SYNOPSIS

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute 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.: CR005473

Title of Study: A Multicenter, Randomized, Open-Label Study to Compare the Safety and Efficacy of i.v. and/or Oral Levofloxacin With That of Ticarcillin/Clavulanate Alone or Followed by Amoxicillin/Clavulanate in the Treatment of Complicated Bacterial Skin and Skin Structure Infections (RWJ 25213-097)

Investigators: 32 investigators; 5 investigators did not enroll any subjects

Study Centres: 28 centers

Publication (Reference): none

Studied Period (years): January 13, 1997 - August 27, 1998 | **Phase of development:** 3B

Objectives: To compare the safety and efficacy of levofloxacin 750 mg (i.v., oral, or i.v./oral) once daily (q.d.) with that of ticarcillin/clavulanate (i.v.) alone or followed by amoxicillin/clavulanate (oral) in the treatment of complicated bacterial skin and skin structure infections.

Methodology: This was a multicenter, open-label, comparative, randomized study conducted in the United States. Subjects were assigned to one of two treatment regimens (levofloxacin or comparator) in a 1:1 ratio according to a randomization schedule stratified by study center and diagnosis of diabetic ulcer. Efficacy evaluations included assessments of posttherapy (two to five days following therapy) clinical response rates, posttherapy microbiologic response rates by pathogen and subject's infection, poststudy (three to four weeks following completion of study drug) clinical relapse/new infection rates, and poststudy microbiologic relapse rates by pathogen and by subject's infection. The clinical success rate (defined as cured + improved) in the group of subjects evaluable for clinical efficacy was the primary efficacy variable for this study. Safety evaluations included incidence of treatment-emergent adverse events and changes from admission to posttherapy in clinical laboratory test results, vital signs, and physical examination findings.

Number of Subjects (planned and analyzed): Planned: 400 subjects, 200 in each treatment group. Enrolled: 400 subjects; one subject was enrolled twice in error, first in the comparator group and later in the levofloxacin group. This subject was counted twice in the safety evaluation (201 levofloxacin and 199 comparator) and once in the efficacy evaluation (intent-to-treat, 200 levofloxacin and 199 comparator; clinically evaluable 138 levofloxacin and 132 comparator; and microbiologically evaluable 98 levofloxacin and 98 comparator).

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older with a diagnosis of complicated bacterial skin and skin structure infection based on at least two of the following signs and symptoms: pain, swelling, erythema, induration, and pus formation. Complicating factors included a pre-existing skin lesion or an underlying condition that adversely affected the delivery of drug to the infected area, the immunologic response, or tissue healing response. A specimen from the infected area for Gram stain, culture, and sensitivity testing was required for entry into the study.

Test Product, Dose and Mode of Administration, Batch No.: Levofloxacin 750 mg i.v., oral, or i.v./oral q.d. Subjects started on i.v. levofloxacin could be switched to oral levofloxacin at the investigator's discretion.

Intravenous levofloxacin 25 mg/mL FD 25213-097-D-45 (Batch Numbers R6377, R6619, and R6709)
Oral levofloxacin 500 mg FD 25213-097-AA-22 (Batch Number 6510, Blistertape R6476; Batch Number 6839, Blistertape R6476; Batch Number R7005, Blistertape R6476)

Oral levofloxacin 250 mg FD 25213-097-AB-22 (Batch Number R6510, Blistertape R5902; Batch Number R6839, Blistertape R6616; Batch Number R7005, Blistertape R6886)

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
The R.W. Johnson Pharmaceutical Research Institute		
NAME OF FINISHED PRODUCT:	Volume:	
LEVAQUIN®		
NAME OF ACTIVE INGREDIENT(S):	Page:	
levofloxacin		

Duration of Treatment: 7 to 14 days for both regimens (levofloxacin and reference therapy) as clinically indicated.

Reference Therapy, Dose and Mode of Administration, Batch No.: Ticarcillin/clavulanate 3.1 g q4-6h i.v. Subjects who achieved significant clinical improvement could be switched to oral amoxicillin/clavulanate 875 mg q12h at the investigator's discretion.

ticarcillin/clavulanate (NDC 00029-6571-26, Batch Number R7162)
amoxicillin/clavulanate (NDC 00029-6086-21, Batch Number R7137)

Criteria for Evaluation:

Efficacy:

- Clinical response assessed posttherapy (test of cure) two to five days following therapy. Posttherapy clinical response categorized as cured, improved, failed, or unable to evaluate.
- Clinical relapse/new infection assessed poststudy (three to four weeks following completion of study drug) for subjects with a successful (cure or improved) clinical outcome at the posttherapy visit. Poststudy clinical response was categorized as cured, clinical relapse/new infection, or unable to evaluate.

Microbiologic outcomes:

- Microbiologic response assessed posttherapy by pathogen, categorized as eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, or unknown.
- Microbiologic response assessed posttherapy by subject's infection, categorized as eradicated, persisted, or unknown.
- Microbiologic relapse assessed poststudy by pathogen, categorized as eradicated, persisted, presumed persisted, microbiological relapse, presumed microbiological relapse, or unknown.
- Microbiologic relapse assessed poststudy by subject's infection, categorized as eradicated, persisted, microbiologic relapse, or unknown.
- Superinfecting pathogens identified up to and including the posttherapy visit. New infectors and reinfections (relapse of original pathogens) identified between the posttherapy visit and the poststudy visit. Colonizers identified at any visit from any site.

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

Statistical Methods: The primary efficacy variable was clinical response at the posttherapy (test of cure) visit based on the group of subjects evaluable for clinical efficacy. Secondary efficacy variables were: 1) posttherapy microbiologic response by pathogen and by infection based on microbiologically evaluable subjects; 2) clinical relapse/new infection assessed poststudy based on the group of subjects evaluable for clinical efficacy; and 3) poststudy assessment of microbiologic relapse by pathogen and by infection based on microbiologically evaluable subjects. Two-sided 95% confidence intervals around the treatment difference (comparator minus levofloxacin) in posttherapy (test of cure) clinical success rates (cured + improved) were used to assess therapeutic equivalence. Two-sided 95% confidence intervals around the treatment difference in posttherapy infection eradication rates overall and for the most prevalent pathogens were computed. Comparability between treatment groups in baseline demographic parameters was determined using a Fisher's Exact test for gender, race, and severity of infection and a two-sided t-test for age, weight, and height.

All subjects who received at least one dose of study medication and relayed safety information were evaluated for safety. Safety data were summarized using descriptive statistics (frequency, mean, standard deviation) for treatment-emergent adverse events reported during the study and for pretherapy to posttherapy changes in laboratory test results, vital signs, and physical findings. Two-sided 95% confidence intervals were calculated to assess equivalence between the two treatment groups in the overall incidence of treatment-emergent adverse event rates and for the incidence of treatment-emergent adverse events for each body system.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
The R.W. Johnson Pharmaceutical Research Institute		
NAME OF FINISHED PRODUCT:	Volume:	
LEVAQUIN®		
NAME OF ACTIVE INGREDIENT(S):	Page:	
levofloxacin		

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Clinical Results at the Posttherapy Visit (test of cure): Among subjects evaluable for clinical efficacy, 116/138 (84.1%) levofloxacin-treated subjects and 106/132 (80.3%) comparator-treated (ticarcillin/clavulanate either alone or followed by amoxicillin/clavulanate) subjects achieved a clinical response of cured or improved (clinical success). The 95% confidence interval of (-13.3, 5.8) for the difference (comparator minus levofloxacin) in clinical success rates is consistent with FDA's guideline for therapeutic equivalence. Clinical success rates (cured + improved) at the posttherapy visit for common pathogens ranged from 60% to 90% in the levofloxacin treatment group with generally comparable results in the comparator treatment group.

Table I: Clinical Response Rates Two to Five Days Posttherapy for Subjects with Pathogens of Primary Interest[a]: Subjects Evaluable for Clinical Efficacy
(Protocol CR005473)

	Levofloxacin 750 mg q.d.				Comparator			
		No. (%) of Subjects				No. (%) of Subjects		
Pathogen(s)	N[b]	Cure	Improved	Failure	N[b]	Cure	Improved	Failure
Staphylococcus aureus	55	28 (50.9)	20 (36.4)	7 (12.7)	50	25 (50.0)	14 (28.0)	11 (22.0)
Streptococcus agalactiae	12	5 (41.7)	3 (25.0)	4 (33.3)	14	3 (21.4)	6 (42.9)	5 (35.7)
Enterococcus faecalis[c]	11	3 (27.3)	6 (54.5)	2 (18.2)	12	3 (25.0)	6 (50.0)	3 (25.0)
Proteus mirabilis	10	6 (60.0)	3 (30.0)	1 (10.0)	12	3 (25.0)	4 (33.3)	5 (41.7)
Enterobacter cloacae	8	3 (37.5)	3 (37.5)	2 (25.0)	5	1 (20.0)	4 (80.0)	0 (0.0)
Streptococcus milleri	8	4 (50.0)	2 (25.0)	2 (25.0)	2	1 (50.0)	1 (50.0)	0 (0.0)
Pseudomonas aeruginosa	7	1 (14.3)	5 (71.4)	1 (14.3)	6	2 (33.3)	4 (66.7)	0 (0.0)
MRSA[d]	6	2 (33.3)	2 (33.3)	2 (33.3)	3	0 (0.0)	1 (33.3)	2 (66.7)
Streptococcus pyogenes	6	4 (66.7)	1 (16.7)	1 (16.7)	7	5 (71.4)	1 (14.3)	1 (14.3)
Escherichia coli	5	0 (0.0)	3 (60.0)	2 (40.0)	3	1 (33.3)	0 (0.0)	2 (66.7)

[a] N≥5 in either treatment group.
[b] N=Number of subjects who had that pathogen alone or in combination with other pathogens.
[c] Formerly known as *Streptococcus faecalis*.
[d] *Staphylococcus aureus* (methicillin-resistant).
NOTE: Comparator=Ticarcillin/clavulanate 3.1 g i.v. q4-6h alone or followed by amoxicillin/clavulanate 875 mg p.o. q12h.

Microbiologic Results: Among subjects evaluable for microbiologic efficacy, levofloxacin eradicated 87.0% of pathogens and the comparator eradicated 73.5% of pathogens (95% CI = -22.5, -4.5). Eradication rates support the efficacy of levofloxacin against those pathogens for which ≥10 isolates were evaluable in both treatment groups (*S. aureus*, *S. agalactiae*, *P. mirabilis*, and *E. faecalis*). For other pathogens in this study (*E. cloacae*, *S. milleri*, *P. aeruginosa,* methicillin-resistant *S. aureus*, *S. pyogenes,* and *E. coli*) too few cases were evaluable for meaningful comparisons between the two treatment groups.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
The R.W. Johnson Pharmaceutical Research Institute		
NAME OF FINISHED PRODUCT:	Volume:	
LEVAQUIN®		
NAME OF ACTIVE INGREDIENT(S):	Page:	
levofloxacin		

Table II: Microbiologic Eradication Rates Two to Five Days Posttherapy Summarized by Pathogen Category and Pathogen: Subjects Evaluable for Microbiologic Efficacy
(Protocol CR005473)

	Levofloxacin 750 mg q.d.			Comparator			
		No.	(%)		No.	(%)	
Pathogen Category/Pathogen[a]	N	Eradicated		N	Eradicated		95% CI[b]
Pathogen Category							
gram-positive aerobic pathogens	108	93	(86.1)	101	75	(74.3)	(-23.1, -0.6)
gram-negative aerobic pathogens	44	37	(84.1)	45	31	(68.9)	(-33.7, 3.2)
gram-positive anaerobic pathogens	4	4	(100.0)	3	3	(100.0)	
gram-negative anaerobic pathogens	13	13	(100.0)	2	2	(100.0)	
Total by pathogen	169	147	(87.0)	151	111	(73.5)	(-22.5, -4.5)
Total by subject[c]	98	82	(83.7)	98	70	(71.4)	(-24.3, -0.2)
Pathogen[a]							
Enterobacter cloacae	8	7	(87.5)	5	3	(60.0)	
Escherichia coli	5	4	(80.0)	3	1	(33.3)	
MRSA[d]	5	4	(80.0)	3	2	(66.7)	
Proteus mirabilis	10	9	(90.0)	12	7	(58.3)	(-70.2, 6.9)
Pseudomonas aeruginosa	7	4	(57.1)	6	5	(83.3)	
Staphylococcus aureus	56	50	(89.3)	49	35	(71.4)	(-33.9, -1.8)
Streptococcus agalactiae	12	9	(75.0)	13	9	(69.2)	(-45.0, 33.5)
Enterococcus faecalis[e]	10	8	(80.0)	11	6	(54.5)	(-68.9, 18.0)
Streptococcus milleri	8	7	(87.5)	2	2	(100.0)	
Streptococcus pyogenes	6	5	(83.3)	7	6	(85.7)	

[a] N≥5 for either treatment group.
[b] Two-sided 95% confidence interval around the difference (comparator minus levofloxacin) in microbiologic eradication rates were calculated for pathogens with 10 or more admission isolates in each treatment group.
[c] Eradication of all pathogens isolated for a subject at admission.
[d] *Staphylococcus aureus* (methicillin-resistant).
[e] Formerly known as *Streptococcus faecalis*.
NOTE: Comparator=Ticarcillin/clavulanate 3.1 g i.v. q4-6h alone or followed by amoxicillin/clavulanate 875 mg p.o. q12h.

SAFETY RESULTS: Both levofloxacin and ticarcillin/clavulanate either alone or followed by amoxicillin/clavulanate were safe and well-tolerated. The type and frequency of treatment-emergent adverse effects reported were consistent with the known safety profiles of these agents. Overall, 45.8% of subjects in the levofloxacin treatment group and 53.8% of subjects in the comparator treatment group reported at least one treatment-emergent adverse event during the study (95% CI [-2.0, 18.0]). The most common adverse events (≥2%) were insomnia, nausea, and constipation in both treatment groups. There were no clinically significant mean changes in laboratory values for any laboratory analyte in either the levofloxacin or comparator treatment groups, with comparable results in both groups. Twenty (10.0%) levofloxacin-treated subjects and 14 (7%) comparator-treated subjects experienced adverse events of marked severity. Thirteen subjects in the levofloxacin treatment group and seven subjects in the comparator treatment group discontinued study therapy prematurely due to adverse events. Twenty (10.0%) levofloxacin-treated subjects experienced 25 serious adverse events, and 18 (9.0%) comparator-treated subjects experienced 21 serious adverse events. Of those serious adverse events where outcome was known, all events resolved, except interstitial nephritis (levofloxacin subject) and malignant breast neoplasm (comparator subject). Outcome was unknown for two serious adverse events (osteomyelitis in 1 levofloxacin subject and 1 comparator subject). Four deaths were reported. One levofloxacin-treated subject died during the study due to respiratory depression, and 1 levofloxacin-treated subject completed the study but died due to pneumonia, dehydration and acute renal failure within one month of completion of therapy. One comparator-treated subject was withdrawn prematurely from the study due to MRSA infection and subsequently died due to hemorrhage, while a second comparator-treated subject died due to a cerebrovascular accident after the 30 days period but within three months of completion of therapy. All deaths were considered unrelated to study therapy.

Serious adverse events occurred in 20 (10.0%) subjects in the levofloxacin treatment group and 18 (9.0%) subjects in the comparator treatment group.

CONCLUSION: Both levofloxacin and ticarcillin/clavulanate either alone or followed by amoxicillin/clavulanate are effective in the treatment of skin and skin structure infections. Levofloxacin 750 mg administered once daily for 7 to 14 days was shown to be as effective as the comparator when administered in multiple daily doses for the same duration. Both study drugs were well-tolerated in this study. There were no unusual or unexpected treatment-emergent adverse events. There were no clinically significant changes pretreatment to posttreatment in physical examination findings, vital signs, or clinical laboratory values.

Date of the report: 5 November 1999

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.