloxacin was given either orally or by i.v. administration. Dosing routes could have been switched at the investigator's discretion.				
<i>Group I (</i> $\geq 6$ <i>months to &lt; 5 years of age):</i> Levofloxacin 10 mg/kg oral suspension b.i.d. (up to 500 mg/day), Batch: R11596 (GFI# 25213-097-FB-030); levofloxacin 10 mg/kg i.v. b.i.d. (up to 500 mg/day), Batch: R11542 (NDC# 0045-0069-51).				
Group II ( $\geq$ 5 to 16 years of age): Levofloxacin 10 mg/kg oral suspension q.d. (up to 500 mg/day), Batch: R11596 (GFI# 25213-097-FB-030); levofloxacin 1-250 mg tablet q.d. (subjects weighing 22.5 to 27.5 kg) or 2-250 mg tablets q.d. (subjects weighing >45.5 kg), Batch: R11543 (NDC# 0045-1520-50); levofloxacin 10 mg/kg i.v. q.d. (up to 500 mg/day), Batch: R11542 (NDC# 0045-0069-51).				
<b>Reference Therapies, Doses and Modes of Administration, Lot Nos.:</b> The comparator treatments were given either orally or by i.v. administration. Dosing routes could have been changed during the study at the investigator's discretion. Non-U.S. sites supplied their own comparators. Lot numbers are provided in Appendix 1.6.2.				
<i>Group I</i> ( $\geq 6$ months to < 5 years of age): amoxicillin + clavulanic acid oral suspension b.i.d. (with dose determined by calculating amoxicillin 22.5 mg/kg, up to 875 mg/day); ceftriaxone 25 mg/kg i.v. b.i.d. (up to 4 g/day).				
<i>Group II (≥5 to 16 years of age):</i> clarithromycin 7.5 mg/kg oral suspension b.i.d. (up to 250 mg b.i.d.); clarithromycin 250 mg oral tablet b.i.d. (up to 250 mg b.i.d.); ceftriaxone 25 mg/kg i.v. b.i.d. (up to 4 g/day) + erythromycin lactobionate 10 mg/kg i.v. q.6.h (up to 4 g/24 hours).				
<b>Duration of Treatment:</b> Study drug was to be administered for 10 days (minimum of 7 to a maximum of 14 days).				
Criteria for Evaluation:				
<u>Pharmacokinetics</u> : Steady-state levofloxacin exposure ( $C_{p,ss}$ ) was estimated from plasma. The levofloxacin exposure ratio between pleural fluid and plasma was also calculated.				
Efficacy: Clinical response (defined as: cured, improved, failure, relapse, or unable to evaluate) and microbiologic response (defined as: eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, microbiologic relapse, or unknown) was determined at the Posttherapy and Test-of-Cure Visits. The primary endpoint was the clinical cure rate (cured vs. not cured) at the Test-of-Cure Visit (10 to 17 days after the last dose) based on resolution of the clinical signs and symptoms of pneumonia and radiologic findings reported at admission. Secondary endpoints included clinical success (cured or improved response categories) at the Posttherapy and Test-of-Cure Visits, and clinical and microbiologic response by age group at the Posttherapy and Test-of-Cure Visits.				
<u>Safety:</u> Safety was evaluated by monitoring treatment-emergent adverse events (with special emphasis on MS adverse events) and changes in clinical laboratory tests, vital signs, and physical examination findings.				

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#### **Statistical Methods:**

<u>Pharmacokinetics</u>: Steady-state levofloxacin exposure  $(C_{p,ss})$  and the exposure ratio between pleural fluid and plasma were tabulated and summarized by postdose time interval, dosing regimen, and age group

Efficacy: The primary efficacy endpoint, clinical cure rate (cured vs. not cured) at the Test-of-Cure Visit, was summarized overall and by age group, sex, race, and country. Secondary endpoints were summarized overall and by age group, country, pathogen, or subject's infection. A 2-sided 95% confidence interval (CI) for the difference in clinical cure, clinical success, and microbiologic eradication rates of subject's infection between the 2 treatment groups (comparator minus levofloxacin) was performed to assess therapeutic non-inferiority. To claim non-inferiority, the upper bound of the 95% CI must have remained below a non-inferiority margin of 10%.

<u>Safety:</u> The incidence of treatment-emergent adverse events was summarized by treatment group, severity, relationship to study drug, age group, sex, and race using a standard adverse event dictionary based on WHOART. Musculoskeletal adverse events were summarized by treatment group and diagnosis and classified as 1 of the following MS disorders: tendinopathy, arthritis, arthralgia, or gait abnormality. Changes in clinical laboratory tests and vital signs were assessed by descriptive statistics and summarized by treatment group. Physical examination abnormalities were listed.

#### SUMMARY – CONCLU.S.IONS:

<u>PHARMACOKINETICS</u>: Steady-state plasma concentrations of levofloxacin in children <5 years of age who received levofloxacin 10 mg/kg b.i.d. were comparable to concentrations in children  $\ge 5$  years of age who received 10 mg/kg q.d. and to concentrations in adults who received the approved adult dosing regimen for CAP (500 mg q.d.).

<u>EFFICACY RESULTS</u>: For the primary efficacy analysis (clinical cure rate at the Test-of-Cure Visit [10 to 17 days after the last dose of study drug]), the clinical cure rate in the levofloxacin group (94.32%) was almost identical to that in the comparator group (94.03%). The upper limit of the CI was less than the non-inferiority margin of 10% for the overall population indicating that levofloxacin treatment is non-inferior to comparator treatment. Levofloxacin treatment was also non-inferior to comparator treatment for each age group.

Microbiologic eradication rates (largely defined by clinical success in subjects with infections caused by *Mycoplasma pneumoniae*) at the Test-of-Cure Visit were similar for subjects exposed to levofloxacin (96.50%) and to comparator (95.74%). One of 28 children with infection caused by *Streptococcus pneumoniae* was presumed to have a persisting infection at the Test-of-Cure Visit.

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<u>SAFETY RESULTS</u>: Levofloxacin 10 mg/kg (up to 500 mg/day) for 10 days was well tolerated in infants and children  $\geq 6$  months to  $\leq 16$  years of age with CAP. Of the 712 subjects evaluable for safety, 275 (52%) levofloxacin-treated subjects and 94 (53%) comparator-treated subjects experienced 1 or more adverse event. Diarrhea was the most frequent adverse event (7% and 11% for levofloxacin and comparator, respectively). Most adverse events were mild or moderate in severity. Seventeen subjects had 23 adverse events of marked severity. Most of the marked events were considered doubtfully related or not related to study drug. Twenty-three subjects experienced MS adverse events. The frequency of MS disorders was comparable in levofloxacin- and comparator-treated subjects (1.69% vs. 1.12%).

Serious adverse events were reported in 33 (6%) levofloxacin-treated subjects and 8 (4%) comparator-treated subjects. Most of the serious adverse events were considered doubtfully related or not related to study drug. Two serious adverse events in levofloxacin-treated subjects resulted in fatal outcomes. Neither death was considered related to levofloxacin. Adverse events leading to treatment discontinuation occurred in 12 (2%) levofloxacin-treated and 2 (1%) comparator-treated subjects.

#### CONCLUSION:

The results of this study suggest that levofloxacin is likely to be as effective as standard-of-care therapies (e.g., amoxicillin, ceftriaxone, clarithromycin) for the treatment of PCAP in infants and children. Levofloxacin 10 mg/kg (up to 500 mg/day) for 10 days was well tolerated in infants and children. There were no significant safety findings. Steady-state plasma concentrations of levofloxacin in children <5 to 16 years of age were comparable to concentrations in adults receiving the approved adult dosing regimen of 500 mg once a day.

Date of the report: 06 September 2005

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