CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020634

Trade Name : LEVAQUIN

Generic Name: Levofloxacin

Sponsor : R. W. Johnson

Approval Date: December 20, 1996

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 20 1996

NDA 20-634

R.W. JOHNSON, Pharmaceutical Research Institute
Attention: Heather Jordan, Associate Director, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Jordan:

Please refer to your December 21, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levaquin® (levofloxacin) 250- and 500- mg Tablets.

We acknowledge receipt of your amendments dated January 19, 1996; February 5, and 9, 1996; March 20, 1996; April 26, 1996; May 31, 1996; July 17, 1996; August 2, and 23, 1996; September 26, 1996; October 28, and 31, 1996; November 11, 14, 20, and 27, 1996; and December 3, and 13, 1996.

We also acknowledge the receipt of your letter dated December 13, 1996, requesting the withdrawal of the

This new drug application provides for the indications of Acute maxillary sinusitis, Acute bacterial exacerbations of chronic bronchitis, Community-acquired pneumonia, Uncomplicated skin and skin structure infections, Complicated urinary tract infections, and Acute pyelonephritis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the December 18, 1996 draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling dated December 18, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-634. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Frances LeSane, Project Manager at 301) 827-2125.

Sincerely yours,

David W Feigal 12-20-96

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

cc:

Original NDA 20-634
HFD-520/Div. file
HFD-2/M.Lumpkin
HFD-104/TNearing
HFD-101/L.Carter (with labeling)
HFD-830/E.Sheinin
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-021/J.Treacy (with labeling)
HFD-520/MO/RHopkins 12/19/96
HFD-520/MO/KFrank 19-Dec-96
HFD-520/CHEM/BShetty
HFD-520/PHARM/SJoshi
HFD-520/BIOPHARM/FAjayi
HFD-520/MICRO/RKing
HFD-520/STAT/NSilliman
HFD-520/PMS/FVLeSane/11-19-96/**revised 12-18-96** 12-18-96

TEAM LEADERS

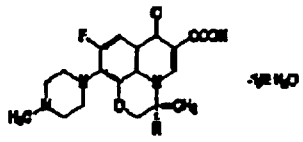
HFD-520/TLMO/MAlbuerne
HFD-520/Act.TLCHEM/DKatague 12/19/96
HFD-520/TLPHARM/ROsterberg 12.9.96
HFD-520/TLBIOPHARM/FPelsor 12/19/96
HFD-520/TLMICRO/ASheldon
HFD-520/TLSTAT/DLin 12/19/96

APPROVAL

Concurrence Only:
HFD-520/TLMO/MAlbuerne NDA 12/12/96
HFD-520/CPMS/JBona

mor/stat

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATIONS
NDA's 20-634 AND 20-635

Applicant Name and Address:	R. W. Johnson Pharmaceutical Research Institute Route 202, P.O. Box 300 Raritan, New Jersey 08869-0602 (908) 704-4600
Date of Submissions:	December 21, 1995
CDER Stamp Date:	December 22, 1995
Date Submissions Received by Reviewer:	December 22, 1995
Date Begun Review:	March 1, 1996
Date Review Completed:	October 30, 1996
Generic Name:	Levofloxacin
Proposed Trade Name:	Levaquin
Chemical Name:	(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-Benzoxazine-6-carboxylic acid hemihydrate
Chemical Structure:	
Molecular formula:	$C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$
Molecular Weight:	370.38
Pharmacologic Category:	Fluoroquinolone
Dosage Forms:	Tablets (NDA 20-634) Solution (NDA 20-635)
Routes of Administration:	Oral (NDA 20-634) Parenteral (NDA 20-635)

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Material Reviewed

This review was done using a computerized new drug application (CANDA) provided by the sponsor. This CANDA provided all study reports and textual information in a read-only WORD format. In addition, complete data listings for all clinical phase 2/3 studies were provided in Microsoft Access. Each study was reviewed on a patient-by-patient basis for efficacy to determine inclusion/exclusion and evaluability/outcome results. The Sponsor's safety data were evaluated by reviewing the summary safety data provided in each study report. In addition, the Integrated Summary of Safety was reviewed in detail using the total safety population. Two Medical Officers (Dr. Karen Frank and Dr. Robert Hopkins) performed the primary medical reviews for these NDAs. Study reports supporting 3 indications (exacerbation of chronic bronchitis, community acquired bacterial pneumonia, and acute bacterial sinusitis) were reviewed by Dr. Frank (see separate Medical Officer's NDA Review) and 4 indications . uncomplicated skin and skin structure infection, complicated urininary tract infection, and acute pyelonephritis) were reviewed by Dr. Hopkins. The Medical Officer's review of the Integrated Summary of Safety and the review of the skin and UTI/acute pyelonephritis indications were conducted jointly with the Statistical Reviewer (Dr. Nancy Silliman).

Regulatory Background

The original IND for levofloxacin tablets was submitted on April 3, 1991. The following items were addressed by the sponsor as a result of issues raised by the FDA:

- Subject diary cards were to be completed by 256 subjects with acute bacterial exacerbation of chronic bronchitis in a comparative Phase 2/3 study (Study M92-024).
- A phase 1 study evaluating blood clotting was to assess the effect of levofloxacin on warfarin disposition (Study LOFBOPH-098).
- Additional safety assessments including ophthalmologic examinations, electroencephalograms, and an evaluation of the phototoxic potential of levofloxacin was to be performed.
- The potential for levofloxacin crystallization in urine was also to be examined in two Phase 1 studies (LOFBO-PHI-101 and LOFBOPHIO-098).
- Renal function tests were to be performed in all patients in phase 2/3 studies.
- Drug interaction studies were to be conducted for sucralfate, probenecid/cimetidine, theophylline, and warfarin. A primary Phase 1 study evaluating the effects of concomitant administration of levofloxacin and antacids was not conducted by RWJPRI since: 1) clinical evidence indicates that there are no stereospecific differences in the absorption of the ofloxacin isomers, and 2) the extent of interaction with aluminum hydroxide is similar for ofloxacin and levofloxacin. It was decided that the levofloxacin label should be identical to ofloxacin with regards to the administration of aluminum or magnesium containing antacids. The effect of different categories of concomitant medications (e.g., antacids, anticoagulants) on adverse event data were to be summarized in Phase 2/3 studies. A levofloxacin/fenbufen interaction was not performed since fenbufen is not approved in the United States.

The proposed clinical development plan was presented to FDA on February 11, 1992. A revised plan based on FDA comments were presented on April 29, 1994. This included two pivotal studies per requested indication for acute bacterial sinusitis, acute exacerbation of chronic bronchitis, community-acquired bacterial pneumonia, complicated UTI/acute pyelonephritis, and , and a single pivotal study for uncomplicated SSSI. RWJPRI also agreed to conduct a study in which adverse event and efficacy endpoints would be correlated with population-derived pharmacokinetic parameters (requested November 18, 1993). An additional pivotal double-blind study of levofloxacin for uncomplicated SSSI was later added to the clinical program and conducted in Latin America.

Of the 12 pivotal Phase 2/3 studies, 10 employed an open-label design and two (Protocol L91-058, complicated UTI and acute pyelonephritis; Protocol L91-031, uncomplicated SSSI) were double-blind studies, with at least one randomized, active-controlled study performed for each of the requested indications. The issue of blinding was discussed with FDA by teleconference on May 4, 1992. FDA accepted RWJPRI's rationale for not blinding the community-acquired pneumonia studies and skin and skin structure studies, indicating that blinding of the investigator at the time of randomization was an important consideration in their acceptance of the proposal. To insure against selection bias by the investigator in open-label studies, rosters of potential subjects were to be maintained by each investigator.

On March 10, 1995 RWJPRI's proposal regarding the handling of safety was discussed. It was agreed that all serious adverse events from the European clinical trials conducted by and its affiliates would be included in the NDA both in hard copy and electronic (CANDA) form, along with all serious adverse events spontaneously reported to

A pre-NDA meeting was held on May 4, 1995, to review the format and content of the Nonclinical, Clinical, and Statistical sections of the NDA including details regarding the anticipated claims for levofloxacin and the planned content of the Integrated Summary of Safety.

At the request of the FDA (July 14, 1995) an additional bioequivalence study was performed (LOFBO-PHI-104) because one subject from a previous study (LOFBO-PHIO-097) was included. RWJPI guaranteed that the pharmacokinetic results of this study would be available as soon as possible.

Foreign Marketing Experience

As of the date of submission, levofloxacin has been marketed in four countries including China, Hong Kong, Korea, and Japan. Levofloxacin tablet formulation is marketed in China, Hong Kong, and Korea. Two levofloxacin formulations (tablet and granule) have been commercially available in Japan since December, 1993. The follwoing table outlines the countries where levofloxacin is currently marketed and the dates of approval and product launch.

Countries Where Levofloxacin is Marketed and Dates of Approval and Product Launch

Country	Date of Approval	Date of Launch
China	May 30, 1995	September 1, 1995
Hong Kong	October 3, 1994	December 1, 1994
Korea	April 30, 1994	September 1, 1994
Japan	October 1, 1993	December 1, 1993

Summary of Clinical Development Program (as contained in NDAs 20-634 and 20-635)

A summary of clinical trial characteristics for individual studies supporting each of the proposed indications is described in the following Table. Studies supporting seven indications were performed. For each indication, a pivotal study enrolling U.S. patients was performed. Most studies were unblinded except for one pivotal study (uncomplicated skin and skin structure infection) and four supportive studies (one supporting acute exacerbation of chronic bronchitis, one supporting community acquired pneumonia, one supporting uncomplicated skin and skin structure infection, and one supporting All studies were controlled except for one pivotal sinusitis study, one supportive sinusitis study and one pivotal community acquired pneumonia study.

Design Characteristics of Studies Supporting Labeled Indications
Levofloxacin NDAs 20-634 and 20-635

Protocol Number/ Study Name	Countries	Pivotal/Supportive	Blinding	Clinical/Micro Endpoint	Controlled	Number of Patients
Acute Bacterial Sinusitis						
M92-040	US	Pivotal	Unblinded	Clinical	Yes	615
N93-006	US	Pivotal	Unblinded	Micro	No	329
F/93/355/01	France	Supportive	Unblinded		No	239
Acute Exacerbation of Chronic Bronchitis						
M92-024	US	Pivotal	Unblinded	Clinical	Yes	373
K90-070	US, Can, CR	Pivotal	Unblinded	Micro	Yes	492
3355E-CLN026	UK, Fr, G, I	Supportive	Double		Yes	246
Community Acquired Bacterial Pneumonia						
K90-071	US, Can	Pivotal	Unblinded	Clinical	Yes	590
M92-075	US	Pivotal	Unblinded	Micro	No	264
3355E-CLN025	UK, Fr, G, I	Supportive	Double		Yes	140
Uncomplicated Skin and Skin Structure Infection						
K90-075	US	Pivotal	Unblinded	Clinical	Yes	469
L91-031	Mex, SA	Pivotal	Double	Clinical	Yes	361
3355E-CLN028	UK, Fr, G	Supportive	Double		Yes	96
Complicated Urinary Tract Infection and Acute Pyelonephritis						
L91-058	US, Can	Pivotal	Double	Micro	Yes	567
L91-059	US	Pivotal	No	Micro	Yes	650
3355E-CLN027	UK, Fr, G, Ir	Supportive	Double		Yes	292
Multiple Indication-Pharmacokinetic/Efficacy Study						
LOFVIV-MULT-011	US	Supportive	Unblinded	N/A	Yes	313

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NA Indication

STUDY K90-075

TITLE

A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of levofloxacin versus ciprofloxacin HCL in the treatment of mild-to-moderate (i.e., uncomplicated) skin and skin structure infections in adults.

INVESTIGATORS

Stanley Cullen, M.D. - Gainesville, FL;
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St. Luke's Episcopal Hospital, Houston, TX;
Hospital Mexico, San Jose, Costa Rica;
Hospital San Juan de Dios, San Jose, Costa Rica;
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Holy Cross Hospital E.D., Salt Lake City, UT;
South West Emergency, West Jordan, UT;
South East Emergency, Salt Lake City, UT;
Nancy Krywonis, M.D. - VA Medical Center, Minneapolis, MN;
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William P. Lascheid, M.D., P.A. - Naples, FL; Naples Community Hospital; Diagnostic Services Inc., Naples, FL;
Richard G. Lathrop, M.D. - Warren, NJ;
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Infectious Disease Consultants, Sarasota, FL;
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Charity Hospital of Louisiana, New Orleans, LA;
George A. Pankey, M.D. - Alton Ochsner Medical Foundation, New Orleans, LA;
Robert Powers, M.D. - University of Virginia Emergency Room, Charlottesville, VA;
Robert Schwartz, M.D. - Associates in Research, Ft. Myers, FL;
Lee Memorial Hospital, Ft. Myers, FL;
Stephen Sokalski, D.O. -
Christ Hospital and Medical Center, Oaklawn, IL;
Christ Hospital and Medical Center, Women's Health Services, Tinley Park, IL;

OBJECTIVES

The objective of this study was to evaluate the safety and efficacy of 488 mg levofloxacin administered orally q24h for 7 to 10 days compared to 500 mg ciprofloxacin administered orally q12h for 7 to 10 days in the treatment of mild-to-moderate (i.e., uncomplicated) SSSI.

OVERVIEW OF STUDY DESIGN

This was a randomized, open-label (i.e., unblinded), active-control, multicenter study designed to evaluate levofloxacin in the treatment of uncomplicated SSSI. This study was conducted in the United States except for one investigator who had several sites in Costa Rica. Approximately 440 adult subjects were to be enrolled to ensure clinically evaluable data from a minimum of 300 subjects (150 subjects per treatment group). Subjects were assigned randomly to receive either 488 mg levofloxacin orally q24h for 7 to 10 days or 500 mg ciprofloxacin orally q12h for 7 to 10 days. The total duration of therapy was 7 to 10 days. The levofloxacin dosing interval was to be increased to 48 hours in subjects with creatinine clearances of 20 to 50 mL/min. Safety and efficacy evaluations were performed according to the schedule presented in Table 1.

Table 1. Schedule of Assessments

(Study K90-075)

Assessment/Procedure	Admission (Day 1)	During Therapy (Days 3 - 5)	Last Day of Therapy	Posttherapy (2 - 7 days PT)[a]
Medical History	X			
Pregnancy Test[b]	X			X
Study Drug Administration	X	———	X[c]	
Efficacy Evaluations: (see Section III.H.2.)				
Clinical:				
-Clinical Signs & Symptoms	X	X		X
-Clinical Response Rating				X
Microbiologic:				
-Culture from Site of Infection	X	X[d]		X[d]
-Susceptibility Test	X	X[d]		X[d]
-Gram Stain of Smear from Site of Infection	X	X[d]		X[d]
-Blood Culture	X[d]	X[e]		X[e]
Safety Assessments: (see Section III.H.4.)				
Adverse Events		X		X
Clinical Laboratory Tests:				
-Hematology	X			X
-Blood Chemistry	X			X
-Urinalysis	X			X
Physical Examination (including Vital Signs)	X			X

[a] Or upon early termination.
[b] Performed on all women of childbearing potential.
[c] Total duration of therapy was to be 7 to 10 days.
[d] Performed only if indicated.
[e] Performed if positive at previous visit.

Subjects who were either bacteremic, had an oral temperature of >101.0°F, or had a white blood cell count of >15,000/μL plus a rating of severe by the investigator for tenderness, erythema, or swelling were considered to have severe infections. All other subjects had mild/moderate infections.

Between Days 3 and 5 of study drug administration, subjects returned for a scheduled on-study visit. Subjects were allowed to remain in the study in the absence of recovery of an admission pathogen if every attempt was made to obtain a pathogen or if the pathogen(s) isolated at admission were resistant to any of the assigned study drugs by in vitro testing as long as in the opinion of the investigator, there had been no deterioration of clinical status.

PROTOCOL AMENDMENTS

Amendment 1, September 17, 1991 (10% enrollment)

- if the admission culture was negative, a provision was added to discontinue the study drug.

Amendment 2, October 22, 1991 (15% enrollment)

- The dose of the study drug was clarified

Amendment 3, May 21, 1992, (60% enrollment)

- the total number of subjects evaluable for efficacy was increased from 200 to a minimum of 300. The planned sample size was recalculated to provide a sufficient number of subjects to demonstrate that levofloxacin was at least as effective as ciprofloxacin.

STUDY POPULATION

1. Overview

Approximately 440 subjects, men and women who were 18 years of age or older with a diagnosis of SSSI, were to be enrolled in this study to ensure 300 clinically evaluable subjects (150 per treatment group).

Medical Officer's Note: This study began in 1991 for subjects with mild-to-moderate skin infections. After the FDA issued the Anti-Infective "Points to Consider" guideline in 1992, each subject's infection was retrospectively classified by the sponsor as uncomplicated or complicated and as mild/moderate or severe. However, for claims of efficacy and safety, complicated and uncomplicated subjects were analyzed together by the sponsor. FDA analyses will include only patients with uncomplicated infections.

Inclusion Criteria

- Men and women, 18 years of age or older, with a diagnosis of SSSI.
- Subjects with multiple sites of infection could be enrolled.
- A culture from the site of infection not greater than 48 hours prior to the start of therapy was required.
- Women were required to be postmenopausal for at least one year, surgically sterile, or using an adequate form of birth control for at least one month prior to the study. Women of childbearing potential were required to have had a normal menstrual flow within one month before study entry and to have had a negative pregnancy test immediately before study entry.
- Subjects with impaired renal function or who required dialysis could have been entered but were to have alternate dosing schedules.

Exclusion Criteria

- Subjects with a history of allergic or serious adverse reactions to levofloxacin, ciprofloxacin, or any other member of the quinolone class of antimicrobial drugs.
- Subjects with severe illness requiring administration of intravenous antimicrobial therapy.
- Subjects who required a second systemic antimicrobial therapy or a topical antimicrobial therapy
- Subjects who received any effective systemic antimicrobial drug within 48 hours before study entry or who used any investigational drug within 30 days before study entry.
- Subjects whose infections required debridement at the infection site.
- Subjects with infections caused by organisms known to be resistant to either study drug before study entry.

- Subjects with osteomyelitis, severe SSSI, signs and symptoms of septic shock, or any disorder or disease that might interfere with the evaluation of the study drug.
- Women who were pregnant or nursing, subjects with serum creatinine levels greater than 2.5 mg/dL.
- Subjects with a seizure disorder or condition requiring major tranquilizers, or who were grossly underweight.

DOSAGE AND ADMINISTRATION

Subjects were assigned randomly to receive either levofloxacin or ciprofloxacin. Subjects assigned to the levofloxacin treatment group received five 97.6-mg levofloxacin tablets once daily for a total daily dose of 488 mg levofloxacin. Subjects assigned to the ciprofloxacin control group received a single 500-mg ciprofloxacin tablet twice daily for a total daily dose of 1000 mg ciprofloxacin. The total duration of therapy was 7 to 10 days for both treatment groups. Renally impaired subjects, those with a creatinine clearance of 20 to 50 mL/min, were to have had their levofloxacin dose regimen adjusted to receive 488 mg levofloxacin every 48 hours.

COMPLIANCE

Compliance was estimated by counting unused study drug tablets in the test medication containers.

CONCOMITANT THERAPY

The use of other medications during the study was to be kept to a minimum. Administration of nonstudy systemic antimicrobials or topical antimicrobials to the infected site(s) was prohibited. Use of aluminum-magnesium based antacids (e.g., Maalox ®) were strongly discouraged. If administration of an antacid was necessary, it was to be administered at least two hours before or after levofloxacin or ciprofloxacin administration. If the administration of any other medication was required, it was reported on the subject's CRF and the study monitor was notified when appropriate.

EFFICACY AND SAFETY EVALUATIONS

Efficacy evaluations included evaluation of clinical signs and symptoms, clinical response rates (assessed as cured, improved, failed, or unable to evaluate) and microbiologic eradication rates by pathogen and infection (assessed as eradicated, persisted, persisted with acquisition of resistance, or unknown). Clinical response in the group of subjects evaluable for clinical efficacy represented the primary efficacy variable for this study. Microbiologic response was a secondary efficacy variable and was based primarily on the group of subjects evaluable for microbiologic efficacy.

Efficacy Evaluations

Clinical Signs and Symptoms

Clinical signs of SSSI, including tenderness, erythema, swelling, drainage, fluctuance, ulceration, and presence of necrotic tissue at the infected site, were graded by the investigator as none, mild, moderate, or severe at admission and at the posttherapy visit two to seven days after the end of therapy. In addition, the subjects provided information regarding symptoms of SSSI (graded as present or absent at admission and at posttherapy) including localized pain, swelling, drainage, fever, and chills. These signs and symptoms were used by the investigator to assign a diagnosis upon admission of a subject into the study. Severity and complexity of each subject's infection were determined retrospectively by the sponsor.

Clinical Response Rating

At the posttherapy visit two to seven days after the end of therapy, the investigator assessed clinical response as cured, improved, failed, or unable to evaluate. The definitions for these assessments are as follows:
Clinical Cure: Resolution of signs and symptoms associated with active infection.
Clinically Improved: Incomplete resolution of signs and symptoms and no additional antimicrobial therapy required.
Clinical Failure: No response to therapy.
Unable to evaluate: Not able to evaluate because subject lost to follow-up.

Clinical success rate was defined as the percentage of subjects who were cured or improved.

Statistical Reviewer's Note: The protocol states that the post-therapy visit would be scheduled for 2 to 7 days after the end of therapy; however, 1 to 10 days after the end of therapy was used for all sponsor analyses. No explanation for this change is given.

There is no later follow-up visit. The November 1992 IDSA Guidelines suggest that the appropriate test of cure is 2 to 4 weeks after completion of therapy. However, this study was initiated in March 1991 before publication of both the IDSA Guidelines and the DAIDP "Points to Consider" document.

Microbiologic Response

The secondary efficacy variable of microbiologic response to treatment was evaluated by the sponsor in terms of pathogen and infection eradication rates. The microbiologic response for pathogens isolated at admission was determined by evaluating the posttherapy/early withdrawal culture results. A culture or evaluation was considered valid if it occurred within 1 to 10 days posttherapy and while the subject was not receiving any effective concomitant systemic antimicrobial treatment. Results were categorized as follows:

Eradicated: Eradication of the admission pathogen as evidenced by no isolation of the pathogen in a valid posttherapy/early termination culture. If clinical improvement occurred such that no culture material was available, then the pathogen was presumed to be eradicated.
Persisted: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/early withdrawal culture. If a subject was discontinued due to a clinical failure and persistence of the admission pathogen was not confirmed by culture results, the pathogen was presumed to persist.
Persisted with Acquisition of Resistance: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/early withdrawal culture with documented acquisition of resistance.
Unknown: No posttherapy/early withdrawal culture results available due to lost-to-follow-up, lost culture, or culture not done while specimen was available. If the culture was performed on the last day of therapy and the subject was not a clinical failure or if the culture was done while subject was receiving effective antimicrobial agent for reasons other than clinical failure, unless persistence was verified or presumed, the response was unknown.

The microbiologic response for the subject's infection was based on eradication of all the pathogens isolated at admission as follows:
Eradicated: Eradication of all admission pathogens.
Persisted: Persistence, presumed persistence, or persistence with acquisition of resistance of at least one pathogen isolated at admission.
Unknown: No culture results available or unknown results for at least one pathogen isolated at admission with no pathogen persisting.

Specimen Collection

- Culture from Infection Site

Specimens were obtained from infected skin and skin structure sites including wound drainage, abscess fluid, aspirate of fluid following injection of nonbacteriostatic saline, or biopsy. Drainage material was to be purulent, with minimal surface contamination. In the case of multiple sites of infection, the site most likely to yield reliable culture results was sampled. Invasive procedures to obtain cultures from a clinically resolved site of infection were not required. At admission (within 48 hours of therapy start), infection site specimens were collected for culture, Gram stain, and susceptibility tests. If indicated, specimens (if available) were obtained during the study between Days 3 and 5 and at the posttherapy visit (two to seven days after the end of therapy) for culture, Gram stain, and susceptibility testing.

- Blood Culture

Blood cultures were obtained within 48 hours of admission from each subject. Two cultures were obtained during

therapy (Days 3-5) and at the Posttherapy Visit (Posttherapy Day 2 to 7), if the subject was bacteremic at admission.

- Susceptibility Testing

The MIC susceptibility was the primary susceptibility criterion. If the MIC values were not available, disks were used to determine susceptibility.

Statistical Reviewer's Note: Subjects were evaluated by the reviewing medical officer to determine FDA evaluability and outcome. Efficacy results for this "FDA evaluable patient group" were compiled by the statistical reviewer and are presented along with those of the sponsor for comparison. Patients with both complicated and uncomplicated infections were enrolled in this study; however, the FDA evaluable patient group (both clinical and microbiologic) includes only those patients considered to have uncomplicated skin and skin structure infections.

Safety Evaluations

- Treatment-Emergent Adverse Events

Adverse events were defined as treatment-emergent signs and symptoms.

- Clinical Laboratory Tests
- Physical Examinations and Vital Signs

REMOVAL OF SUBJECTS FROM THE STUDY

After a sufficient course of treatment, subjects could be discontinued from the study if the admission culture obtained from the site of infection was negative or if the pathogen isolated at admission was resistant to the assigned study drug and there was no significant clinical improvement. Subjects could also be discontinued from the study due to adverse events, significant protocol violation, intercurrent illness, treatment failure, or at the request of the subject. At the time of premature withdrawal from the study, posttherapy evaluations were to be performed including physical examination and vital signs, evaluation of the signs and symptoms of SSSI, cultures, Gram stain, and susceptibility tests of material from the infected site, if indicated, and clinical laboratory tests.

EVALUABILITY AND STATISTICAL METHODS

To be considered evaluable for clinical efficacy by the sponsor, subjects were not to be classified in any of the following categories (in decreasing hierarchical order):

- not evaluable for safety (did not take at least one dose of study drug or did not relay any postadmission safety data);
- unconfirmed clinical diagnosis; insufficient course of therapy (minimum of five days of therapy; subjects who received study drug for >48 hours but less than five days because of clinical failure could be considered clinically evaluable);
- effective concomitant systemic antimicrobial therapy or curative surgical intervention (unless a clinical failure) while on study;
- posttherapy clinical evaluation not done on Posttherapy Days 1-10 (if subject discontinued due to a persistent pathogen or clinical failure and posttherapy culture obtained on last day of therapy, subject is clinically evaluable);
- lost to follow-up but provided safety information; or other protocol violation (e.g., subject reentered study or was generally noncompliant with respect to dosing regimen).

To be evaluable for microbiologic efficacy by the sponsor, subjects were not to be classified in any of the following categories (in decreasing hierarchial order):

- not evaluable for safety (subject did not take at least one dose of study drug or did not relay any postadmission safety data);
- absence of bacteriologically proven infection; unconfirmed clinical diagnosis; insufficient course of therapy (minimum of five days of therapy and not a clinical failure); effective concomitant systemic antimicrobial therapy or surgical intervention; inappropriate bacteriologic culture (>48 hours prior to admission, outside of acceptable window of 1-10 days posttherapy, or adequate microbiologic data is not available);

- lost to follow-up but provided safety information; or other protocol violation (e.g., subject reentered study or was generally noncompliant with respect to dosing regimen).

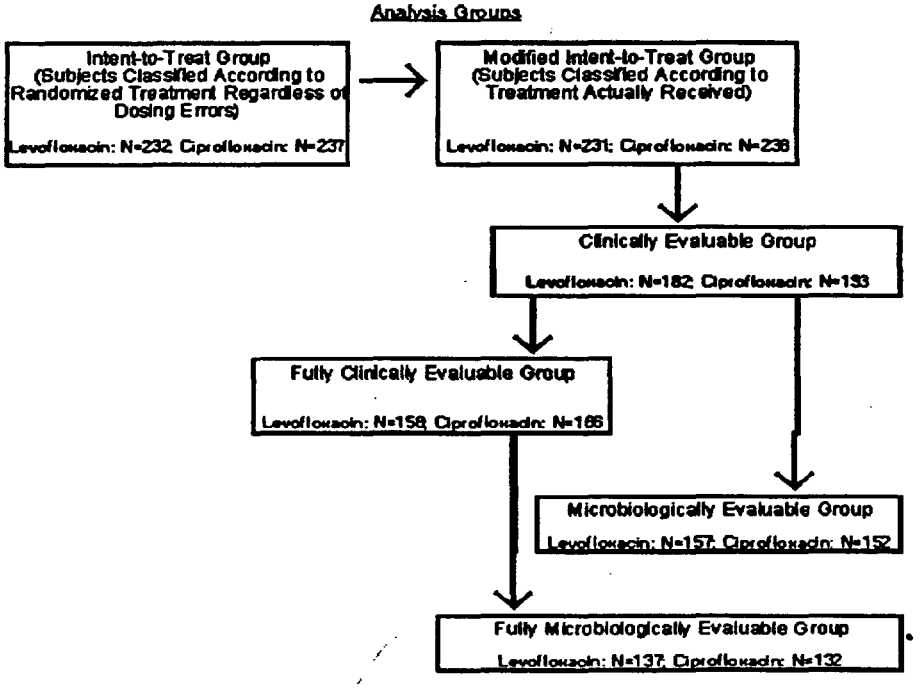
The sample size assumed clinical success rates of 89% for ciprofloxacin and 85% for levofloxacin, and a significance level of 2.5%, 150 subjects per treatment group were required to demonstrate with 80% power that the difference in clinical success rates was less than 15%. With an estimated clinical evaluability rate of 68%, approximately 440 subjects were to be enrolled.

Supportive efficacy analyses:
- Intent-to-Treat
- Modified Intent-to-Treat Analysis was to take into account dispensing errors.

Statistical Reviewer's Note: In this study report, the sponsor uses the phrase "modified intent-to-treat analysis" to mean an intent-to-treat analysis where patients are grouped according to the drug they actually received, rather than to the drug to which they were randomized. This should not be confused with the usual DAIDP definition of modified intent-to-treat analysis, which is an intent-to-treat analysis excluding patients who have no valid admission pathogen.

A final supportive efficacy analysis was based on subjects enrolled at study centers with a total enrollment of at least 10 clinically evaluable subjects in each treatment group — the Fully Clinically Evaluable group was composed of all clinically evaluable subjects enrolled at such study centers, and the Fully Microbiologically Evaluable group was the subset of Fully Clinically Evaluable subjects who were microbiologically evaluable.

The relationships between the Sponsor's efficacy analyses are summarized below.



RESULTS

Table 2 summarizes all sponsor analysis groups and corresponding analyses performed.

Table 2: Numbers of Subjects and Summaries Provided for Each Analysis Group (Study K90-075)

	Clinically Evaluable	Micro-biologically Evaluable	Modified Intent-to-Treat	Intent-to-Treat	Fully Clinically Evaluable	Fully Micro-biologically Evaluable	Safety Evaluable
Levofloxacin Treatment Group	162	157	231	232	158	137	230
Ciprofloxacin Treatment Group	193	152	238	237	165	132	232
Analyses or Summaries Performed:							
Demographics	X	X	X	X	X	X	X
Extent of Therapy	X	X	X		X	X	X
Clinical Response	X	X	X	X	X	X	
Signs/Symptoms	X	X	X				
Microbiologic Response	X	X	X	X	X	X	
Adverse Events							X
Laboratory Results							X
Vital Signs							X

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Four hundred sixty-nine subjects were enrolled in this study at 13 of the 14 centers (one investigator did not enroll any subjects). The sponsor intent-to-treat group included 232 subjects who were randomized to the levofloxacin treatment group and 237 subjects who were randomized to the ciprofloxacin treatment group. One subject randomized to receive levofloxacin actually received ciprofloxacin; hence, the numbers of subjects who received levofloxacin and ciprofloxacin were 231 and 238, respectively, and collectively comprise the sponsor modified intent-to-treat group. The demographic and baseline (admission) characteristics for the sponsor modified intent-to-treat group are summarized in Table 3. Characteristics for sponsor clinically and sponsor microbiologically evaluable patients were similar to those of the modified intent-to-treat group. There were no statistically significant differences between the two treatment groups for any of the demographic features tested (i.e., age, sex, race) for any of the analysis groups.

Potential subject rosters were maintained by the investigators. These rosters were designed to record the severity of a potential subject's disease, the reason a potential subject was excluded from the study, and the drug assignment if the subject was enrolled. The most frequent reasons for not entering a potential subject were existing antimicrobial therapy, no culturable material, and absence of admission pathogen.

Table 3. Demographic Characteristics: Sponsor Modified Intent-to-Treat Subjects

(Study K90-075)

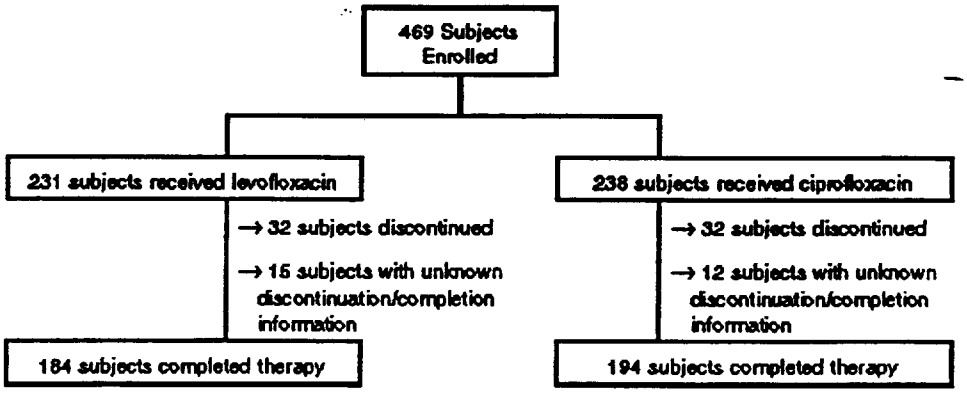
	Levofloxacin (N=231)		Ciprofloxacin (N=238)		Overall Total (N=469)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	124	(53.7)	116	(49.6)	242	(51.6)
Women	107	(46.3)	120	(50.4)	227	(48.4)
Race						
Caucasian	168	(72.7)	174	(73.1)	342	(72.9)
Black	52	(22.5)	55	(23.1)	107	(22.8)
Hispanic	9	(3.9)	7	(2.9)	16	(3.4)
Other	2	(0.9)	2	(0.8)	4	(0.9)
Age (Years)						
≤45	140	(60.6)	137	(57.6)	277	(59.1)
46-64	51	(22.1)	46	(19.3)	97	(20.7)
≥65	40	(17.3)	55	(23.1)	95	(20.3)
N	231		238		469	
Mean±SD	42.8±16.2		45.2±19.0		44.0±18.6	
Range						
Weight						
N	219		224		443	
Mean±SD	175.4±43.2		169.7±41.9		172.5±42.6	
Range	[redacted]		[redacted]		[redacted]	
Missing	12		14		26	
Diagnosis						
Cellulitis	110	(47.6)	110	(46.2)	220	(46.9)
Pyoderma	23	(10.0)	23	(9.7)	46	(9.8)
Cellulitis with Abscess	22	(9.5)	30	(12.6)	52	(11.1)
Surgical Wound Infection	19	(8.2)	16	(6.7)	35	(7.5)
Impetigo	14	(6.1)	13	(5.5)	27	(5.8)
Abscess	11	(4.8)	10	(4.2)	21	(4.5)
Cellulitis with Other*	9	(3.9)	6	(2.5)	15	(3.2)
Wound Infection	9	(3.9)	8	(3.4)	17	(3.6)
Infected Ulcer	7	(3.0)	9	(3.8)	16	(3.4)
Diabetic Foot Ulcer	3	(1.3)	6	(2.5)	9	(1.9)
Infected Decubitus Ulcer	2	(0.9)	0	(0.0)	2	(0.4)
Abscess with Other*	1	(0.4)	1	(0.4)	2	(0.4)
Hidradenitis Suppurativa	1	(0.4)	4	(1.7)	5	(1.1)
Burn Infection	0	(0.0)	2	(0.8)	2	(0.4)
Complicated						
Severe	2	(0.9)	3	(1.3)	5	(1.1)
Mild/Moderate	24	(10.4)	33	(13.9)	57	(12.2)
Total Complicated	26	(11.3)	36	(15.1)	62	(13.2)
Uncomplicated						
Severe	8	(3.5)	8	(3.4)	16	(3.4)
Mild/Moderate	197	(85.3)	194	(81.5)	391	(83.4)
Total Uncomplicated	205	(88.7)	202	(84.9)	407	(86.8)
Complicated and Uncomplicated						
Total Severe	10	(4.3)	11	(4.6)	21	(4.5)
Total Mild/Moderate	221	(95.7)	227	(95.4)	448	(95.5)

*Other infection or associated clinical symptoms.
NOTE: Values represent numbers of subjects except as otherwise indicated.

DISCONTINUATION/COMPLETION INFORMATION

Of the 469 subjects enrolled in the study, 231 received levofloxacin and 238 received ciprofloxacin (sponsor modified intent-to-treat group). Discontinuations are shown in Figure 1.

Figure 1: Discontinuation/Completion Information: Modified Intent-to-Treat Subjects (Study K90-075)



The reasons for premature discontinuation and extent of drug exposure are outlined in Table 4 and Table 5.

Table 4: Reasons for Premature Discontinuation of Therapy: Modified Intent-to-Treat Subjects (Study K90-075)

Reason	Levofloxacin (N=231)		Ciprofloxacin (N=238)	
	No.	(%)*	No.	(%)*
No Admission Pathogen	22	(10.2)	19	(8.4)
Adverse Event	4	(1.9)	5	(2.2)
Resistant Pathogen	2	(0.9)	2	(0.9)
Clinical Failure	1	(0.5)	4	(1.8)
Other	3	(1.4)	2	(0.9)
Total Discontinued	32	(14.8)	32	(14.2)
Total with Discontinuation/Completion Information	216	(100.0)	226	(100.0)
Total with Unknown Discontinuation/Completion Information	15		12	

* Percentages based on total number with discontinuation/completion information.

Table 5: Extent of Exposure to Therapy: Modified Intent-to-Treat Subjects (Study K90-075)

Extent Of Therapy	Levofloxacin (N=231)	Ciprofloxacin (N=238)
Days On Therapy*		
Unknown*	16	11
1	3	3
2	3	2
3	13	7
4	5	7
5	2	7
6	4	2
7	14	16
8	10	10
9	5	4
10	135	104
11	7	41
12	5	9
13	2	1
14	5	2
15	1	6
16	0	2
20	1	2
21	0	2
Mean±SD	9.0±2.7	9.6±3.1
Median	10	10
Number of Doses*		
Total With Dosing Information	216	227
Total With Unknown Dosing Information	15	11
Mean±SD	9.0±2.6	18.1±5.9
Median	10	20
Range	1-20	1-40

NOTE: Levofloxacin had a q24h dosing schedule and ciprofloxacin had a q12h dosing schedule.
* Days on therapy was defined as (last day - first day) +1.
* One subject had missing data for days on therapy but had data for number of doses.

EFFICACY RESULTS

The total numbers of subjects evaluable by the sponsor for clinical and microbiologic efficacy at each study center are shown in Table 6. One hundred eighty-two (78.8%) subjects in the levofloxacin treatment group and 193 (81.1%) subjects in the ciprofloxacin treatment group were clinically evaluable. One hundred fifty-seven (68.0%) subjects in the levofloxacin group and 152 (63.9%) subjects in the ciprofloxacin group were microbiologically evaluable. The primary reasons (subjects only counted once) for exclusion from either the clinical or microbiologic analyses of efficacy are summarized in Table 7. The main reasons that subjects were excluded from clinical efficacy were insufficient course of therapy (levofloxacin group) and inappropriate posttherapy clinical evaluation (ciprofloxacin group), whereas the major reason that subjects were not microbiologically evaluable in both treatment groups was absence of bacteriologically proven infection.

Table 6. Number of subjects by Sponsor Analysis Group and Center

(Study K90-075)

	Levofloxacin			Ciprofloxacin		
Investigator*	Modified Intent-to-Treat	Clinically Evaluable	Microbiologically Evaluable	Modified Intent-to-Treat	Clinically Evaluable	Microbiologically Evaluable
Cullen	14	11 (78.6)	11 (78.6)	15	14 (93.3)	12 (80.0)
Gentry	31	29 (93.5)	27 (87.1)	30	28 (93.3)	26 (86.7)
Gezon	19	13 (68.4)	13 (68.4)	22	13 (59.1)	10 (45.5)
Kryvonis	2	1 (50.0)	1 (50.0)	0	0 --	0 --
Kurz	25	16 (64.0)	11 (44.0)	25	20 (80.0)	11 (44.0)
Lascheid	10	3 (30.0)	2 (20.0)	10	4 (40.0)	3 (30.0)
LeFrock	8	7 (87.5)	7 (87.5)	9	8 (88.9)	8 (88.9)
Morman	25	24 (96.0)	19 (76.0)	25	24 (96.0)	18 (72.0)
Nichols	47	36 (76.6)	34 (72.3)	50	35 (70.0)	31 (62.0)
Pankey	10	8 (80.0)	7 (70.0)	10	8 (80.0)	4 (40.0)
Powers	14	13 (92.9)	9 (64.3)	14	11 (78.6)	9 (64.3)
Schwartz	19	16 (84.2)	13 (68.4)	21	21 (100.0)	15 (71.4)
Sokalski	7	5 (71.4)	3 (42.9)	7	7 (100.0)	5 (71.4)
Total	231	182 (78.8)	157 (68.0)	238	193 (81.1)	152 (63.9)

Numbers shown in parentheses are percentages for that category.
* One investigator (Lathrop) did not enroll any subjects.

Table 7. Primary Reason for Clinical or Microbiologic Unevaluablility (Sponsor)

Modified Intent-to-Treat Subjects
(Study K90-075)

Reasons	Levofloxacin (N=231)		Ciprofloxacin (N=238)	
Clinical Efficacy				
Insufficient Course Of Therapy	24		15	
No Posttherapy Evaluation	15		5	
Inappropriate Posttherapy Evaluation	7		18	
Effective Concomitant Therapy	2		1	
Unevaluable for Safety	1		6	
Total Unevaluable For Clinical Efficacy	49	(21.2%)	45	(18.9%)
Microbiologic Efficacy				
Infection Not Bacteriologically Proven	48		60	
No Posttherapy Evaluation	13		5	
Insufficient Course Of Therapy	7		7	
Inappropriate Bacteriologic Culture	3		7	
Effective Concomitant Therapy	2		1	
Unevaluable for Safety	1		6	
Total Unevaluable For Microbiologic Efficacy	74	(32.0%)	86	(36.1%)

* Subjects only counted once.

Sponsor Results

The clinical response to therapy for subjects considered clinically evaluable by the sponsor is summarized by treatment group and study center in Table 8a. Among clinically evaluable subjects in the levofloxacin treatment group, 83.0% and 14.8% were cured and improved, respectively, compared with 80.3% and 14.0% in the ciprofloxacin treatment group, respectively. Four (2.2%) subjects in the levofloxacin treatment group and 11 (5.7%) subjects in the ciprofloxacin treatment group failed treatment.

In the sponsor MITT group, levofloxacin treatment resulted in 67.1% cure, 21.6% improvement, and 2.6% failure; 8.7% of subjects could not be evaluated. Ciprofloxacin treatment resulted in 70.6% cure, 16.8% improvement, and 6.7% failure; 5.9% of subjects could not be evaluated. Similar results were found in the sponsor intent-to-treat group.

Table 8a. Clinical Response Rate By Center: Sponsor Clinically Evaluable Subjects (K90-075)

	Levofloxacin							Ciprofloxacin						
Investigator	N	Cured*		Improved*		Failed*		N	Cured*		Improved*		Failed*	
Cullen	11	11	(100)	0	(0.0)	0	(0.0)	14	13	(92.9)	1	(7.1)	0	(0.0)
Gentry	29	28	(96.5)	1	(3.4)	0	(0.0)	28	26	(92.9)	2	(7.1)	0	(0.0)
Gezon	13	13	(100)	0	(0.0)	0	(0.0)	13	13	(100)	0	(0.0)	0	(0.0)
Kywonis	1	0	(0.0)	1	(100)	0	(0.0)	0	0	--	0	--	0	--
Kurz	16	12	(75.0)	4	(25.0)	0	(0.0)	20	17	(85.0)	2	(10.0)	1	(5.0)
Lascheid	3	2	(66.7)	1	(33.3)	0	(0.0)	4	3	(75.0)	1	(25.0)	0	(0.0)
LaFrock	7	5	(71.4)	2	(28.6)	0	(0.0)	8	4	(50.0)	3	(37.5)	1	(2.5)
Morman	24	16	(66.7)	6	(25.0)	2	(8.3)	24	16	(66.7)	7	(29.2)	1	(4.2)
Nichols	36	29	(80.6)	6	(16.7)	1	(2.8)	35	25	(71.4)	6	(17.1)	4	(11.4)
Pankey	8	3	(37.5)	4	(50.0)	1	(12.5)	8	4	(50.0)	3	(37.5)	1	(12.5)
Powers	13	11	(84.6)	2	(15.4)	0	(0.0)	11	10	(90.9)	0	(0.0)	1	(9.1)
Schwartz	16	16	(100)	0	(0.0)	0	(0.0)	21	19	(90.5)	2	(9.5)	0	(0.0)
Sokalski	5	5	(100))	0	(0.0)	0	(0.0)	7	5	(71.4)	0	(0.0)	2	(28.6)
Combined*	24	15	(62.5)	8	(33.3)	1	(4.2)	27	16	(59.3)	7	(25.9)	4	(14.8)
Total	182	151	(83.0)	27	(14.8)	4	(2.2)	193	155	(80.3)	27	(14.0)	11	(5.7)

* Numbers shown in parentheses are percentages for that category.

* Combined-those study centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Kywonis, Lascheid, LaFrock, Pankey, and Sokalski.

FDA Results

Clinical response to therapy for FDA clinically evaluable subjects is summarized in Table 8b. The number of evaluable patients is somewhat smaller in the FDA group, due mainly to the fact that only patients with uncomplicated skin and skin structure infections were included in FDA analyses. No statistically significant treatment difference was found; the overall cure rates for all centers combined were therapeutically equivalent in FDA's clinically evaluable patient group; 95% confidence interval for Ciprofloxacin minus levofloxacin was $_{125,139}(-11.7, 7.0)_{94\%,95\%}$.

Table 8b. Clinical Response Rate By Study Center: FDA Clinically Evaluable Subjects (Uncomplicated SSSI Only)

	Levofloxacin				Ciprofloxacin			
Investigator	N	Cure	Improve	Fail	N	Cure	Improve	Fail
Cullen	11	11 (100)	0 (0)	0 (0)	12	11 (92)	1 (8)	0 (0)
Gentry	21	21 (100)	0 (0)	0 (0)	20	19 (95)	1 (5)	0 (0)
Gezon	13	13 (100)	0 (0)	0 (0)	11	10 (91)	1 (9)	0 (0)
Krywonis	1	0 (0)	1 (100)	0 (0)	0	0 (-)	0 (-)	0 (-)
Kurtz	8	7 (88)	1 (12)	0 (0)	8	7 (88)	1 (12)	0 (0)
Lascheid	2	2 (100)	0 (0)	0 (0)	3	3 (100)	0 (0)	0 (0)
Lefrock	3	3 (100)	0 (0)	0 (0)	3	3 (100)	0 (0)	0 (0)
Morman	20	16 (80)	3 (15)	1 (5)	17	11 (65)	5 (29)	1 (6)
Nichols	29	22 (76)	6 (21)	1 (3)	22	17 (77)	2 (9)	3 (14)
Pankey	6	2 (33)	3 (50)	1 (17)	4	2 (50)	2 (50)	0 (0)
Powers	9	7 (78)	2 (22)	0 (0)	8	7 (88)	0 (0)	1 (12)
Schwartz	13	13 (100)	0 (0)	0 (0)	14	13 (93)	1 (7)	0 (0)
Sokalski	3	3 (100)	0 (0)	0 (0)	3	2 (67)	0 (0)	1 (33)
Total	139	120 (86)	16 (12)	3 (2)	125	105 (84)	14 (11)	6 (5)

Numbers shown in parentheses are percentages for that category.

Statistical Reviewer's Note: To compare treatment differences (e.g., in cure rates), the sponsor provides 95% confidence intervals for the difference "ciprofloxacin minus levofloxacin". FDA usually calculates these confidence intervals in reverse order, i.e. "new drug minus comparator". To be consistent, FDA confidence intervals are calculated the same way as those provided by the sponsor. Thus, in this application we are interested in the upper bound of the confidence interval instead of the lower bound. All confidence intervals produced by the sponsor and FDA are based on the normal approximation to the binomial distribution using the continuity correction.

Tables 9a and 9b summarize clinical success (cured plus improved) rates for sponsor and FDA clinically evaluable patients, respectively. In both analyses, no statistically significant treatment difference was found and levofloxacin is considered therapeutically equivalent to ciprofloxacin.

Table 9a: Clinical Success Rates and Confidence Intervals by Study Center: Sponsor Clinically Evaluable Subjects

Clinically Evaluable Subjects
(Study K90-075)

	Levofloxacin			Ciprofloxacin			
Investigator	N	Success[b]	Failure[b]	N	Success[b]	Failure[b]	95% Confidence[a] Interval
Cullen	11	11 (100.0)	0 (0.0)	14	14 (100.0)	0 (0.0)	(-4.5, 4.5)
Gentry	29	29 (100.0)	0 (0.0)	28	28 (100.0)	0 (0.0)	(-1.8, 1.8)
Gezon	13	13 (100.0)	0 (0.0)	13	13 (100.0)	0 (0.0)	(-3.8, 3.8)
Krywonis	1	1 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	-
Kurtz	16	16 (100.0)	0 (0.0)	20	19 (95.0)	1 (5.0)	(-17.7, 7.7)
Lascheid	3	3 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	-
LeFrock	7	7 (100.0)	0 (0.0)	8	7 (87.5)	1 (12.5)	-
Morman	24	22 (91.7)	2 (8.3)	24	23 (95.8)	1 (4.2)	(-11.5, 19.9)
Nichols	36	36 (97.2)	1 (2.8)	35	31 (88.5)	4 (11.4)	(-21.9, 4.5)
Pankey	8	7 (87.5)	1 (12.5)	8	7 (87.5)	1 (12.5)	-
Powers	13	13 (100.0)	0 (0.0)	11	10 (90.9)	1 (9.1)	(-30.6, 12.4)
Schwartz	16	16 (100.0)	0 (0.0)	21	21 (100.0)	0 (0.0)	(-3.1, 3.1)
Sokalski	6	6 (100.0)	0 (0.0)	7	5 (71.4)	2 (28.6)	-
Combined[c]	24	23 (95.8)	1 (4.2)	27	23 (85.2)	4 (14.8)	(-26.3, 7.0)
Total	182	178 (97.8)	4 (2.2)	193	182 (94.3)	11 (5.7)	(-7.7, 0.7)

[a] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in clinical success rates (cured + improved) were calculated for study centers enrolling 10 or more clinically evaluable subjects in each treatment group.

[b] Numbers shown in parentheses are percentages for that category.

[c] Combined=those study centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Krywonis, Lascheid, LeFrock, Pankey, and Sokalski.

Table 9b: Clinical Success Rates and Confidence Intervals by Study Center: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[b]
	N	Success[a]	N	Success[a]	
Cullen	11	11 (100)	12	12 (100)	N/A[c]
Gentry	21	21 (100)	20	20 (100)	N/A
Gezon	13	13 (100)	11	11 (100)	N/A
Krywonis	1	1 (100)	0	0 (-)	-
Kurtz	8	8 (100)	8	8 (100)	-
Lascheid	2	2 (100)	3	3 (100)	-
Lefrock	3	3 (100)	3	3 (100)	-
Morman	20	19 (95)	17	16 (94)	(-21.0, 19.3)
Nichols	29	28 (97)	22	19 (86)	(-30.0, 9.6)
Pankey	6	5 (83)	4	4 (100)	-
Powers	9	9 (100)	8	7 (88)	-
Schwartz	13	13 (100)	14	14 (100)	N/A
Sokalski	3	3 (100)	3	2 (67)	-
Total	139	136 (98)	125	119 (95)	(-7.9, 2.6)

[a]Clinical success is defined as either cure or improvement. Numbers shown in parenth
[b]Two-sided confidence interval for the difference (Cipro minus levo) in clinical succes clinically evaluable subjects in each treatment group.
[c]N/A=not applicable.

Clinical Response by Pathogen

Clinical response rates for sponsor clinically evaluable subjects infected with pathogens of interest alone or in combination with other pathogens are presented in Table 10a. Table 10b presents corresponding results for patients considered clinically evaluable by FDA (for pathogens requested in the sponsor's label).

Table 10a. Clinical Response Rates for Subjects with Pathogens of Primary Interest: Sponsor Clinically Evaluable Subjects

(Study K90-075)

Pathogen(s)	Levofloxacin				Ciprofloxacin			
	N*	Cured	Improved	Failed	N*	Cured	Improved	Failed
Staphylococcus aureus	85	76 (89.4)	8 (9.4)	1 (1.2)	89	71 (79.8)	14 (15.7)	4 (4.5)
Streptococcus pyogenes	14	14(100.0)	0 (0.0)	0 (0.0)	20	18 (90.0)	1 (5.0)	1 (5.0)
Enterobacter cloacae	9	5 (55.6)	2 (22.2)	2(22.2)	9	7 (77.8)	0 (0.0)	2 (22.2)
Acinetobacter calcoaceticus	8	7 (87.5)	1 (12.5	0 (0.0)	7	5 (71.4)	1 (14.3)	1 (14.3)
Pseudomonas aeruginosa	8	5 (62.5)	3 (37.5)	0 (0.0)	10	7 (70.0)	2 (20.0)	1 (10.0)
Klebsiella pneumoniae	6	6(100.0)	0 (0.0)	0 (0.0)	8	6 (75.0)	2 (25.0)	0 (0.0)
Escherichia coli	6	6(100.0)	0 (0.0)	0 (0.0)	11	5 (45.5)	5 (45.5)	1 (9.1)
Streptococcus faecalis	4	2 (50.0)	2 (50.0)	0 (0.0)	10	8 (80.0)	2 (20.0)	0 (0.0)

* N=number of subjects who had that pathogen alone or in combination with other pathogens.
Numbers shown in parentheses are percentages for that category.

Table 10b. Clinical Response Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only)

	Levofloxacin				Ciprofloxacin			
Pathogen	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Staphylococcus aureus	81	73 (90)	7 (9)	1 (1)	80	68 (85)	9 (11)	3 (4)
Streptococcus pyogenes	14	14 (100)	0 (0)	0 (0)	20	18 (90)	1 (5)	1 (5)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that pathogen alone or in combination with other pathogens.

Clinical Response by Diagnosis

Clinical response rates are summarized by diagnosis in Table 11a for sponsor clinically evaluable subjects and in Table 11b for FDA clinically evaluable subjects. The most common diagnosis in both analysis groups was cellulitis.

Table 11a. Clinical Response by Diagnosis; Sponsor Clinically Evaluable Subjects
(Study K90-075)

	Levofloxacin						Ciprofloxacin					
Diagnosis	N[a]	Cured		Improved		Failed	N[a]	Cured		Improved		Failed
Cellulitis	79	71	(89.9)	7	(8.9)	1 (1.3)	85	79	(92.9)	2	(2.4)	4 (4.7)
Pyoderma	20	12	(60.0)	8	(40.0)	0 (0.0)	21	16	(76.4)	5	(23.8)	1 (4.8)
Cellulitis with Abscess	19	17	(89.5)	2	(10.5)	0 (0.0)	22	17	(77.3)	4	(18.2)	1 (4.5)
Surgical Wound Infection	14	11	(78.6)	2	(14.3)	1 (7.1)	13	7	(53.8)	6	(46.2)	0 (0.0)
Impetigo	13	13	(100.0)	0	(0.0)	0 (0.0)	13	13	(100.0)	0	(0.0)	0 (0.0)
Abscess	9	8	(88.9)	0	(0.0)	1 (11.1)	9	6	(66.7)	2	(22.2)	1 (11.1)
Wound Infection	8	7	(77.8)	2	(22.2)	0 (0.0)	8	6	(75.0)	1	(12.5)	1 (12.5)
Cellulitis with Other	6	3	(50.0)	2	(33.3)	1 (16.7)	4	2	(50.0)	2	(50.0)	0 (0.0)
Infected Ulcer	6	4	(66.7)	2	(33.3)	0 (0.0)	8	5	(62.5)	3	(37.5)	0 (0.0)
Diabetic Foot Ulcer	3	1	(33.3)	2	(66.7)	0 (0.0)	6	4	(66.7)	0	(0.0)	2 (33.3)
Infected Decubitus Ulcer	2	2	(100.0)	0	(0.0)	0 (0.0)	0	0	(0.0)	0	(0.0)	0 (0.0)
Abscess with Other[b]	1	1	(100.0)	0	(0.0)	0 (0.0)	0	0	(0.0)	0	(0.0)	0 (0.0)
Hidradenitis Suppurativa	1	1	(100.0)	0	(0.0)	0 (0.0)	3	0	(0.0)	2	(66.7)	1 (33.3)
Burn Infection	0	0	(0.0)	0	(0.0)	0 (0.0)	1	1	(100.0)	0	(0.0)	0 (0.0)
Overall Total	182	161	(88.5)	27	(14.8)	4 (2.2)	193	165	(85.5)	27	(14.0)	11 (5.7)

Numbers shown in parentheses are percentages for that category.
[a] N=number of subjects who had that diagnosis.
[b] Other infection or associated clinical symptoms.

Table 11b. Clinical Response by Diagnosis; FDA Clinically Evaluable Subjects (Uncomplicated Infections Only)

	Levofloxacin								Ciprofloxacin							
Diagnosis	N[a]	Cure		Improve		Fail			N[a]	Cure		Improve		Fail		
Cellulitis	66	61	(92)	4	(6)	1	(2)		62	55	(89)	3	(5)	4	(6)	
Infected Ulcer	2	2	(100)	0	(0)	0	(0)		0	0	(-)	0	(-)	0	(-)	
Surgical Wound Infection	11	8	(73)	2	(18)	1	(9)		8	4	(50)	4	(50)	0	(0)	
Abscess	5	5	(100)	0	(0)	0	(0)		5	5	(100)	0	(0)	0	(0)	
Abscess with Other	1	1	(100)	0	(0)	0	(0)		0	0	(-)	0	(-)	0	(-)	
Cellulitis with Abscess	14	13	(93)	1	(7)	0	(0)		15	14	(93)	1	(7)	0	(0)	
Cellulitis with Other[b]	6	3	(50)	2	(33)	1	(17)		3	2	(67)	1	(33)	0	(0)	
Wound Infection	7	6	(86)	1	(14)	0	(0)		6	4	(67)	1	(17)	1	(17)	
Impetigo	11	11	(100)	0	(0)	0	(0)		10	10	(100)	0	(0)	0	(0)	
Pyoderma	16	10	(63)	6	(37)	0	(0)		16	11	(69)	4	(25)	1	(6)	
Total	139	120	(86)	16	(12)	3	(2)		125	105	(84)	14	(11)	6	(5)	

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that diagnosis.
[b]Other infection or associated clinical symptoms.

Clinical Response by Complexity and Severity of Infection

Clinical response rates for sponsor clinically evaluable subjects are summarized by complexity and severity of infection in Table 12a. Of the 156 subjects in the levofloxacin treatment group with mild/moderate uncomplicated infections, 97.4% were cured or improved, while the four subjects with severe uncomplicated infections were all cured. The clinical success rate for the 156 subjects in the ciprofloxacin treatment group with mild/moderate uncomplicated infections was 96.8%. Five of six subjects (83.3%) in the ciprofloxacin group with a severe

uncomplicated infection were cured. Clinical success rates (cured + improved) for subjects with mild/moderate complicated infections in the levofloxacin and ciprofloxacin treatment groups were 100% and 82.8%, respectively. Success rates for subjects with severe complicated infections treated with levofloxacin (N=2) and ciprofloxacin (N=2) were 100% for both groups, including cure rates of 100% vs. 50%.

Table 12a. Clinical Response by Complexity and Severity of Infection: Sponsor Clinically Evaluable Subjects

Clinically Evaluable Subjects
(Study K90-075)

	Levofloxacin						Ciprofloxacin					
	N	Cured		Improved		Failed	N	Cured		Improved		Failed
Complicated												
Severe	2	2	(100.0)	0	(0.0)	0 (0.0)	2	1	(50.0)	1	(50.0)	0 (0.0)
Mild/Moderate	20	12	(60.0)	8	(40.0)	0 (0.0)	29	16	(55.2)	8	(27.6)	5 (17.2)
Total Complicated	22	14	(63.6)	8	(36.4)	0 (0.0)	31	17	(54.8)	9	(29.0)	5 (16.1)
Uncomplicated												
Severe	4	4	(100.0)	0	(0.0)	0 (0.0)	6	5	(83.3)	0	(0.0)	1 (16.7)
Mild/Moderate	155	133	(85.3)	19	(12.2)	4 (2.6)	156	133	(85.3)	18	(11.5)	5 (3.2)
Total Uncomplicated	160	137	(85.6)	19	(11.9)	4 (2.5)	162	138	(85.2)	18	(11.1)	6 (3.7)
Total Evaluable for Clinical Efficacy	182	151	(83.0)	27	(14.8)	4 (2.2)	193	155	(80.3)	27	(14.0)	11 (5.7)

Numbers shown in parentheses are percentages for that category.

Clinical response rates for FDA clinically evaluable subjects are summarized by severity of infection in Table 12b (note: no patients with complicated infections were considered evaluable by FDA).

Table 12b. Clinical Response by Severity of Infection: FDA Clinically Evaluable Subjects
(Uncomplicated Infections Only)

	Levofloxacin				Ciprofloxacin			
Severity	N	Cure	Improve	Fail	N	Cure	Improve	Fail
Severe	4	4 (100)	0 (0)	0 (0)	5	4 (80)	0 (0)	1 (20)
Mild/Moderate	135	116 (86)	16 (12)	3 (2)	120	101 (84)	14 (12)	5 (4)

Numbers shown in parentheses are percentages for that category.

Microbiologic Eradication Rates

Microbiologic eradication rates are summarized by pathogen in Table 13a for sponsor microbiologically evaluable patients and in Table 13b for FDA microbiologically evaluable patients (note: Table 13b contains specific pathogen data for the two pathogens that the sponsor wishes to have in the label). The most prevalent pathogens for both levofloxacin and ciprofloxacin treatment groups (in both analyses) were gram-positive and gram-negative aerobes. Microbiologic eradication rates by subject, by pathogen, and for *Staphylococcus aureus* were statistically significantly higher in levofloxacin patients than in ciprofloxacin patients, both in sponsor and in FDA analysis.

Table 13a. Microbiologic Eradication Rates by Pathogen Category and Pathogen: Sponsor Microbiologically Evaluable Population

(Study K90-075)

Pathogen Category/Pathogen	Levofloxacin N	Levofloxacin Eradicated[a]	Ciprofloxacin N	Ciprofloxacin Eradicated[a]	95% Confidence Interval[b]
Pathogen Category					
Gram-positive aerobic pathogens	142	140 (98.6)	140	133 (89.3)	(-15.0, -3.6)
Gram-negative aerobic pathogens	67	65 (97.0)	60	65 (94.2)	(-10.4, 4.8)
Gram-positive anaerobic pathogens	12	12 (100.0)	3	1 (33.3)	–
Gram-negative anaerobic pathogens	12	12 (100.0)	3	3 (100.0)	–
Other pathogens	1	1 (100.0)	0	0 (0.0)	–
Total by pathogen	234	230 (98.3)	224	202 (90.2)	(-12.6, -3.7)
Total by subject	167	163 (97.6)	162	135 (83.8)	(-14.6, -2.7)
Pathogen[c]					
Staphylococcus aureus	87	87 (100.0)	87	75 (87.4)	(-20.2, -5.1)
Streptococcus pyogenes	14	14 (100.0)	20	18 (90.0)	(-25.7, 6.7)
Acinetobacter calcoaceticus	10	10 (100.0)	7	6 (85.7)	–
Enterobacter cloacae	9	9 (100.0)	9	7 (77.8)	–
Pseudomonas aeruginosa	8	7 (87.5)	10	10 (100.0)	–
Proteus mirabilis	7	7 (100.0)	4	4 (100.0)	–
Streptococcus agalactiae	6	6 (83.3)	1	1 (100.0)	–
Streptococcus milleri	6	6 (100.0)	0	0 (0.0)	–
Escherichia coli	5	5 (100.0)	11	11 (100.0)	–
Klebsiella pneumoniae	5	5 (100.0)	8	8 (100.0)	–
Streptococcus faecalis	4	4 (100.0)	10	10 (100.0)	–

[a] Numbers shown in parentheses are percentages for that category.

[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rates were calculated for pathogens with 10 or more admission isolates in each treatment group.

[c] N≥5 for either treatment group.

Table 13b. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Population (Uncomplicated Infections Only)

Pathogen Category/Pathogen	Levofloxacin N	Levofloxacin Eradicated[a]	Ciprofloxacin N	Ciprofloxacin Eradicated[a]	95% Confidence Interval[b]
Pathogen Category					
Gram-positive aerobic pathogens	130	130 (100)	122	110 (90)	(-15.9, -3.8)
Gram-negative aerobic pathogens	51	50 (98)	42	40 (95)	(-12.5, 6.9)
Gram-positive anaerobic pathogens	11	11 (100)	3	1 (33)	-
Gram-negative anaerobic pathogens	11	11 (100)	3	3 (100)	-
Total by pathogen	203	202 (99)	170	154 (91)	(-14.0, -3.9)
Total by subject	137	136 (99)	123	111 (90)	(-15.2, -2.8)
Pathogen					
Staphylococcus aureus	83	83 (100)	77	68 (88)	(-20.1, -3.3)
Streptococcus pyogenes	14	14 (100)	20	18 (90)	(-29.2, 9.2)

[a] Numbers shown in parentheses are percentages for that category.

[b] A two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Microbiologic Eradication Rates by Diagnosis

The microbiologic eradication rates achieved for sponsor microbiologically evaluable subjects in each treatment group are summarized by diagnosis in Table 14a. Corresponding information for FDA microbiologically evaluable subjects is given in Table 14b.

Table 14a. Microbiologic Eradication Rates Summarized by Diagnosis: Sponsor Microbiologically Evaluable Subjects

Microbiologically Evaluable Subjects
(Study K90-075)

	Levofloxacin					Ciprofloxacin				
Diagnosis	N	Eradicated*		Persisted*		N	Eradicated*		Persisted*	
Cellulitis										
Total by Pathogen	109	108	(99.1)	1	(0.9)	85	80	(94.1)	5	(5.9)
Total by Subject	70	69	(98.6)	1	(1.4)	63	59	(93.7)	4	(6.3)
Cellulitis with Abscess										
Total by Pathogen	29	28	(96.6)	1	(3.4)	26	24	(92.3)	2	(7.7)
Total by Subject	19	18	(94.7)	1	(5.3)	20	19	(95.0)	1	(5.0)
Pyoderma										
Total by Pathogen	20	20	(100.0)	0	(0.0)	23	17	(73.9)	6	(26.1)
Total by Subject	16	16	(100.0)	0	(0.0)	17	12	(70.6)	5	(29.4)
Impetigo										
Total by Pathogen	12	12	(100.0)	0	(0.0)	15	15	(100.0)	0	(0.0)
Total by Subject	11	11	(100.0)	0	(0.0)	10	10	(100.0)	0	(0.0)
Surgical Wound Infection										
Total by Pathogen	12	12	(100.0)	0	(0.0)	11	10	(90.9)	1	(9.1)
Total by Subject	10	10	(100.0)	0	(0.0)	7	6	(85.7)	1	(14.3)
Wound Infection										
Total by Pathogen	10	10	(100.0)	0	(0.0)	11	8	(72.7)	3	(27.3)
Total by Subject	7	7	(100.0)	0	(0.0)	6	5	(83.3)	1	(16.7)
Cellulitis with Other†										
Total by Pathogen	11	11	(100.0)	0	(0.0)	10	9	(90.0)	1	(10.0)
Total by Subject	6	6	(100.0)	0	(0.0)	4	3	(75.0)	1	(25.0)
Infected Ulcer										
Total by Pathogen	6	6	(100.0)	0	(0.0)	14	13	(92.9)	1	(7.1)
Total by Subject	6	6	(100.0)	0	(0.0)	7	6	(85.7)	1	(14.3)
Abscess										
Total by Pathogen	12	12	(100.0)	0	(0.0)	12	11	(91.7)	1	(8.3)
Total by Subject	8	8	(100.0)	0	(0.0)	8	7	(87.5)	1	(12.5)
Diabetic Foot Ulcer										
Total by Pathogen	5	3	(60.0)	2	(40.0)	11	9	(81.8)	2	(18.2)
Total by Subject	3	1	(33.3)	2	(66.7)	6	4	(66.7)	2	(33.3)
Infected Decubitus Ulcer										
Total by Pathogen	5	5	(100.0)	0	(0.0)	0	0	(0.0)	0	(0.0)
Total by Subject	2	2	(100.0)	0	(0.0)	0	0	(0.0)	0	(0.0)
Abscess with Other†										
Total by Pathogen	1	1	(100.0)	0	(0.0)	0	0	(0.0)	0	(0.0)
Total by Subject	1	1	(100.0)	0	(0.0)	0	0	(0.0)	0	(0.0)
Hidradenitis Suppurativa										
Total by Pathogen	2	2	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)
Total by Subject	1	1	(100.0)	0	(0.0)	3	3	(100.0)	0	(0.0)
Burn Infection										
Total by Pathogen	0	0	(0.0)	0	(0.0)	1	1	(100.0)	0	(0.0)
Total by Subject	0	0	(0.0)	0	(0.0)	1	1	(100.0)	0	(0.0)
Overall Total										
By Pathogen	234	230	(98.3)	4	(1.7)	224	202	(90.2)	22	(9.8)
By Subject	157	153	(97.5)	4	(2.5)	122	135	(88.8)	17	(11.2)

* Numbers shown in parentheses are percentages for that category.
† Other infection or associated clinical symptoms.

Table 14b. Microbiologic Eradication Rates Summarized by Diagnosis:
FDA Microbiologically Evaluable Subjects (Uncomplicated Infections Only)

Diagnosis	Levofloxacin		Ciprofloxacin	
	N	Eradicated[a]	N	Eradicated[a]
Cellulitis				
Total by pathogen	102	101 (99)	82	77 (94)
Total by subject	65	64 (98)	61	57 (93)
Surgical Wound Infection				
Total by pathogen	12	12 (100)	11	10 (91)
Total by subject	10	10 (100)	7	6 (86)
Infected Ulcer				
Total by pathogen	2	2 (100)	0	0 (-)
Total by subject	2	2 (100)	0	0 (-)
Abscess				
Total by pathogen	12	12 (100)	7	7 (100)
Total by subject	5	5 (100)	5	5 (100)
Abscess with Other				
Total by pathogen	1	1 (100)	0	0 (-)
Total by subject	1	1 (100)	0	0 (-)
Cellulitis with Abscess				
Total by pathogen	22	22 (100)	19	19 (100)
Total by subject	14	14 (100)	15	15 (100)
Cellulitis with Other[b]				
Total by pathogen	11	11 (100)	5	4 (80)
Total by subject	6	6 (100)	3	2 (67)
Wound Infection				
Total by pathogen	10	10 (100)	11	8 (73)
Total by subject	7	7 (100)	6	5 (83)
Impetigo				
Total by pathogen	12	12 (100)	15	15 (100)
Total by subject	11	11 (100)	10	10 (100)
Pyoderma				
Total by pathogen	20	20 (100)	20	14 (70)
Total by subject	16	16 (100)	16	11 (69)
Overall Total				
Total by pathogen	204	203 (99)	170	154 (91)
Total by subject	137	136 (99)	123	111 (90)

[a]Numbers shown in parentheses are percentages for that category.
[b]Other infection or associated clinical symptoms.

Summary of Key Efficacy Results

The clinical response rates for the sponsor modified intent-to-treat, sponsor clinically evaluable, and sponsor fully clinically evaluable groups, along with microbiologic eradication rates for the sponsor microbiologically evaluable, sponsor modified intent-to-treat, and sponsor fully microbiologically evaluable groups are summarized in Table 15a.

Table 15a. Summary of Sponsor Efficacy Results

(Study K90-075)

Clinical and Microbiologic Response

Response/Group	Levofloxacin N	Levofloxacin Clinical Success or Microbiologic Eradication Rates[a]	Ciprofloxacin N	Ciprofloxacin Clinical Success or Microbiologic Eradication Rates[a]	95% Confidence Interval[b]
Clinical Response					
Clinically Evaluable	182	178 (97.8)	193	182 (94.3)	(-7.7 0.7)
Modified Intent-to-Treat	231	205 (88.7)	236	208 (87.4)	(-7.4, 4.7)
Fully Clinically Evaluable	168	165 (98.1)	165	159 (96.8)	(-6.4, 1.7)
Microbiologic Response					
Microbiologically Evaluable	167	163 (97.6)	152	135 (88.8)	(-14.5, -2.7)
Modified Intent-to-Treat[c]	183	157 (85.8)	177	141 (79.7)	(-14.2, 1.9)
Fully Microbiologically Evaluable	137	135 (98.5)	132	119 (90.2)	(-14.2, -2.5)

Microbiologic Response Versus Clinical Response[d]

	Clinical Response							
	Levofloxacin				Ciprofloxacin			
Microbiologic Response	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Eradicated	153	132 (86.3)	18 (11.8)	3 (2.0)	135	119 (88.1)	14 (10.4)	2 (1.5)
Persisted	4	0 (0.0)	4 (100.0)	0 (0.0)	17	1 (5.9)	7 (41.2)	9 (52.9)

[a] Denominator for clinical success rate=cured + improved + failed + unable to evaluate.

[a] Denominator for microbiologic eradication rate=eradication + persistence + unknown.

[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in clinical success or microbiologic eradication rates.

[c] Only subjects with admission pathogens.

[d] Based on microbiologically evaluable subgroup.

NOTE: All microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a given subject at admission.

Table 15b summarizes "overall success rate", defined as clinical cure or improvement with microbiologic eradication, by center for subjects considered both clinically and microbiologically evaluable by FDA. The overall success rate for levofloxacin was statistically significantly higher than for ciprofloxacin.

Table 15b. Overall Success Rates[a] and Confidence Intervals By Study Center:
FDA Microbiologically AND Clinically Evaluable Subjects (Uncomplicated Infections Only)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[c]
	N	Overall Success[b]	N	Overall Success[b]	
Cullen	11	11 (100)	12	11 (92)	(-32.7, 16.0)
Gentry	21	21 (100)	20	19 (95)	(-19.4, 9.4)
Gezon	13	13 (100)	11	11 (100)	N/A[d]
Krywonis	1	1 (100)	0	0 (-)	-
Kurtz	8	7 (88)	7	7 (100)	-
Lascheid	2	2 (100)	3	3 (100)	-
Lefrock	3	3 (100)	3	3 (100)	-
Morman	18	17 (94)	17	13 (76)	(-46.5, 10.5)
Nichols	29	28 (97)	22	18 (82)	(-36.2, 6.7)
Pankey	6	5 (83)	3	2 (67)	-
Powers	9	9 (100)	8	7 (88)	-
Schwartz	13	13 (100)	14	14 (100)	N/A
Sokalski	3	3 (100)	3	2 (67)	-
Total	137	133 (97)	123	110 (89)	(-14.5, -0.8)

[a]Overall success is defined as clinical cure or improvement with microbiologic eradication.
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (cipro minus levo) in overall success rate. This was calculated for study centers enrolling 10 or more clinically and microbiologically evaluable subjects in each treatment group.
[d]N/A=not applicable.

SAFETY RESULTS

Table 16 and Table 17 summarize the incidence of adverse events by body system and frequently reported adverse events by body system, respectively. The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal and nervous systems, and consisted primarily of nausea, diarrhea, and headache. There were no serious or potentially serious adverse events reported and no deaths occurred during the study.

Table 16. Incidence of Adverse Events by Body System

Subjects Evaluable for Safety
(Study K90-075)

Body System	Levofloxacin (N=230)		Ciprofloxacin (N=232)		95% Confidence Interval[a]	
Gastrointestinal system disorders	31	(13.5)	28	(12.1)	(-7.7,	4.9)
Central & peripheral nervous system	14	(6.1)	11	(4.7)	(-5.7,	3.0)
Body as a whole - general disorders	10	(4.3)	2	(0.9)	(-6.6,	-0.4)
Psychiatric disorders	9	(3.9)	5	(2.2)	(-5.1,	1.6)
Skin and appendages disorders	4	(1.7)	7	(3.0)	(-1.7,	4.3)
Musculoskeletal system disorders	3	(1.3)	0	(0.0)	(-3.0,	0.4)
Metabolic and nutritional disorders	3	(1.3)	1	(0.4)	(-2.6,	1.0)
Respiratory system disorders	2	(0.9)	2	(0.9)	(-1.9,	1.9)
Platelet, bleeding, and clotting disorders	2	(0.9)	1	(0.4)	(-2.1,	1.2)
Resistance mechanism disorders	2	(0.9)	2	(0.9)	(-1.9,	1.9)
Vision disorders	1	(0.4)	0	(0.0)	(-1.5,	0.6)
Hearing and vestibular disorders	1	(0.4)	0	(0.0)	(-1.5,	0.6)
Special senses other, disorders	1	(0.4)	2	(0.9)	(-1.3,	2.1)
Cardiovascular disorders, general	1	(0.4)	0	(0.0)	(-1.5,	0.6)
Heart rate and rhythm disorders	1	(0.4)	0	(0.0)	(-1.5,	0.6)
Vascular (extracardiac) disorders	1	(0.4)	0	(0.0)	(-1.5,	0.6)
Urinary system disorders	0	(0.0)	2	(0.9)	(-0.5,	2.3)
Reproductive disorders, female	0	(0.0)	1	(0.9)	(-1.3,	3.0)
Total with adverse events (%)	53	(25.7)	45	(19.4)	(-14.1,	1.6)

[a] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in incidence of adverse events.

[b] Percentages calculated from total number of women in each treatment group. The total number of women who received levofloxacin was 106 and the total number of women who received ciprofloxacin was 117.

Table 17. Incidence of Frequently Reported (> OR = 2.0%)a Adverse Events Summarized by Body System and Primary Term: Subjects Evaluable for Safety

(Study K90-075)

Body System/Primary Term	Levofloxacin (N=230)		Ciprofloxacin (N=232)	
	No.	(%)	No.	(%)
All Body Systems	59	(25.7)	45	(19.4)
Gastro-Intestinal System Disorders				
Nausea	14	(6.1)	14	(6.0)
Diarrhea	12	(5.2)	7	(3.0)
Abdominal Pain	3	(1.3)	5	(2.2)
Central & Peripheral Nervous System Disorders				
Headache	8	(3.5)	9	(3.9)

[a] Primary term reported by ≥2.0% of subjects in either treatment group.

Deaths or Discontinuations

Nine (1.9%) subjects discontinued the study drug due to adverse events, including seven on the first or second day of therapy (Table 18). Four (1.7%) subjects were in the levofloxacin treatment group and five (2.2%) were in the ciprofloxacin treatment group. The treatment-limiting events in the levofloxacin treatment group consisted primarily of nervous system events (e.g., dizziness and hyperkinesia) and gastrointestinal complaints (nausea, vomiting, and diarrhea). In the ciprofloxacin treatment group, the treatment-limiting adverse events consisted primarily of headache and gastrointestinal complaints (nausea, vomiting, diarrhea, and abdominal pain). No deaths occurred during the study.

Table 18. Summary of Patients who Discontinued Therapy Due to Adverse Events

(Study K90-075)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day Of Onset[a]	Severity	Relationship To Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	25	F	Diarrhea	2	Mild	Probable	1
			Vomiting		Moderate	Probable	
			Nausea		Moderate	Probable	
	75	M	Dizziness	2	Mild	Possible	1
	19	M	Dizziness	1	Mild	Remote	2
	34	F	Aggressive reaction	1	Marked	Probable	3
			Hyperkinesia		Marked	Probable	
			Nervousness		Marked	Probable	
Ciprofloxacin							
	30	F	Taste Perversion	1	Moderate	Possible	1
			Diarrhea		Marked	Probable	
	31	F	Headache	1	Marked	Possible	2
			Nausea		Marked	Possible	
	83	F	Nausea	4	Mild	None	4
			Pruritus		Moderate	Remote	
	24	F	Nausea	5	Marked	Possible	5
			Vomiting		Marked	Possible	
	24	F	Headache	1	Moderate	Probable	4

[a] Relative to start of therapy (Day 1).
[b] Based on investigator's assessment.

Clinical Laboratory Tests

A summary of markedly abnormal laboratory values after therapy start in subjects with admission data available is shown in Tables 19 and 20, respectively.

Table 19. Incidence of Treatment Emergent Markedly Abnormal Laboratory Values

Subjects Evaluable for Safety
(Study K90-075)

	Levofloxacin		Ciprofloxacin	
Laboratory Test	Proportion[a]	%	Proportion[a]	%
Blood Chemistry				
Decreased Glucose	5/182	2.7	1/195	0.5
Elevated SGPT	4/191	2.1	2/202	1.0
Elevated SGOT	2/191	1.0	2/202	1.0
Elevated Glucose	1/182	0.5	3/195	1.5
Elevated Bilirubin	1/187	0.5	0/198	0.0
Elevated Potassium	0/184	0.0	1/193	0.5
Hematology				
Decreased Lymphocytes	1/175	0.6	0/186	0.0

[a] Numerator = number of subjects with a treatment-emergent markedly abnormal test value and denominator = number of subjects evaluable (i.e., valid admission and posttherapy data available) for that analyte.

Table 20. Subjects with Treatment Emergent Markedly Abnormal Laboratory Values

Values: Subjects Evaluable for Safety
(Study K90-075)

Subject Number	Age	Sex	Laboratory Test (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day [b]	Follow-up Value	Duration of Therapy (Days)
Levofloxacin								
	64	M	Glucose (<70 or >200 mg/dL)	98	251	8PT	–	14
	41	M	SGPT (>75 U/L)	22	85	3	28	10
	65	F	Glucose (<70 or >200 mg/dL)	101	63	3PT	–	10
	26	M	SGPT (>75 U/L)	31	94	8	63	10
	28	F	Glucose (<70 or >200 mg/dL)	84	64	4PT	–	7
	20	F	Glucose (<70 or >200 mg/dL)	97	36	4PT	–	10
			Total Bilirubin (>1.5 mg/dL)	0.9	1.80		–	
	34	M	SGOT (>75 U/L)	27	98	4PT	–	10
			SGPT (>75 U/L)	32	128		–	
	37	F	Lymphocytes (<1.0x10^9/L)	2.92	0.90	4	–	9
	60	M	SGOT (>75 U/L)	21	115	2PT	19	10
			SGPT (>75 U/L)	25	160		33	
	64	F	Glucose (<70 or >200 mg/dL)	131	60	3PT	–	10
	31	F	Glucose (<70 or >200 mg/dL)	98	60	2PT	–	10
Ciprofloxacin								
	37	F	Potassium (<3.0 or >6.0 mEq/L)	6.2	6.4	15PT	–	6
	43	F	Glucose (<70 or >200 mg/dL)	147	283	5PT	–	7
	31	M	SGOT (>75 U/L)	84	232	4PT	–	15
			SGPT (>75 U/L)	43	135		–	
	38	M	Glucose (<70 or >200 mg/dL)	228	586	1PT	–	10
	47	M	Glucose (<70 or >200 mg/dL)	147	277	5PT	–	10
	37	M	SGOT (>75 U/L)	49	115	3PT	–	15
			SGPT (>75 U/L)	47	107		–	
	29	M	Glucose (<70 or >200 mg/dL)	99	64	6PT	–	10

[a] Only range given in table. For complete criteria see Attachment 25a.
[b] Relative to start of therapy (Day 1). Note: PT refers to the number of days posttherapy, relative to the last day of study drug administration.
[c] Subject had additional laboratory abnormal values reported by the investigator as an adverse event, which did not meet marked abnormality criteria.

SUMMARY AND DISCUSSION

The objective of this study was to evaluate the safety and efficacy of levofloxacin versus ciprofloxacin in the treatment of mild-to-moderate skin and skin structure infections in adults. The study could have enrolled subjects with either complicated or uncomplicated SSSI, but most subjects (86.8%) had uncomplicated infections. Clinical response to treatment (evaluated by the investigator as cured, improved, failed, or unable to evaluate) was the primary efficacy variable and was based on the group of subjects evaluable for clinical efficacy. Levofloxacin treatment provided comparable clinical responses to that observed with ciprofloxacin in both sponsor and FDA analysis groups. *S. aureus* and *S. pyogenes* were the two most frequent pathogens isolated in both treatment groups. Among sponsor clinically evaluable subjects in the levofloxacin group, 83.0% were cured compared with 80.3% in the ciprofloxacin group. When the Sponsor's clinical response categories "cured" and "improved" were combined into a single category of "clinical success", levofloxacin treatment resulted in 97.8% clinical success for sponsor clinically evaluable subjects, while ciprofloxacin treatment resulted in 94.3% clinical success. The Sponsor's 95% confidence interval was (-7.7, 0.7) for the difference (ciprofloxacin minus levofloxacin) in success rates.

The clinical success rates in the two treatment groups were comparable for the most common diagnosis of cellulitis (98.7% for levofloxacin, 95.3% for ciprofloxacin in the sponsor clinically evaluable group). Levofloxacin-treated subjects with the most common pathogen, *S. aureus*, had a higher clinical cure rate (89.4%) than subjects treated with ciprofloxacin (79.8%). Similarly, the clinical response by severity and complexity was comparable for both treatment groups. The comparability in response rates between the two treatment groups was demonstrated for subjects with mild-to-moderate uncomplicated infections, which represented the majority of subjects enrolled in the study. For

Sponsor microbiologically evaluable subjects, comparable-to-higher microbiologic eradication rates were found in the levofloxacin treatment group, with an overall infection eradication rate of 97.5% for levofloxacin compared with 88.8% for ciprofloxacin. FDA results were similar. When the microbiologic eradication rates were stratified by diagnosis, the eradication rates between the two treatment groups were similar for the most prevalent infection, cellulitis (98.6% versus 93.7% for ciprofloxacin, sponsor microbiologically evaluable group), and for most of the other infections. There was 100.0% eradication of the two most common pathogens (*S. aureus* and *S. pyogenes*) in the levofloxacin treatment group (for both the Sponsor and FDA analyses) versus 87.4% and 90.0% eradication, respectively, in the ciprofloxacin treatment group (sponsor microbiologically evaluable group) and 88% and 90% eradication, respectively, in the ciprofloxacin treatment group (FDA microbiologically evaluable group); in the case of *S. aureus*, the 95% confidence interval around the difference between treatments was in favor of levofloxacin (note: this was also true in FDA analysis). Levofloxacin and ciprofloxacin were both effective at eradicating 100% of all methicillin-resistant S. aureus organisms (N=4 for both groups, Sponsor analyses).

The levofloxacin and ciprofloxacin treatment groups had similar safety profiles. The overall incidence of adverse events in the levofloxacin and ciprofloxacin treatment groups was 25.7% and 19.4%, respectively. The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal and nervous systems and consisted primarily of nausea, diarrhea, and headache. The incidence of these three adverse events ranged from 3.5% to 6.1% in the levofloxacin group and was similar in the ciprofloxacin group.

CONCLUSIONS

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with uncomplicated SSSI. The clinical success rate in the levofloxacin treatment group was therapeutically equivalent to that observed in the ciprofloxacin group. Moreover, the microbiologic eradication rates were equivalent to those of ciprofloxacin with some suggestion of higher eradication rates for *S. aureus*. This study supports the use of levofloxacin 488 mg po q day for 7 to 10 days in uncomplicated skin and skin structure infections due to *Staphylococcus aureus* and *Streptococcus pyogenes*. Those uncomplicated skin and skin structure diagnoses supported by this study include cellulitis, abscess, wound infection, surgical wound infection, impetigo, and pyoderma.

STUDY L91-031 (FOREIGN)

TITLE
A multicenter, double-blind, randomized study to compare the safety and efficacy of oral levofloxacin with that of ciprofloxacin HCL in the treatment of uncomplicated skin and skin structure infections in adults.

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OBJECTIVES
The objective of this study was to compare the safety and efficacy of 500 mg levofloxacin administered orally once daily for seven days with that of 500 mg ciprofloxacin administered orally twice daily for 10 days in the treatment of uncomplicated SSSI due to susceptible organisms in adults.

STUDY DESIGN The schedule of assessments is outlined in Table 1.

Table 1: Schedule of Assessments (Study L91-031)

Assessment/Procedure	Admission (Day 1)	During Therapy (Days 3 - 5)	Last Day Of Therapy	Posttherapy (2 - 7 days PT)[a]
Medical History	X			
Pregnancy Test[b]	X			X
Study Drug Administration	X	———	X[c]	
Efficacy Evaluations: (see Section III.H.2.)				
Clinical				
-Clinical Signs and Symptoms of SSSI	X	X[d]		X
-Clinical Response Rating				X
Microbiologic:				
-Culture from Site of Infection	X	X[e]		X[e]
-Susceptibility Test	X	X[e]		X[e]
-Gram Stain of Smear from Site of Infection	X	X[e]		X[e]
-Blood Culture	X[e]	X[e,f]		X[e,f]
Safety Assessments: (see Section III.H.4.)				
Adverse Events		X	X	X
Clinical Laboratory Tests:				
-Hematology	X			X
-Chemistry	X			X
-Urinalysis	X			X
Physical Examination (including Vital Signs)	X			X

[a] Or upon early termination.
[b] Performed on all women of childbearing potential.
[c] Levofloxacin was to be administered for seven days followed by placebo for three days and ciprofloxacin was to be administered for 10 days.
[d] Signs and symptoms were monitored only; grades were not recorded.
[e] Performed only if indicated (i.e., if specimen available).
[f] Performed if positive at admission.

MAJOR DIFFERENCES BETWEEN STUDY K90-075 AND STUDY L91-031

Characteristic	Protocol K90-075	Protocol L91-031
Blinding	Open-label	Double blind
Initial Objective	Mild to Moderate SSSI	Uncomplicated SSSI in susceptible infections
Location	United States and Costa Rica	South America
Levofloxacin Dose	488 mg po q 24 hrs for 7 - 10 days	500 mg po q 24 hrs for 10 days
Ciprofloxacin Dose	500 mg po q 12 hrs for 7 - 10 days	500 mg po q 12 hrs for 10 days

STATISTICAL METHODS

The statistical methods and analyses were similar for study K90-075 and study L91-031 except for the following:

Due to inadequate monitoring, the subjects from three Mexican Investigators (Drs. R. Flores Guerreo, J. Salcedo, and I. Zavala-Trujillo) were not included in the sponsor's efficacy analyses. *Note: Data from these three investigators are also excluded from FDA analyses, with the exception of Table 9c which examines clinical success rates by investigator and overall including these three centers.*

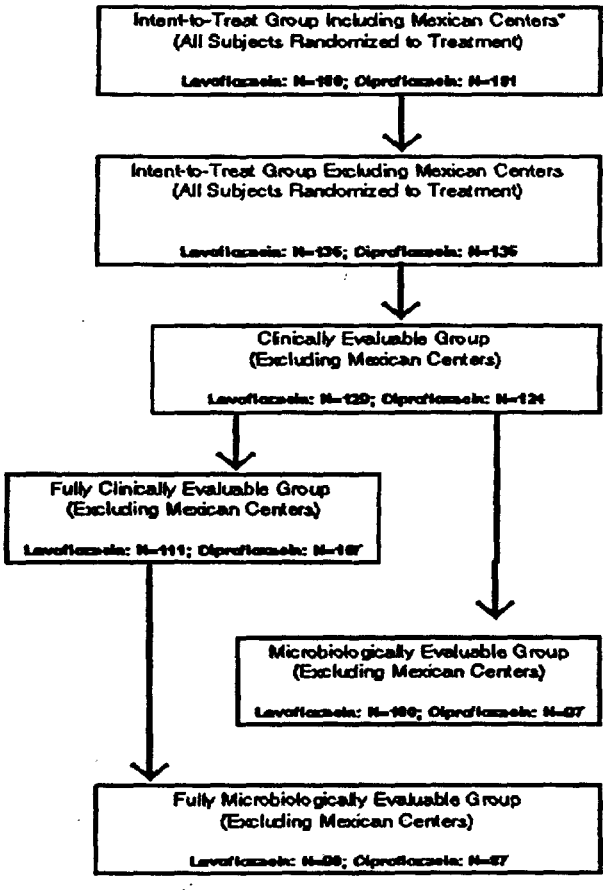
For consistency with other studies, the window of 1 to 10 days posttherapy used for sponsor evaluability of clinical and microbiologic data varied from the window of 1 to 8 days specified in the study protocol. *Note: Again, this follow-up is somewhat earlier than desired. The November 1992 IDSA Guidelines suggest that the appropriate test of cure is 2 to 4 weeks after completion of therapy.*

Retrospective assessment of severity and complexity of infection differed in that the assessment was performed retrospectively, but prior to unblinding.

Statistical Reviewer's Note: As in the other uncomplicated SSSI study, the 95% confidence intervals provided by the sponsor to assess treatment differences are for the difference "ciprofloxacin minus levofloxacin". FDA usually calculates these confidence intervals for the difference "levofloxacin minus ciprofloxacin" (i.e., "new drug minus comparator"); however, to be consistent FDA confidence intervals will be provided in the same format as those of the sponsor. Thus, we will be interested in the upper, rather than the lower, bound of the confidence interval for determining therapeutic equivalence. All confidence intervals, both those produced by the sponsor and by FDA, are based on the normal approximation to the binomial distribution with the continuity correction.

Although this study was only to enroll patients with uncomplicated skin and skin structure infections, several patients with complicated infections were enrolled. FDA analysis excludes such patients (i.e., those with complicated SSSI).

The relationships among the various sponsor efficacy analysis groups are illustrated below.



ANALYSIS GROUPS

Table 2 summarizes all analysis groups and corresponding analyses performed by the sponsor. Data for subjects enrolled at three Mexican study centers are excluded from the sponsor's main efficacy analyses.

Table 2: Numbers in Sponsor Analysis Groups and Corresponding Analyses Performed (Excluding Mexican Centers)

(Study L91-031)

	Clinically Evaluable	Micro-biologically Evaluable	Intent-to-Treat	Fully Clinically Evaluable	Fully Micro-biologically Evaluable	Safety
Levofloxacin Treatment Group	129	100	136	111	90	179
Ciprofloxacin Treatment Group	124	97	136	107	87	178
Analyses or Summaries Provided:						
Demographics	X	X	X	X	X	X
Extent of Therapy	X	X	X	X	X	X
Clinical Response	X	X	X	X	X	
Signs/Symptoms	X	X	X			
Microbiologic Response	X	X	X	X	X	
Adverse Events						X
Laboratory Results						X
Vital Signs						X

* Three Mexican study centers are excluded from all analysis groups except safety (see Section III.J., Statistical Methods).

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The protocol indicated that approximately 400 subjects were to be enrolled to ensure clinically evaluable data from 300 subjects. However, the study was terminated early when the target number of evaluable subjects was estimated to have been achieved. Three hundred sixty-one subjects were enrolled in this study at 15 centers, including 89 subjects enrolled at the three Mexican centers. The sponsor intent-to-treat group, which excluded these 89 subjects, included 272 subjects, 136 who were randomized to the levofloxacin treatment group and 136 who were randomized to the ciprofloxacin treatment group.

The sponsor's clinically evaluable patient group consisted of 129 levofloxacin and 124 ciprofloxacin patients. Their microbiologically evaluable patient group had 100 levofloxacin and 97 ciprofloxacin patients. The demographic and baseline (admission) characteristics for the sponsor clinically and sponsor microbiologically evaluable groups are summarized in Table 3. Characteristics of clinically and microbiologically evaluable subjects were generally comparable across treatment groups except for a slightly higher percentage of men in the ciprofloxacin group. The majority of subjects were Hispanic. A statistically significant difference was found in the fully microbiologically evaluable group (p=0.02) for proportion of men (43.3% in the levofloxacin group and 62.1% in the ciprofloxacin group).

Table 3. Demographic and Baseline Characteristics:
Sponsor Clinically Evaluable and Sponsor Microbiologically Evaluable Subjects (Excluding Mexican Centers)
(Study L91-031)

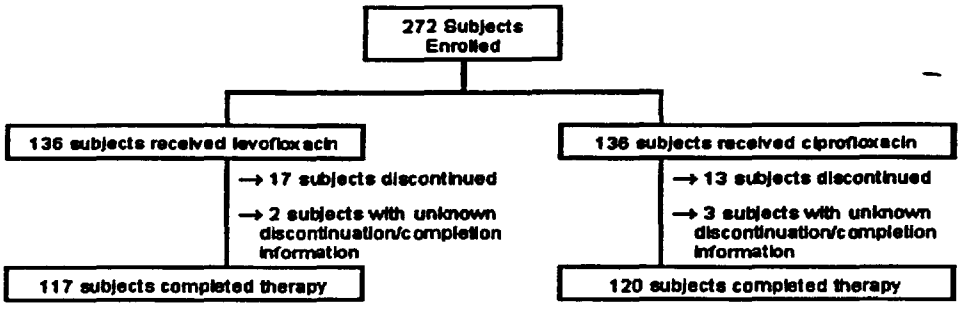
	Levofloxacin		Ciprofloxacin	
	Clinically Evaluable (N = 129)	Microbiologically Evaluable (N = 100)	Clinically Evaluable (N=124)	Microbiologically Evaluable (N = 97)
Sex				
Men	63	45	68	57
Women	66	55	56	40
Race				
Caucasian	49	36	43	36
Black	6	6	11	9
Oriental	2	1	1	1
Hispanic	72	57	69	51
Age (Years)				
≤45	77	59	73	60
46-64	34	29	25	18
≥65	18	12	26	19
N	129	100	124	97
Mean±SD	42.4±16.8	42.2±16.1	44.6±18.0	43.6±17.7
Range	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)				
N	129	100	123	96
Mean±SD	68.5±15.2	68.2±14.3	71.2±14.1	71.3±13.0
Range	[redacted]	[redacted]	[redacted]	[redacted]
Missing	0	0	1	1
Height (cm)				
N	129	100	123	96
Mean±SD	165±9.8	165±9.8	168±9.8	169±8.7
Range	[redacted]	[redacted]	[redacted]	[redacted]
Missing	0	0	1	1
Diagnosis				
Abscess	28	22	22	19
Impetigo	25	19	19	14
Furuncle	18	14	22	13
Cellulitis	18	13	18	13
Pyoderma	8	6	12	11
Cellulitis with Condition*	7	4	3	3
Erysipelas	7	6	9	7
Wound Infection	7	5	6	6
Surgical Wound Infection	6	6	9	8
Other Infection/Symptoms	2	2	2	1
Cellulitis with Abscess	1	1	1	1
Abscess with Other Infection/Symptoms	1	1	0	0
Infected Ulcer	1	1	1	1
Complicated				
Severe	2	1	1	1
Mild/Moderate	17	13	15	12
Total Complicated	19	14	16	13
Uncomplicated				
Severe	0	0	5	4
Mild/Moderate	110	86	103	80
Total Uncomplicated	110	86	108	84
Complicated and Uncomplicated				
Total Severe	2	1	6	5
Total Mild/Moderate	127	99	118	92

NOTE: Values represent numbers of subjects unless otherwise indicated.
* Included cellulitis in association with decubitus ulcers or occurring in the setting of a complicating disease.

DISCONTINUATION/COMPLETION INFORMATION

Of the 272 subjects enrolled in the study, 136 received levofloxacin and 136 received ciprofloxacin (sponsor intent-to-treat group). Discontinuations are shown in Figure 1.

Figure 1: Discontinuation/Completion Information: Intent-to-Treat Subjects (Excluding Mexican Centers) (Study L91-031)



Reasons for premature discontinuation and extent of drug exposure are outlined in Table 4 and Table 5, respectively.

Table 4: Reasons for Premature Discontinuation of Therapy: Intent-to-Treat Subjects (Excluding Mexican Centers)[a] (Study L91-031)

	Levofloxacin (N = 136)		Ciprofloxacin (N = 136)	
Reason	No.	(%)[b]	No.	(%)[b]
Adverse Event	5	(3.7)	2	(1.5)
No Admission Pathogen	2	(1.5)	3	(2.3)
Clinical Failure	1	(0.7)	1	(0.8)
Personal Reason	1	(0.7)	0	(0.0)
Resistant Pathogen	0	(0.0)	1	(0.8)
Other[c]	8	(6.0)	6	(4.5)
Total Discontinued	17	(12.7)	13	(9.8)
Total with Discontinuation/Completion Information	134		133	
Total With Unknown Discontinuation/Completion Information	2		3	

[a] Of the 88 subjects who were enrolled at the three Mexican centers and for whom discontinuation/completion information was available, one levofloxacin-treated subject discontinued therapy prematurely due to clinical failure and two ciprofloxacin-treated subjects discontinued (one due to clinical failure and one due to personal reasons). See Appendix 23d.

[b] Percentages based on total number with discontinuation/completion information.

[c] Other reasons for discontinuation include: Levofloxacin: clinical cure (subjects [redacted]; investigator's judgement (subjects [redacted]; renal insufficiency (subject [redacted]. Ciprofloxacin: clinical cure (subjects [redacted]; investigator's judgement (subjects [redacted]; incorrect initial diagnosis (subject [redacted]

Table 5: Extent of Exposure to Therapy: Intent-to-Treat Subjects (Excluding Mexican Centers) (Study L91-031)

Extent of Exposure	Levofloxacin (N = 136)	Ciprofloxacin (N = 136)
Days on Therapy[a]		
Unknown	1	3
2	1	0
3	1	1
5	2	3
6	1	1
7	130	4
8	0	4
10	0	107
11	0	13
Mean±SD	6.9±0.6	9.8±1.2
Median	7	10
Number of Doses		
Total with Dosing Information	135	133
Total Unknown Dosing Information	1	3
Mean±SD	6.9±0.6	19.2±2.4
Median	7	20
Range	2-7	5-20

NOTE: Levofloxacin had a q24h dosing schedule; the total planned duration of therapy was seven days followed by three days of placebo administration. Ciprofloxacin had a q12h dosing schedule. The total planned duration of therapy was 10 days.
[a] Days on therapy was defined as (last day of active drug - first day) + 1.

EFFICACY RESULTS

The total number of subjects evaluable by the sponsor for clinical and microbiologic efficacy at each study center is shown in Table 6. Table 7 summarizes the reasons patients were considered unevaluable by the sponsor for clinical and/or microbiologic efficacy analysis.

Table 6. Number of Subjects by Sponsor Analysis Group and Center (Excluding Mexico Study Sites)

(Study L91-031)

	Levofloxacin				Ciprofloxacin			
Investigator	Intent-to Treat	Clinical Efficacy		Microbiologic Efficacy	Intent-to Treat	Clinical Efficacy		Microbiologic Efficacy	
Barona	5	5	(100.0)	2 (40.0)	5	3	(60.0)	2	(40.0)
Galimberti	16	16	(100.0)	8 (50.0)	16	16	(100.0)	10	(62.5)
Jasovich	16	14	(87.5)	11 (68.8)	16	14	(87.5)	12	(75.0)
Marques	4	4	(100.0)	3 (75.0)	4	4	(100.0)	2	(50.0)
Nicodemo	25	24	(96.0)	22 (88.0)	26	23	(88.5)	21	(80.8)
Robledo	17	17	(100.0)	15 (88.2)	16	14	(87.5)	11	(68.8)
Roselino	12	11	(91.7)	9 (75.0)	12	12	(100.0)	10	(83.3)
Saravia	2	2	(100.0)	0 (0.0)	2	2	(100.0)	1	(50.0)
Sussman	14	13	(92.9)	10 (71.4)	13	12	(92.3)	10	(76.9)
Torres	16	16	(100.0)	15 (93.8)	16	16	(100.0)	13	(81.3)
Wey	5	4	(80.0)	2 (40.0)	6	4	(66.7)	2	(33.3)
Zaltz	4	3	(75.0)	3 (75.0)	4	4	(100.0)	3	(75.0)
Total	136	129	(94.9)	100 (73.5)	136	124	(91.2)	97	(71.3)

Numbers shown in parentheses are percentages for that category.

Table 7. Primary Reason for Clinical or Microbiologic Unevaluablitiy: Sponsor Intent to Treat Subjects (Excluding Mexican Centers)

(Study L91-031)

Reasons	Levofloxacin (N = 136)		Ciprofloxacin (N = 136)	
Clinical Efficacy				
Inappropriate Posttherapy Evaluation	3		7	
Insufficient Course of Therapy	2		0	
No Posttherapy Evaluation	1		1	
Unevaluable for Safety	1		2	
Clinical Diagnosis Unconfirmed	0		1	
Effective Concomitant Therapy	0		1	
Total Unevaluable For Clinical Efficacy	7	(5.1%)	12	(8.8%)
Microbiologic Efficacy				
Infection Not Bacteriologically Proven	24		22	
Inappropriate Bacteriologic Culture	10		13	
No Posttherapy Evaluation	1		1	
Unevaluable for Safety	1		2	
Effective Concomitant Therapy	0		1	
Total Unevaluable For Microbiologic Efficacy	36	(26.5%)	39	(28.7%)

* Subjects counted only once.

Clinical Response

Sponsor Results

Clinical response to therapy for subjects considered clinically evaluable by the sponsor is summarized by treatment group and study center in Table 8a. Among subjects in the levofloxacin treatment group, 80.6% were cured and 15.5% were improved, compared with 75.0% and 18.5% in the ciprofloxacin treatment group, respectively. Five (3.9%) subjects in the levofloxacin treatment group and eight (6.5%) subjects in the ciprofloxacin treatment group failed treatment.

In the Sponsor's intent-to-treat group, levofloxacin treatment resulted in 77.9% cure, 16.2% improvement, and 4.4% failure; 1.5% of subjects could not be evaluated. Ciprofloxacin treatment resulted in 72.8% cure, 18.4% improvement, and 5.9% failure; 2.9% of subjects could not be evaluated.

Table 8a. Clinical Response Rate for Each Center: Sponsor Clinically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

	Levofloxacin				Ciprofloxacin			
Investigator	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Barona	5	4 (80.0)	1 (20.0)	0 (0.0)	3	2 (66.7)	1 (33.3)	0 (0.0)
Galimberti	16	12 (75.0)	2 (12.5)	2(12.5)	16	9 (56.3)	5 (31.3)	2(12.5)
Jasovich	14	12 (85.7)	2 (14.3)	0 (0.0)	14	13 (92.9)	1 (7.1)	0 (0.0)
Marques	4	3 (75.0)	1 (25.0)	0 (0.0)	4	4(100.0)	0 (0.0)	0 (0.0)
Nicodemo	24	24(100.0)	0 (0.0)	0 (0.0)	23	22 (95.7)	0 (0.0)	1 (4.3)
Robledo	17	15 (88.2)	0 (0.0)	2(11.8)	14	12 (85.7)	0 (0.0)	2(14.3)
Roselino	11	8 (72.7)	3 (27.3)	0 (0.0)	12	5 (41.7)	6 (50.0)	1 (8.3)
Saravia	2	1 (50.0)	1 (50.0)	0 (0.0)	2	2(100.0)	0 (0.0)	0 (0.0)
Sussman	13	11 (84.6)	2 (15.4)	0 (0.0)	12	10 (83.3)	2 (16.7)	0 (0.0)
Torres	16	10 (62.5)	6 (37.5)	0 (0.0)	16	7 (43.8)	8 (50.0)	1 (6.3)
Wey	4	3 (75.0)	1 (25.0)	0 (0.0)	4	3 (75.0)	0 (0.0)	1(25.0)
Zaltz	3	1 (33.3)	1 (33.3)	1(33.3)	4	4(100.0)	0 (0.0)	0 (0.0)
Combined*	18	12 (66.7)	5 (27.8)	1 (5.6)	17	15 (88.2)	1 (5.9)	1 (5.9)
Total	129	104 (80.6)	20 (15.5)	5 (3.9)	124	93 (75.0)	23 (18.5)	8 (6.5)

Numbers shown in parentheses are percentages for that category.

* Combined = those study centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Barona, Marques, Saravia, Wey, and Zaltz.

FDA Results

Clinical response to therapy for FDA clinically evaluable patients is summarized in Table 8b. No statistically significant treatment difference was found; the overall cure rates for all centers combined were therapeutically equivalent in FDA's clinically evaluable patient group; 95% confidence interval for ciprofloxacin minus-levofloxacin $_{95\%}(-14.6, 9.7)_{95\%}$

Table 8b. Clinical Response Rate for Each Center: FDA Clinically Evaluable Subjects
(Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin						Ciprofloxacin					
Investigator	N	Cure		Improve		Fail	N	Cure		Improve		Fail
Barona	2	1	(50)	1	(50)	0 (0)	2	2	(100)	0	(0)	0 (0)
Galimberti	7	6	(86)	0	(0)	1 (14)	10	5	(50)	3	(30)	2 (20)
Jasovich	9	8	(89)	1	(11)	0 (0)	11	10	(91)	1	(9)	0 (0)
Marques	3	2	(67)	1	(33)	0 (0)	2	2	(100)	0	(0)	0 (0)
Nicodemo	21	21	(100)	0	(0)	0 (0)	20	20	(100)	0	(0)	0 (0)
Robledo	15	14	(93)	0	(0)	1 (7)	11	10	(91)	0	(0)	1 (9)
Roselino	7	5	(71)	2	(29)	0 (0)	9	5	(56)	4	(44)	0 (0)
Saravia	0	0	(-)	0	(-)	0 (-)	1	1	(100)	0	(0)	0 (0)
Sussman	10	8	(80)	2	(20)	0 (0)	7	7	(100)	0	(0)	0 (0)
Torres	11	8	(73)	3	(27)	0 (0)	11	6	(55)	5	(45)	0 (0)
Wey	1	1	(100)	0	(0)	0 (0)	1	1	(100)	0	(0)	0 (0)
Zaitz	3	1	(33)	1	(33)	1 (33)	3	3	(100)	0	(0)	0 (0)
Total	89	75	(84)	11	(12)	3 (3)	88	72	(82)	13	(15)	3 (3)

Numbers shown in parentheses are percentages for that category.

Tables 9a and 9b summarize clinical success (cured plus improved) rates by center and overall for sponsor and FDA clinically evaluable patients, respectively. In both analyses, no statistically significant treatment difference is detected and levofloxacin is considered therapeutically equivalent to ciprofloxacin. Table 9c summarizes clinical success rates for FDA clinically evaluable subjects, including the three Mexican sites that were otherwise excluded from analysis. Again, no significant treatment difference is detected and the two drugs are considered therapeutically equivalent.

Table 9a. Clinical Success/Failure Rates and Confidence Intervals by Study Center: Sponsor Clinically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

	Levofloxacin			Ciprofloxacin			
Investigator	N	Success[b]	Failure[b]	N	Success[b]	Failure[b]	95% Confidence Interval[a]
Barona	5	5 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	—
Galimberti	16	14 (87.5)	2 (12.5)	16	14 (87.5)	2 (12.5)	(-26.0, 26.0)
Jasovich	14	14 (100.0)	0 (0.0)	14	14 (100.0)	0 (0.0)	(-3.6, 3.6)
Marques	4	4 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	—
Nicodemo	24	24 (100.0)	0 (0.0)	23	22 (95.7)	1 (4.3)	(-14.9, 6.2)
Robledo	17	15 (88.2)	2 (11.8)	14	12 (85.7)	2 (14.3)	(-30.0, 24.9)
Roselino	11	11 (100.0)	0 (0.0)	12	11 (91.7)	1 (8.3)	(-28.5, 11.9)
Saravia	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	—
Sussman	13	13 (100.0)	0 (0.0)	12	12 (100.0)	0 (0.0)	(-4.2, 4.2)
Torres	16	16 (100.0)	0 (0.0)	16	15 (93.8)	1 (6.3)	(-21.2, 8.7)
Wey	4	4 (100.0)	0 (0.0)	4	3 (75.0)	1 (25.0)	—
Zaitz	3	2 (66.7)	1 (33.3)	4	4 (100.0)	0 (0.0)	—
Combined[c]	18	17 (94.4)	1 (5.6)	17	16 (94.1)	1 (5.9)	(-18.7, 18.0)
Total	129	124 (96.1)	5 (3.9)	124	116 (93.5)	8 (6.5)	(-8.4, 3.3)

[a] Two-sided 95% confidence intervals around the difference (ciprofloxacin minus levofloxacin) in clinical success rates (cured and improved) were calculated for study centers enrolling 10 or more clinically evaluable subjects in each treatment group.
[b] Numbers shown in parentheses are percentages for that category.
[c] Combined = centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Barona, Marques, Saravia, Wey, and Zaitz.

Table 9b. Clinical Success/Failure Rates and Confidence Intervals by Study Center: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin		Ciprofloxacin		
Investigator	N	Success[a]	N	Success[a]	95% Confidence Interval[b]
Barona	2	2 (100)	2	2 (100)	-
Galimberti	7	6 (86)	10	8 (80)	-
Jasovich	9	9 (100)	11	11 (100)	-
Marques	3	3 (100)	2	2 (100)	-
Nicodemo	21	21 (100)	20	20 (100)	N/A[c]
Robledo	15	14 (93)	11	10 (91)	(-31.5, 26.6)
Roselino	7	7 (100)	9	9 (100)	-
Saravia	0	0 (-)	1	1 (100)	-
Sussman	10	10 (100)	7	7 (100)	-
Torres	11	11 (100)	11	11 (100)	N/A
Wey	1	1 (100)	1	1 (100)	-
Zaitz	3	2 (67)	3	3 (100)	-
Total	89	86 (97)	88	85 (97)	(-6.5, 6.4)

[a] Clinical success is defined as either clinical cure or clinical improvement. Numbers shown in parentheses are percentages for that category.
[b] Two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in clinical success rate. This was calculated for study centers enrolling 10 or more clinically evaluable subjects in each treatment group.
[c] N/A=not applicable.

Table 9c. Clinical Success/Failure Rates and Confidence Intervals by Study Center: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only; Including Mexican Centers)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[b]
	N	Success[a]	N	Success[a]	
Barona	2	2 (100)	2	2 (100)	-
Flores-Guerrero	6	6 (100)	3	3 (100)	-
Galimberti	7	6 (86)	10	8 (80)	-
Jasovich	9	9 (100)	11	11 (100)	-
Marques	3	3 (100)	2	2 (100)	-
Nicodemo	21	21 (100)	20	20 (100)	N/A[c]
Robledo	15	14 (93)	11	10 (91)	(-31.5, 26.6)
Roselino	7	7 (100)	9	9 (100)	-
Salcedo	12	12 (100)	7	7 (100)	-
Saravia	0	0 (-)	1	1 (100)	-
Sussman	10	10 (100)	7	7 (100)	-
Torres	11	11 (100)	11	11 (100)	N/A
Wey	1	1 (100)	1	1 (100)	-
Zaitz	3	2 (67)	3	3 (100)	-
Zavala-Trujillo	4	4 (100)	6	5 (83)	-
Total	111	108 (97)	104	100 (96)	(-6.8, 4.6)

[a]Clinical success is defined as either clinical cure or clinical improvement. Numbers shown in parentheses are percentages for that category.
[b]Two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in clinical success rate. This was calculated for study centers enrolling 10 or more clinically evaluable subjects in each treatment group.
[c]N/A=not applicable.

Clinical Response by Pathogen

Clinical response rates for sponsor and FDA clinically evaluable subjects infected with key pathogens alone or in combination with other pathogens are shown in Tables 10a and 10b, respectively (*note: the FDA table includes only those pathogens requested by the sponsor for inclusion in their label). S. aureus* was the most prevalent pathogen in both treatment groups and in both analyses; clinical success rates (cured + improved) in subjects infected with this pathogen were similar between the two treatment groups (97.3% for levofloxacin and 96.2% for ciprofloxacin for sponsor clinically evaluable patients).

Table 10a. Clinical Response for Subjects with Pathogens of Primary Interest: Sponsor Clinically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

Pathogen(s)[a]	Levofloxacin				Ciprofloxacin			
	N[b]	Cured	Improved	Failed	N[b]	Cured	Improved	Failed
Staphylococcus aureus	75	63 (84.0)	10 (13.3)	2 (2.7)	78	62 (79.5)	13 (16.7)	3 (3.8)
Streptococcus pyogenes	19	16 (84.2)	1 (5.3)	2 (10.5)	13	11 (84.6)	1 (7.7)	1 (7.7)
Escherichia coli	7	6 (85.7)	1 (14.3)	0 (0.0)	8	5 (62.5)	3 (37.5)	0 (0.0)
Streptococcus sp.	8	6 (75.0)	2 (25.0)	0 (0.0)	6	3 (50.0)	3 (50.0)	0 (0.0)

Numbers shown in parentheses are percentages for that category.
[a] N≥5 in either treatment group.
[b] N = number of subjects who had that pathogen alone or in combination with other pathogens.

Table 10b. Clinical Response for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin				Ciprofloxacin			
Pathogen	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Staphylococcus aureus	64	56 (88)	6 (9)	2 (3)	71	59 (83)	10 (14)	2 (3)
Streptococcus pyogenes	18	16 (89)	0 (0)	2 (11)	13	11 (85)	1 (8)	1 (8)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that pathogen alone or in combination with other pathogens.

Clinical Response by Diagnosis

Clinical response rates for sponsor clinically evaluable subjects are summarized by diagnosis in Table 11a . The most common diagnoses in the levofloxacin treatment group were abscess and impetigo and in the ciprofloxacin treatment group were abscess and furuncle. Cellulitis and furuncle were also observed in >10 subjects in each treatment group. The clinical success rate (cured + improved) in the levofloxacin and ciprofloxacin treatment groups for subjects with an abscess was 92.9% and 95.5%, respectively, and for subjects with impetigo was 92.0% and 89.5%, respectively. The clinical success rate,was 100% in the levofloxacin and ciprofloxacin treatment groups for subjects with a furuncle and 94.4% and 100%, respectively, for subjects with cellulitis.

Table 11b summarizes clinical response rates by diagnosis for FDA clinically evaluable subjects.

Table 11a. Clinical Response by Diagnosis: Sponsor Clinically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

	Levofloxacin				Ciprofloxacin			
Diagnosis	N[a]	Cured	Improved	Failed	N[a]	Cured	Improved	Failed
Abscess	28	23 (82.1)	3 (10.7)	2 (7.1)	22	20 (90.9)	1 (4.5)	1 (4.5)
Impetigo	25	22 (88.0)	1 (4.0)	2 (8.0)	19	15 (78.9)	2 (10.5)	2 (10.5)
Cellulitis	18	13 (72.2)	4 (22.2)	1 (5.6)	18	9 (50.0)	9 (50.0)	0 (0.0)
Furuncle	18	15 (83.3)	3 (16.7)	0 (0.0)	22	20 (90.9)	2 (9.1)	0 (0.0)
Pyoderma	8	4 (50.0)	4 (50.0)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)
Cellulitis with Condition[b]	7	6 (85.7)	1 (14.3)	0 (0.0)	3	2 (66.7)	1 (33.3)	0 (0.0)
Erysipelas	7	7 (100.0)	0 (0.0)	0 (0.0)	9	4 (44.4)	2 (22.2)	3 (33.3)
Wound Infection	7	6 (85.7)	1 (14.3)	0 (0.0)	6	5 (83.3)	1 (16.7)	0 (0.0)
Surgical Wound Infection	6	4 (66.7)	2 (33.3)	0 (0.0)	9	7 (77.8)	1 (11.1)	1 (11.1)
Other Infection/Symptoms	2	1 (50.0)	1 (50.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	0 (0.0)
Cellulitis with Abscess	1	1 (100.0)	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	0 (0.0)
Abscess with Other[c]	1	1 (100.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)
Infected Ulcer	1	1 (100.0)	0 (0.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0 (0.0)
Total	129	104 (80.6)	20 (15.5)	5 (3.9)	124	93 (75.0)	23 (18.5)	8 (6.5)

Numbers in parentheses are percentages for that category.
[a] N = number of subjects who had that diagnosis.
[b] Includes cellulitis in association with decubitus ulcers or occurring in the setting of a complicating disease.
[c] Other infection or associated clinical symptoms.

Table 12a. Clinical Response by Complexity and Severity of Infection: Sponsor Clinically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

	Levofloxacin				Ciprofloxacin			
	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Complicated								
Severe	2	1 (50.0)	1 (50.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0 (0.0)
Mild/Moderate	17	9 (52.9)	6 (35.3)	2 (11.8)	15	6 (40.0)	5 (33.3)	4 (26.7)
Total Complicated	19	10 (52.6)	7 (36.8)	2 (10.5)	16	6 (37.5)	6 (37.5)	4 (25.0)
Uncomplicated								
Severe	0	0 –	0 –	0 –	5	3 (60.0)	1 (20.0)	1 (20.0)
Mild/Moderate	110	94 (85.5)	13 (11.8)	3 (2.7)	103	84 (81.6)	16 (15.5)	3 (2.9)
Total Uncomplicated	110	94 (85.5)	13 (11.8)	3 (2.7)	108	87 (80.6)	17 (15.7)	4 (3.7)
Total Evaluable for Clinical Efficacy	129	104 (80.6)	20 (15.5)	5 (3.9)	124	93 (75.0)	23 (18.5)	8 (6.5)

Numbers in parentheses are percentages for that category.

Table 12b. Clinical Response by Severity of Infection: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin				Ciprofloxacin			
Severity	N	Cure	Improve	Fail	N	Cure	Improve	Fail
Severe	0	0 (-)	0 (-)	0 (-)	4	3 (75)	1 (25)	0 (0)
Mild/Moderate	89	75 (84)	11 (12)	3 (3)	84	69 (82)	12 (14)	3 (4)

Numbers shown in parentheses are percentages for that category.

Microbiologic Eradication

The microbiologic eradication rates achieved for sponsor microbiologically evaluable subjects in each treatment group are summarized by pathogen in Table 13a. Table 13b summarizes the same information for FDA microbiologically evaluable subjects (*note: the only pathogens included in the FDA table are those requested by the sponsor for their label).* Gram-positive and gram-negative aerobes were the most prevalent pathogens in both treatment groups (in both analyses). No statistically significant treatment differences were detected in microbiologic eradication rates by subject, pathogen, for *Staphylococcus aureus*, or for *Streptococcus pyogenes*, in both the sponsor and FDA analysis.

Table 10b. Clinical Response for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin				Ciprofloxacin			
Pathogen	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Staphylococcus aureus	64	56 (88)	6 (9)	2 (3)	71	59 (83)	10 (14)	2 (3)
Streptococcus pyogenes	18	16 (89)	0 (0)	2 (11)	13	11 (85)	1 (8)	1 (8)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that pathogen alone or in combination with other pathogens.

Clinical Response by Diagnosis

Clinical response rates for sponsor clinically evaluable subjects are summarized by diagnosis in Table 11a . The most common diagnoses in the levofloxacin treatment group were abscess and impetigo and in the ciprofloxacin treatment group were abscess and furuncle. Cellulitis and furuncle were also observed in >10 subjects in each treatment group. The clinical success rate (cured + improved) in the levofloxacin and ciprofloxacin treatment groups for subjects with an abscess was 92.9% and 95.5%, respectively, and for subjects with impetigo was 92.0% and 89.5%, respectively. The clinical success rate,was 100% in the levofloxacin and ciprofloxacin treatment groups for subjects with a furuncle and 94.4% and 100%, respectively, for subjects with cellulitis.

Table 11b summarizes clinical response rates by diagnosis for FDA clinically evaluable subjects.

Table 11a. Clinical Response by Diagnosis: Sponsor Clinically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

	Levofloxacin				Ciprofloxacin			
Diagnosis	N[a]	Cured	Improved	Failed	N[a]	Cured	Improved	Failed
Abscess	28	23 (82.1)	3 (10.7)	2 (7.1)	22	20 (90.9)	1 (4.5)	1 (4.5)
Impetigo	25	22 (88.0)	1 (4.0)	2 (8.0)	19	15 (78.9)	2 (10.5)	2 (10.5)
Cellulitis	18	13 (72.2)	4 (22.2)	1 (5.6)	18	9 (50.0)	9 (50.0)	0 (0.0)
Furuncle	18	15 (83.3)	3 (16.7)	0 (0.0)	22	20 (90.9)	2 (9.1)	0 (0.0)
Pyoderma	8	4 (50.0)	4 (50.0)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)
Cellulitis with Condition[b]	7	6 (85.7)	1 (14.3)	0 (0.0)	3	2 (66.7)	1 (33.3)	0 (0.0)
Erysipelas	7	7 (100.0)	0 (0.0)	0 (0.0)	9	4 (44.4)	2 (22.2)	3 (33.3)
Wound Infection	7	6 (85.7)	1 (14.3)	0 (0.0)	6	5 (83.3)	1 (16.7)	0 (0.0)
Surgical Wound Infection	6	4 (66.7)	2 (33.3)	0 (0.0)	9	7 (77.8)	1 (11.1)	1 (11.1)
Other Infection/Symptoms[c]	2	1 (50.0)	1 (50.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	0 (0.0)
Cellulitis with Abscess	1	1 (100.0)	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	0 (0.0)
Abscess with Other[c]	1	1 (100.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)
Infected Ulcer	1	1 (100.0)	0 (0.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0 (0.0)
Total	129	104 (80.6)	20 (15.5)	5 (3.9)	124	93 (75.0)	23 (18.5)	8 (6.5)

Numbers in parentheses are percentages for that category.
[a] N = number of subjects who had that diagnosis.
[b] Includes cellulitis in association with decubitus ulcers or occurring in the setting of a complicating disease.
[c] Other infection or associated clinical symptoms.

Table 11b. Clinical Response by Diagnosis: FDA Clinically Evaluable Subjects
(Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin				Ciprofloxacin			
Diagnosis	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Cellulitis	10	6 (60)	3 (30)	1 (10)	11	6 (55)	5 (45)	0 (0)
Infected Ulcer	1	1 (100)	0 (0)	0 (0)	0	0 (-)	0 (-)	0 (-)
Surgical Wound Infection	4	4 (100)	0 (0)	0 (0)	5	4 (80)	1 (20)	0 (0)
Abscess	19	18 (95)	1 (5)	0 (0)	19	17 (89)	1 (5)	1 (5)
Abscess with Other	1	1 (100)	0 (0)	0 (0)	0	0 (-)	0 (-)	0 (-)
Cellulitis with Abscess	1	1 (100)	0 (0)	0 (0)	1	1 (100)	0 (0)	0 (0)
Cellulitis with Condition	4	4 (100)	0 (0)	0 (0)	3	2 (67)	1 (33)	0 (0)
Furuncle	14	12 (86)	2 (14)	0 (0)	14	13 (93)	1 (7)	0 (0)
Erysipelas	4	4 (100)	0 (0)	0 (0)	5	4 (80)	1 (20)	0 (0)
Wound Infection	4	3 (75)	1 (25)	0 (0)	6	5 (83)	1 (17)	0 (0)
Impetigo	20	18 (90)	0 (0)	2 (10)	14	12 (86)	0 (0)	2 (14)
Pyoderma	5	2 (40)	3 (60)	0 (0)	10	8 (80)	2 (20)	0 (0)
Other	2	1 (50)	1 (50)	0 (0)	0	0 (-)	0 (-)	0 (-)
Total	89	75 (84)	11 (12)	3 (3)	88	72 (82)	13 (15)	3 (3)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that diagnosis.

Clinical Response by Complexity and Severity of Infection

Clinical response rates for sponsor clinically evaluable subjects are summarized by complexity and severity of infection in Table 12a. Clinical response rates for FDA clinically evaluable subjects are summarized by severity of infection in Table 12b (*note: all patients with complicated infections were considered unevaluable by FDA).*

Table 12a. Clinical Response by Complexity and Severity of Infection: Sponsor Clinically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

	Levofloxacin				Ciprofloxacin			
	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Complicated								
Severe	2	1 (50.0)	1 (50.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0 (0.0)
Mild/Moderate	17	9 (52.9)	6 (35.3)	2 (11.8)	15	6 (40.0)	5 (33.3)	4 (26.7)
Total Complicated	19	10 (52.6)	7 (36.8)	2 (10.5)	16	6 (37.5)	6 (37.5)	4 (25.0)
Uncomplicated								
Severe	0	0 –	0 –	0 –	5	3 (60.0)	1 (20.0)	1 (20.0)
Mild/Moderate	110	94 (85.5)	13 (11.8)	3 (2.7)	103	84 (81.6)	16 (15.5)	3 (2.9)
Total Uncomplicated	110	94 (85.5)	13 (11.8)	3 (2.7)	108	87 (80.6)	17 (15.7)	4 (3.7)
Total Evaluable for Clinical Efficacy	129	104 (80.6)	20 (15.5)	5 (3.9)	124	93 (75.0)	23 (18.5)	8 (6.5)

Numbers in parentheses are percentages for that category.

Table 12b. Clinical Response by Severity of Infection: FDA Clinically Evaluable Subjects (Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin				Ciprofloxacin			
Severity	N	Cure	Improve	Fail	N	Cure	Improve	Fail
Severe	0	0 (-)	0 (-)	0 (-)	4	3 (75)	1 (25)	0 (0)
Mild/Moderate	89	75 (84)	11 (12)	3 (3)	84	69 (82)	12 (14)	3 (4)

Numbers shown in parentheses are percentages for that category.

Microbiologic Eradication

The microbiologic eradication rates achieved for sponsor microbiologically evaluable subjects in each treatment group are summarized by pathogen in Table 13a. Table 13b summarizes the same information for FDA microbiologically evaluable subjects (*note: the only pathogens included in the FDA table are those requested by the sponsor for their label).* Gram-positive and gram-negative aerobes were the most prevalent pathogens in both treatment groups (in both analyses). No statistically significant treatment differences were detected in microbiologic eradication rates by subject, pathogen, for *Staphylococcus aureus*, or for *Streptococcus pyogenes*, in both the sponsor and FDA analysis.

Table 13a. Microbiologic Eradication Rates by Pathogen Category and Pathogen: Sponsor Microbiologically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

Pathogen Category/Pathogen	Levofloxacin N	Levofloxacin Eradicated[a]	Ciprofloxacin N	Ciprofloxacin Eradicated[a]	95% Confidence Interval[b]
Pathogen Category					
Gram-Positive Aerobic Pathogens	102	95 (93.1)	100	91 (91.0)	(-10.1, 5.6)
Gram-Negative Aerobic Pathogens	26	26 (100.0)	27	25 (92.6)	(-19.2, 4.4)
Gram-Positive Anaerobic Pathogens	1	1 (100.0)	2	2 (100.0)	-
Gram-Negative Anaerobic Pathogens	3	1 (33.3)	3	3 (100.0)	-
Total by pathogen	132	123 (93.2)	132	121 (91.7)	(-8.3, 5.2)
Total by subject	100	93 (93.0)	97	87 (89.7)	(-11.7, 5.1)
Pathogen[c]					
Staphylococcus aureus	70	66 (94.3)	75	70 (93.3)	(-8.5, 7.6)
Streptococcus pyogenes	18	17 (94.4)	13	12 (92.3)	(-23.9, 19.6)
Streptococcus sp.	8	7 (87.5)	5	3 (60.0)	-
Escherichia coli	7	7 (100.0)	8	8 (100.0)	-
Pseudomonas aeruginosa	5	5 (100.0)	5	5 (100.0)	-

[a] Numbers shown in parentheses are percentages for that category.
[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rates were calculated for pathogens with 10 or more admission isolates in each treatment group.
[c] N≥5 for either treatment group.

Table 13b. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Uncomplicated Infections Only; Excluding Mexican Centers)

Pathogen Category/Pathogen	Levofloxacin N	Levofloxacin Eradicated[a]	Ciprofloxacin N	Ciprofloxacin Eradicated[a]	95% Confidence Interval[b]
Pathogen Category					
Gram-positive aerobic pathogens	92	86 (93)	91	85 (93)	(-8.3, 8.2)
Gram-negative aerobic pathogens	22	22 (100)	16	16 (100)	N/A[c]
Gram-positive anaerobic pathogens	0	0 (-)	2	2 (100)	-
Gram-negative anaerobic pathogens	1	1 (100)	2	2 (100)	-
Total by pathogen	115	109 (95)	111	105 (95)	(-6.9, 6.5)
Total by subject	90	84 (93)	87	81 (93)	(-8.8, 8.3)
Pathogen					
Staphylococcus aureus	64	60 (94)	71	67 (94)	(-8.9, 10.1)
Streptococcus pyogenes	18	17 (94)	13	12 (92)	(-26.7, 22.4)

[a] Numbers shown in parentheses are percentages for that category.
[b] A two-sided confidence interval for the difference (Ciprofloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.
[c] N/A=not applicable.

The microbiologic eradication rates achieved for sponsor and FDA microbiologically evaluable subjects in each treatment group are summarized by diagnosis in Tables 14a and 14b, respectively.

Table 14a. Microbiologic Eradication Rates Summarized by Diagnosis: Sponsor Microbiologically Evaluable Subjects (Excluding Mexican Centers)

(Study L91-031)

	Levofloxacin			Ciprofloxacin		
Diagnosis	N	Eradicated[a]	Persisted[a]	N	Eradicated[a]	Persisted[a]
Abscess						
Total by Pathogen	26	23 (88.5)	3 (11.5)	22	20 (90.9)	2 (9.1)
Total by Subject	22	21 (95.5)	1 (4.5)	19	17 (89.5)	2 (10.5)
Impetigo						
Total by Pathogen	25	24 (96.0)	1 (4.0)	22	20 (90.9)	2 (9.1)
Total by Subject	19	18 (94.7)	1 (5.3)	14	12 (85.7)	2 (14.3)
Furuncle						
Total by Pathogen	14	14 (100.0)	0 (0.0)	14	14 (100.0)	0 (0.0)
Total by Subject	14	14 (100.0)	0 (0.0)	13	13 (100.0)	0 (0.0)
Cellulitis						
Total by Pathogen	21	20 (95.2)	1 (4.8)	15	14 (93.3)	1 (6.7)
Total by Subject	13	12 (92.3)	1 (7.7)	13	12 (92.3)	1 (7.7)
Surgical Wound Infection						
Total by Pathogen	8	7 (87.5)	1 (12.5)	11	9 (81.8)	2 (18.2)
Total by Subject	6	5 (83.3)	1 (16.7)	8	6 (75.0)	2 (25.0)
Erysipelas						
Total by Pathogen	8	8 (100.0)	0 (0.0)	12	11 (91.7)	1 (8.3)
Total by Subject	6	6 (100.0)	0 (0.0)	7	6 (85.7)	1 (14.3)
Pyoderma						
Total by Pathogen	9	7 (77.8)	2 (22.2)	18	18 (100.0)	0 (0.0)
Total by Subject	6	4 (66.7)	2 (33.3)	11	11 (100.0)	0 (0.0)
Wound Infection						
Total by Pathogen	9	9 (100.0)	0 (0.0)	7	7 (100.0)	0 (0.0)
Total by Subject	5	5 (100.0)	0 (0.0)	6	6 (100.0)	0 (0.0)
Cellulitis with Condition[b]						
Total by Pathogen	6	6 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)
Total by Subject	4	4 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)
Other Infection/Symptoms						
Total by Pathogen	2	1 (50.0)	1 (50.0)	6	4 (66.7)	2 (33.3)
Total by Subject	2	1 (50.0)	1 (50.0)	1	0 (0.0)	1 (100.0)
Cellulitis with Abscess						
Total by Pathogen	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Total by Subject	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Abscess with Other Infection/Symptoms						
Total by Pathogen	1	1 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Total by Subject	1	1 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Infected Ulcer						
Total by Pathogen	2	2 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)
Total by Subject	1	1 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)
Overall Total by Pathogen	132	123 (93.2)	9 (6.8)	132	121 (91.7)	11 (8.3)
Overall Total by Subject	100	93 (93.0)	7 (7.0)	97	87 (89.7)	10 (10.3)

[a] Numbers shown in parentheses are percentages for that category.

[b] Includes cellulitis in association with decubitus ulcers or occurring in the setting of a complicating disease.

Table 14b. FDA Microbiologic Eradication Rates Summarized by Diagnosis: Uncomplicated Infections Only

Diagnosis	Levofloxacin		Ciprofloxacin	
	N	Eradicated[a]	N	Eradicated[a]
Cellulitis				
Total by pathogen	17	16 (94)	12	11 (92)
Total by subject	10	9 (90)	11	10 (91)
Surgical Wound Infection				
Total by pathogen	4	4 (100)	7	6 (86)
Total by subject	4	4 (100)	5	4 (80)
Infected Ulcer				
Total by pathogen	2	2 (100)	0	0 (-)
Total by subject	1	1 (100)	0	0 (-)
Abscess				
Total by pathogen	20	20 (100)	22	20 (91)
Total by subject	19	19 (100)	19	17 (89)
Abscess with Other				
Total by pathogen	1	1 (100)	0	0 (-)
Total by subject	1	1 (100)	0	0 (-)
Cellulitis with Abscess				
Total by pathogen	1	1 (100)	1	1 (100)
Total by subject	1	1 (100)	1	1 (100)
Cellulitis with Condition				
Total by pathogen	7	7 (100)	3	3 (100)
Total by subject	5	5 (100)	3	3 (100)
Furuncle				
Total by pathogen	14	14 (100)	15	15 (100)
Total by subject	14	14 (100)	14	14 (100)
Wound Infection				
Total by pathogen	8	8 (100)	7	7 (100)
Total by subject	4	4 (100)	6	6 (100)
Erysipelas				
Total by pathogen	5	5 (100)	8	8 (100)
Total by subject	4	4 (100)	5	5 (100)
Impetigo				
Total by pathogen	27	25 (93)	20	18 (90)
Total by subject	20	18 (90)	13	11 (85)
Pyoderma				
Total by pathogen	7	5 (71)	16	16 (100)
Total by subject	5	3 (60)	10	10 (100)
Other				
Total by pathogen	2	1 (50)	0	0 (-)
Total by subject	2	1 (50)	0	0 (-)
Overall Total				
Total by pathogen	115	109 (95)	111	105 (95)
Total by subject	90	84 (93)	87	81 (93)

[a]Numbers shown in parentheses are percentages for that category.

Summary of Key Efficacy Results

The clinical response rates for the sponsor intent-to-treat, sponsor clinically evaluable, and sponsor fully-clinically evaluable groups, along with the microbiologic eradication rates for the sponsor intent-to-treat, sponsor microbiologically evaluable, and sponsor fully microbiologically evaluable groups are summarized in Table 15a.

Table 15a. Summary of Sponsor Key Efficacy Results (Excluding Mexico Centers)

(Study L91-031)

Clinical and Microbiologic Response

Response/Group	Levofloxacin: Clinical Success or Microbiologic Eradication Rates[a]	Ciprofloxacin: Clinical Success or Microbiologic Eradication Rates[a]	95% Confidence Interval[b]
Clinical Response			
Clinically Evaluable	124/129 (96.1)	116/124 (93.5)	(-6.4, 3.3)
Intent-to-Treat	128/136 (94.1)	124/136 (91.2)	(-6.5, 3.6)
Fully Clinically Evaluable	107/111 (96.4)	100/107 (93.5)	(-6.2, 3.4)
Microbiologic Response			
Microbiologically Evaluable	93/100 (93.0)	87/97 (89.7)	(-11.7, 5.1)
Intent-to-Treat[c]	99/112 (88.4)	96/114 (84.2)	(-13.6, 5.2)
Fully Microbiologically Evaluable	85/90 (94.4)	77/87 (88.5)	(-14.7, 2.8)

Microbiologic Response Versus Clinical Response[d]

	Clinical Response							
	Levofloxacin				Ciprofloxacin			
Microbiologic Response	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Eradicated	93	81 (87.1)	11(11.8)	1 (1.1)	87	75 (86.2)	10 (11.5)	2 (2.3)
Persisted	7	0 (0.0)	4(57.1)	3 (42.9)	10	0 (0.0)	5 (50.0)	5 (50.0)
Total Evaluable	100	81 (81.0)	15(15.0)	4 (4.0)	97	75(77.3)	15 (15.5)	7 (7.2)

[a] Denominator for clinical success rate = cured + improved + failed + unable to evaluate. Denominator for microbiologic eradication rate = eradication + persistence + unknown.
[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in clinical success or microbiologic eradication rates.
[c] Only subjects with admission pathogens.
[d] Based on microbiologically evaluable group.
NOTE: Microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a subject at admission.

Table 15b summarizes "overall success rate", defined as clinical cure or improvement with microbiologic eradication, by center for subjects considered both clinically and microbiologically evaluable by FDA. The overall success rate for levofloxacin was considered therapeutically equivalent to that of ciprofloxacin.

Table 15b. Overall Success Rates[a] and Confidence Intervals By Study Center:
FDA Microbiologically AND Clinically Evaluable Subjects
(Uncomplicated Infections Only; Excluding 3 Mexican Centers)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[c]
	N	Overall Success[b]	N	Overall Success[b]	
Barona	2	2 (100)	2	2 (100)	-
Galimberti	7	6 (86)	10	6 (60)	-
Jasovich	9	8 (89)	11	11 (100)	-
Marques	3	3 (100)	2	2 (100)	-
Nicodemo	21	21 (100)	20	20 (100)	N/A[d]
Robledo	15	14 (93)	11	10 (91)	(-31.5, 26.6)
Roselino	7	6 (86)	8	7 (88)	-
Saravia	0	0 (-)	1	1 (100)	-
Sussman	10	10 (100)	7	7 (100)	-
Torres	11	11 (100)	11	11 (100)	N/A
Wey	1	1 (100)	1	1 (100)	-
Zaitz	3	1 (33)	3	3 (100)	-
Total	89	83 (93)	87	81 (93)	(-8.7, 8.4)

[a]Overall success is defined as clinical cure or improvement with microbiologic eradication.
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (cipro minus levo) in overall success rate. This was calculated for study centers enrolling 10 or more clinically and microbiologically evaluable subjects in each treatment group.
[d]N/A=not applicable.

SAFETY RESULTS

Safety data from all study centers, including those in Mexico, are included in all sponsor safety analyses. Tables 16 and 17 summarize the incidence of adverse events by body system and frequently reported adverse events by body system, respectively. Adverse events were most common in the gastrointestinal system, with similar incidence rates in the levofloxacin (12.3%) and ciprofloxacin (10.7%) treatment groups. For the remaining body systems, the frequency of adverse events was low (5.6%) and similar in both treatment groups except for a slightly higher incidence of central and peripheral nervous system disorders (mostly dizziness) in the levofloxacin group (5.6%) than in the ciprofloxacin group (2.2%).

Table 16. Incidence of Adverse Events by Body System (Including Mexican Centers)

Study L91-031

Body System	Levofloxacin (N = 175) N	(%)	Ciprofloxacin (N = 176) N	(%)	95% Confidence Interval*
Gastrointestinal System Disorders	22	(12.3)	19	(10.7)	(-6.2, 5.0)
Central & Peripheral Nervous System Disorders	10	(5.6)	4	(2.2)	(-7.3, 0.7)
Psychiatric Disorders	10	(5.6)	10	(5.6)	(-4.7, 4.8)
Skin and Appendages Disorders	4	(2.2)	2	(1.1)	(-3.8, 1.8)
Body as a Whole–General Disorders	2	(1.1)	2	(1.1)	(-2.2, 2.2)
Vision Disorders	1	(0.6)	0	(0.0)	(-1.7, 0.5)
Special Senses (Other), Disorders	1	(0.6)	0	(0.0)	(-1.7, 0.5)
Cardiovascular Disorders, General	1	(0.6)	0	(0.0)	(-1.7, 0.5)
Urinary System Disorders	1	(0.6)	0	(0.0)	(-1.7, 0.5)
Neoplasms[b]	1	(0.6)	0	(0.0)	(-1.7, 0.5)
Respiratory System Disorders	0	(0.0)	1	(0.6)	(-0.5, 1.7)
Total with Adverse Events (%)	39	(21.8)	29	(16.3)	(-13.6, 2.6)

[a] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in incidence of adverse events.
[b] This subject (303) is described in detail in Section IV.1.3.a., Serious or Potentially Serious Adverse Events, Including Death and in Table 28.

Table 17. Incidence of Frequently Reported (>2.0%) Adverse Events Summarized by Body System and Primary Term: Subjects Evaluable for Safety (Including Mexican Centers)

Study L91-031

Body System/Primary Term	Levofloxacin (N=175) N	(%)	Ciprofloxacin (N=176) N	(%)
All Body Systems	39	(21.8)	29	(16.3)
Central & Peripheral Nervous System Disorders				
Dizziness	8	(4.5)	3	(1.7)
Headache	4	(2.2)	1	(0.6)
Psychiatric Disorders				
Somnolence	6	(3.4)	5	(2.8)
Insomnia	2	(1.1)	4	(2.2)
Gastrointestinal System Disorders				
Nausea	10	(5.6)	6	(3.4)
Diarrhea	9	(5.0)	4	(2.2)
Abdominal Pain	3	(1.7)	7	(3.9)

[a] Primary term reported by ≥2.0% of subjects in either treatment group.

Discontinuations Due to Adverse Events

Seven subjects discontinued the study drug due to adverse events, five (2.8%) subjects in the levofloxacin treatment group and two (1.1%) in the ciprofloxacin treatment group (Table 18). Most of the discontinuations were associated with gastrointestinal complaints.

Table 18. Summary of Patients who Discontinued Therapy Due to Adverse Events

(Study L91-031)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset[a]	Severity	Relationship To Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	51	M	Abdominal Pain	6	Moderate	Probable	5
			Vomiting	6	Moderate	Probable	
	18	F	Taste Perversion	1	Mild	Definite	7
			Somnolence	3	Mild	Probable	
	29	F	Nausea	2	Moderate	Probable	7
	79	F	Diarrhea	5	Marked	Probable	5
	74	F	Headache	2	Marked	Possible	2
Ciprofloxacin							
	64	F	Diarrhea	8	Moderate	Possible	8
			Vomiting	8	Moderate	Possible	
			Rash	9	Moderate	Possible	
	46	M	Abdominal pain	5	Marked	Probable	5
			Vomiting	5	Moderate	Probable	

[a] Relative to start of therapy.
[b] Based on investigator's assessment.
[c] Subject also had a markedly abnormal laboratory value. (See Table 32)

Serious or Potentially Serious Adverse Events, Including Death

Two subjects in the levofloxacin treatment group (303, 712) and one subject in the ciprofloxacin treatment group (417) reported a serious or potentially serious adverse event during or up to approximately two weeks after completing study therapy. None of these three events were considered related to treatment with study drug. The sponsor's description of these patients are presented below:

Subject [redacted] was a 62-year-old Hispanic female with a diagnosis of abscess and a history of Hodgkin's lymphoma. Approximately one month prior to entering the study, the subject underwent tests to stage the Hodgkin's lymphoma; at that time it was suspected that the original diagnosis of Hodgkin's lymphoma was incorrect. Levofloxacin 500 mg q24h was administered for a total of 7 days. Concomitant medications were diazepam, enteral diet, a nonsteroidal anti-inflammatory drug, acetaminophen, and lorezepam. On the tenth day of the study, the subject's prior diagnosis of Hodgkin's lymphoma was changed to non-Hodgkin's lymphoma of moderate severity. In the opinion of the investigator, this event was unrelated to study drug administration. The subject received treatment for this event by another physician and the outcome is unknown.

Subject [redacted] was a 20-year-old Black male with a diagnosis of impetigo and no significant medical history. Levofloxacin 500 mg q24h was administered for a total of seven days. The subject was receiving no concomitant medications. The subject was lost to follow-up after the Day 3 visit, however, it was subsequently learned that he had been hospitalized to receive treatment for injuries resulting from a fight. The date of the hospitalization and the outcome of this event are unknown. In the opinion of the investigator, this event was of remote relationship to study drug administration.

Subject [redacted] was a 54-year-old Caucasian male with a diagnosis of erysipelas and a history of peripheral vascular disease and uncontrolled hypertension. Ciprofloxacin 500 mg q12h was administered for a total of 11 days. Concomitant medications were nifedipine and hydrochlorothiazide. On Posttherapy Day 11, the subject had marked elevations in serum creatinine (2.6 mg/dL, admission value 1.3 mg/dL), blood urea nitrogen (178.0 mg/dL, admission value 39.0 mg/dL), uric acid (17.0 mg/dL, admission value 8.5 mg/dL), and inorganic phosphorus (6.0 mg/dL, admission value 3.1 mg/dL) as also shown in Table 32. On Posttherapy Day 13, the subject was hospitalized with cardiac failure and died the same day. In the opinion of the investigator, these events were of remote relationship to study drug administration. An IND Safety Report was filed with the FDA for this case.

Clinical Laboratory Tests

A summary of markedly abnormal laboratory values after the start of therapy in subjects with admission data available is shown in Tables 19 and 20, respectively.

Table 19. Incidence of Treatment Emergent Markedly Abnormal Laboratory Values

(Study L91-031)

	Levofloxacin		Ciprofloxacin	
Laboratory Test	Proportion*	%	Proportion*	%
Blood Chemistry				
Elevated Glucose	0/143	0.0	2/143	1.4
Decreased Glucose	1/143	0.7	2/143	1.4
Decreased Calcium	1/114	0.9	1/116	0.8
Elevated Sodium	0/122	0.0	1/125	0.8
Decreased Potassium	0/122	0.0	1/125	0.8
Elevated Phosphorus	3/114	2.6	1/108	0.9
Elevated BUN	7/141	5.0	5/143	3.5
Decreased Albumin	0/116	0.0	1/117	0.9
Elevated Uric Acid	0/116	0.0	1/119	0.8
Elevated Creatinine	2/143	1.4	1/142	0.7
Elevated Bilirubin	1/108	0.9	2/110	1.8
Hematology				
Decreased Hemoglobin	0/142	0.0	1/143	0.7
Decreased Neutrophils	1/142	0.7	0/139	0.0
Decreased Lymphocytes	0/142	0.0	1/141	0.7

*Numerator = number of subjects with a treatment-emergent markedly abnormal test value and denominator = number of subjects evaluable (i.e., admission and postherapy data available) for that analyte.

Table 20. Subjects with Treatment Emergent Markedly Abnormal Laboratory Values

(Study L91-031)

Subject Number	Age	Sex	Laboratory Test[a] (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[b]	Duration of Active Drug Therapy (Days)
Levofloxacin							
	69	F	Creatinine (>1.5 mg/dL)	1.0	1.8	10	7
			Blood Urea Nitrogen (>40 mg/dL)	19.0	83.0	10	
	41	M	Total Bilirubin (>1.5 mg/dL)	0.5	6.5[c]	14 (4 PT)	7
	28	F	Calcium (<7.5 or >11.5 mg/dL)	9.0	7.3	28 (16 PT)	7
			Glucose (<70 or >200 mg/dL)	95.0	48.0	28 (16 PT)	
	47	F	Phosphorus, Inorg. (<2.0 or >5.0 mg/dL)	3.5	7.7	16 (5 PT)	7
	30	M	Neutrophils (<1.0 x 10^3/µL)	3.42	0.57	13 (3 PT)	7
	33	F	Blood Urea Nitrogen (>40 mg/dL)	22.0	41.0[d]	14 (4 PT)	7
	51	M	Blood Urea Nitrogen (>40 mg/dL)	28.0	67.0	16 (10 PT)	6
	75	F	Phosphorus, Inorg. (<2.0 or >5.0 mg/dL)	2.8	6.3	20 (10 PT)	7
	42	M	Phosphorus, Inorg. (<2.0 or >5.0 mg/dL)	4.0	6.8	15 (5 PT)	7
	20	F	Blood Urea Nitrogen (>40 mg/dL)	20.0	45.0	20 (10 PT)	7
	22	M	Blood Urea Nitrogen (>40 mg/dL)	21.0	50.0	15 (5 PT)	7
	49	F	Blood Urea Nitrogen (>40 mg/dL)	11.0	90.0	13 (3 PT)	7
	59	M	Blood Urea Nitrogen (>40 mg/dL)	15.0	90.0	12 (2 PT)	7
	64	M	Creatinine (>1.5 mg/dL)	1.3	2.5	12 (2 PT)	7
Ciprofloxacin							
	44	M	Blood Urea Nitrogen (>40 mg/dL)	26.0	66.0	7	10
	26	M	Total Bilirubin (>1.5 mg/dL)	1.3	2.5	7	10
	43	M	Potassium (<3.0 or >5.0 mEq/L)	3.8	2.47	18 (8 PT)	10
			Glucose (<70 or >200 mg/dL)	66.0	213.0	18 (8 PT)	
	25	M	Glucose (<70 or >200 mg/dL)	270.0	56.0	13 (3 PT)	10
	54	M	Creatinine (>1.5 mg/dL)	1.3	2.5	22 (11 PT)	11
			Blood Urea Nitrogen (>40 mg/dL)	39.0	178.0	22 (11 PT)	
			Uric Acid (>10.0 mg/dL)	6.5	17.0	22 (11 PT)	
			Phosphorus, Inorg. (<2.0 or >5.0 mg/dL)	3.1	6.3	22 (11 PT)	
	72	F	Sodium (<120 or >155 mEq/L)	140.0	159.0	15 (5 PT)	10
			Hemoglobin (<12.0 g/dL)	12.5	9.5	15 (5 PT)	
	70	M	Total Bilirubin (>1.5 mg/dL)	0.7	2.5	15 (5 PT)	10
	67	M	Blood Urea Nitrogen (>40 mg/dL)	16.0	90.0	11 (1 PT)	10
			Glucose (<70 or >200 mg/dL)	142.0	252.0	11 (1 PT)	
	81	M	Blood Urea Nitrogen (>40 mg/dL)	13.0	80.0	11 (3 PT)	8
	24	F	Blood Urea Nitrogen (>40 mg/dL)	18.0	48.0	16 (5 PT)	10
	77	M	Calcium (<7.5 or >11.5 mg/dL)	9.6	7.2	22 (12 PT)	10
	66	M	Lymphocytes (<1.0 x 10^3/µL)	2.16	0.79	15 (5 PT)	10
	36	M	Glucose (<70 or >200 mg/dL)	69.16	36.0	14 (4 PT)	10
	26	F	Albumin (<2.0 g/dL)	4.76	1.17[e]	16 (5 PT)	10

[a] Only range given in table. For complete criteria see Attachment 2.6.

[b] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy relative to the last day of study drug administration (including placebo, if applicable, for levofloxacin-treated subjects).

[c] Represents database error; actual value (0.5 mg/dL) was within the investigator's reference range (0.2-1.0 mg/dL).

[d] The blood urea nitrogen value for this subject was within the investigator's reference range (10.0-45.0 mg/dL).

[e] Represents database error; actual value (4.17 g/dL) was within the investigator's reference range (3.8-5.0 g/dL).

* Subject discontinued due to an adverse event. (See Table 27)

‡ Subject also had serious or potentially serious adverse event. (See Table 28)

SUMMARY AND DISCUSSION

The objective of this double-blind, active-control, multicenter study conducted in Latin America was to compare the safety and efficacy of levofloxacin versus ciprofloxacin in the treatment of uncomplicated skin and skin structure infections in adults. In all analysis groups examined, levofloxacin was both effective and safe in the treatment of these infections. The sponsor states that the results are applicable to the U.S. population, given that the distribution of pathogens studied were typical of those likely to be encountered in a similar study conducted in the U.S.

Levofloxacin treatment provided comparable clinical responses to those observed with ciprofloxacin. The two

pathogens most frequently isolated from subjects in this study were *S. aureus* and *S. pyogenes*. Among sponsor clinically evaluable subjects in the levofloxacin treatment group, 80.6% were cured and 15.5% were improved, compared with 75.0% and 18.5% in the ciprofloxacin treatment group, respectively. When the clinical response categories "cured" and "improved" were combined into a single category of "clinical success," levofloxacin treatment resulted in 96.1% clinical success, while ciprofloxacin treatment resulted in 93.5% clinical success. The 95% confidence interval of the difference in success rates was (-8.4, 3.3). FDA results were similar.

For sponsor microbiologically evaluable subjects, the overall microbiologic infection eradication rates were comparable for the levofloxacin-treated and ciprofloxacin-treated groups (93.0% and 89.7%, respectively). Among all subjects with a diagnosis of abscess (the most common diagnosis in both treatment groups), the eradication rates by subject were 95.5% and 89.5%, respectively, for levofloxacin- and ciprofloxacin-treated subjects. For the most common pathogen (*S. aureus*), there was 94.3% eradication in the levofloxacin group and a 93.3% eradication in the ciprofloxacin group across all diagnoses. The respective eradication rates for the second most common pathogen (*S. pyogenes*) were 94.4% in the levofloxacin group and 92.3% in the ciprofloxacin group. FDA results were similar.

The levofloxacin and ciprofloxacin treatment groups also had similar safety profiles, including incidence and severity of adverse events, numbers of subjects who stopped drug prematurely due to adverse events, serious adverse events, laboratory abnormalities, vital signs, and physical examinations. The overall incidence of adverse events in the levofloxacin and ciprofloxacin treatment groups was 21.8% and 16.3%, respectively. The most frequently reported adverse events were nausea (5.6% incidence rate for levofloxacin-treated subjects versus 3.4% for ciprofloxacin-treated subjects), diarrhea (5.0% versus 2.2%), dizziness (4.5% versus 1.7%), and somnolence (3.4% versus 2.8%).

CONCLUSIONS

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with uncomplicated skin and skin structure infections. No statistically significant treatment differences were detected in clinical success and microbiologic eradication rates, and rates observed in the levofloxacin treatment group were considered therapeutically equivalent to those in the ciprofloxacin group. This study supports the use of levofloxacin 500 mg q 24 hours for 10 days in the treatment of uncomplicated skin and skin structure infections. Both *Staphylococcus aureus* and *Streptococcus pyogenes* are supported by this study. The diagnostic groups supported by this study include cellulitis, abscess, furuncle, and impetigo. This study (alone) does not support the use of levofloxacin for the treatment of surgical wound infection, erysipelas, pyoderma, wound infection, or infected ulcer.

REVEIWER'S CONCLUSIONS OF EFFICACY FOR UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS (Studies K90-075 and K91-031)

The evaluation of daily levofloxacin was done with two pivotal studies. Study K90-075 was an open-labeled study in patients with mild to moderate skin and skin structure infections performed in the United States and Costa Rica. Study L91-031 was a double-blinded study in patients with uncomplicated skin and skin structure infections performed in South America. Combined analyses of clinical response by diagnosis in the clinically evaluable subjects is presented in Table 1. Combined analyses of microbiologic eradication in the microbiologically evaluable subjects is presented in Table 2.

Table 1: Combined Analysis for Studies K90-075 and L91-031
Clinical Response by Diagnosis: FDA Clinically Evaluable Subjects
(Uncomplicated Infections Only; Excluding Mexican Centers)

	Levofloxacin					Ciprofloxacin				
Diagnosis	N[a]	Cure		Improve		Fail	N[a]	Cure		Improve		Fail
Cellulitis	76	67	(88)	7	(9)	2 (3)	73	61	(84)	8	(11)	4 (5)
Infected Ulcer	3	3	(100)	0	(0)	0 (0)	0	0	(-)	0	(-)	0 (-)
Surgical Wound Infection	15	12	(80)	2	(13)	1 (7)	13	8	(62)	5	(38)	0 (0)
Abscess	24	23	(95)	1	(5)	0 (0)	24	22	(92)	1	(4)	1 (4)
Abscess with Other	2	2	(100)	0	(0)	0 (0)	0	0	(-)	0	(-)	0 (-)
Cellulitis with Abscess	15	14	(93)	1	(7)	0 (0)	16	15	(94)	1	(6)	0 (0)
Cellulitis with Condition	10	7	(70)	2	(20)	1 (10)	6	4	(67)	2	(33)	0 (0)
Furuncle	14	12	(86)	2	(14)	0 (0)	14	13	(93)	1	(7)	0 (0)
Erysipelas	4	4	(100)	0	(0)	0 (0)	5	4	(80)	1	(20)	0 (0)
Wound Infection	11	9	(81)	2	(9)	0 (0)	12	9	(75)	2	(17)	1 (8)
Impetigo	31	29	(94)	0	(0)	2 (6)	24	22	(91)	0	(0)	2 (8)
Pyoderma	21	12	(57)	9	(43)	0 (0)	26	19	(73)	6	(23)	1 (4)
Other	2	1	(50)	1	(50)	0 (0)	0	0	(-)	0	(-)	0 (-)
Total	228	195	(85)	27	(12)	6 (3)	213	177	(83)	27	(13)	9 (4)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that diagnosis.

Table 2. Combined Analysis of Studies K90-075 and L91-031
FDA Microbiologic Eradication Rates Summarized by Diagnosis: Uncomplicated Infections Only

Diagnosis	Levofloxacin		Ciprofloxacin	
	N	Eradicated[a]	N	Eradicated[a]
Cellulitis				
Total by pathogen	119	117 (98)	94	88 (94)
Total by subject	75	73 (97)	72	72 (100)
Surgical Wound Infection				
Total by pathogen	16	16 (100)	18	16 (89)
Total by subject	14	14 (100)	12	11 (92)
Infected Ulcer				
Total by pathogen	4	4 (100)	0	0 (-)
Total by subject	3	3 (100)	0	0 (-)
Abscess				
Total by pathogen	32	32 (100)	29	27 (93)
Total by subject	24	24 (100)	24	22 (92)
Abscess with Other				
Total by pathogen	2	2 (100)	0	0 (-)
Total by subject	2	2 (100)	0	0 (-)
Cellulitis with Abscess				
Total by pathogen	23	23 (100)	20	16 (100)
Total by subject	15	15 (100)	20	16 (100)
Cellulitis with Condition				
Total by pathogen	18	18 (100)	8	7 (88)
Total by subject	11	11 (100)	6	5 (83)
Furuncle				
Total by pathogen	14	14 (100)	15	15 (100)
Total by subject	14	14 (100)	14	14 (100)
Wound Infection				
Total by pathogen	18	18 (100)	18	13 (72)
Total by subject	11	11 (100)	12	11 (92)
Erysipelas				
Total by pathogen	5	5 (100)	8	8 (100)
Total by subject	4	4 (100)	5	5 (100)
Impetigo				
Total by pathogen	39	37 (95)	35	33 (94)
Total by subject	31	29 (94)	23	21 (91)
Pyoderma				
Total by pathogen	27	25 (92)	36	30 (83)
Total by subject	21	19 (90)	26	21 (81)
Other				
Total by pathogen	2	1 (50)	0	0 (-)
Total by subject	2	1 (50)	0	0 (-)
Overall Total				
Total by pathogen	319	312 (98)	281	253 (90)
Total by subject	227	220 (97)	214	198 (93)

Together, studies K90-075 and L91-038 support the use of levofloxacin for cellulitis, abscess, furuncle, impetigo, pyoderma, wound infection, and surgical wound infection. The diagnosis of erysipelas is not supported by the combined analyses of these studies. Eradication of the two most common organisms in these studies (*Staphylococcus aureus* and *Streptococcus pyogenes*) for uncomplicated skin and skin structure infections is supported by these studies.

STUDY L91-058

TITLE

A multicenter, double-blind, randomized study to compare the safety and efficacy of oral levofloxacin with that of ciprofloxacin HCL in the treatment of complicated urinary tract infections (UTI) in adults

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* The study was prematurely terminated at this site for administrative reasons and data obtained at this site was not be used to support efficacy. This investigator was not terminated due to either lack of efficacy or serious adverse events.

OBJECTIVES

The objective of this study was to compare the safety and efficacy of 250 mg of levofloxacin administered orally once daily for 10 days with that of 500 mg of ciprofloxacin administered orally twice daily for 10 days in the treatment of complicated UTI or acute pyelonephritis due to susceptible organisms in adults.

TREATMENTS

Duration of treatment 10 days

C Levofloxacin 250 mg q 24 hours
C Ciprofloxacin 500 mg q 12 hours

STUDY DESIGN

The schedule of assessments are described in Table 1. Between Days 3 and 5, subjects returned for a scheduled "on-study visit". A subject was not allowed to remain in the study if the admission culture was negative. In addition, if the subject's admission pathogen was found to be resistant to either study drug, and there was no improvement in the subject's symptoms, the subject was discontinued as a failure. At this visit, two blood cultures were obtained from subjects who were bacteremic at admission, adverse events were assessed, and a urine specimen was obtained for culture, susceptibility testing, and urinalysis. If the on-therapy urine culture showed a colony count of $\$ 10^4$ organisms per milliliter of the same bacterial species isolated on admission, the study drug was to be discontinued and the subject was considered a failure. A posttherapy visit was scheduled five to nine days after the subject completed therapy, and was considered the primary visit for efficacy outcome analyses. At this visit, two blood cultures were obtained for subjects who were bacteremic at admission, adverse events were assessed, and a urine specimen was obtained for culture, susceptibility testing, and urinalysis. Pertinent physical examinations and clinical laboratory tests were repeated, and women of childbearing potential had a pregnancy test. The investigator determined the clinical response by comparing the subject's posttherapy signs and symptoms to those observed at admission. A long-term follow-up visit was scheduled four to six weeks after the completion of therapy. At that visit, clinical signs and symptoms were assessed and a urine specimen was obtained for culture, susceptibility testing, and urinalysis.

Table 1. Schedule of Assessments

(Study L91-058)

Assessment/Procedure	Admission (Day 1)	During Therapy (Days 3 - 5)	Posttherapy (6 - 9 days PT)[a]	Long-Term Follow-Up (4 - 6 weeks PT)
Pertinent Medical History	X			
Pregnancy Test[b]	X		X	
Study Drug Administration	X	——X[c]		
Efficacy Evaluations: (see Section III.H.2.)				
Clinical:				
-Clinical Signs and Symptoms	X		X	X
-Clinical Response Rating			X	
Microbiologic:				
-Urine Culture	X	X	X	X
-Susceptibility Test	X	X	X	X
-Blood Culture	X[d]	X[e]	X[e]	
Safety Assessments: (see Section III.H.4.)				
Adverse Events		X	X	
Clinical Laboratory Tests:				
-Hematology	X		X	
-Chemistry	X		X	
-Urinalysis	X	X	X	X
Pertinent Physical Examination (Including Vital Signs)	X		X	

[a] Or upon early withdrawal.
[b] Performed on all women of childbearing potential.
[c] Levofloxacin and ciprofloxacin were to be administered for 10 days.
[d] Performed only if indicated.
[e] Performed if positive at admission.
PT=Posttherapy

PROTOCOL AMENDMENTS

March 8, 1994 (30% enrollment)

C The definition of the clinical response of "improved" was modified to add the statement "and not requiring additional antimicrobial therapy", the definition of "unable to evaluate" was further clarified, and a provision was added to allow subjects with a resistant pathogen to continue in the study if clinical improvement was seen. Several changes in evaluability criteria for the efficacy analysis were also made:

(I) specification that subjects with clinical failure receiving greater than 48 hours but less than five days of therapy should be considered evaluable;

(ii) requirement that bacteriologic cultures be obtained between five and 12 days posttherapy rather than one to nine days posttherapy for subjects to be evaluable;

(iii) omission of the provisions that subjects who had taken study drug for more than 20 days (unless due to a persistent pathogen) or who failed to meet specific entrance criteria would be excluded from the efficacy analysis;

(iv) deletion of resistance to study drug as a criterion for classifying a subject as microbiologically unevaluable.

C Changes were also made in response to the Infectious Diseases Society of America (IDSA) Guidelines for the evaluation of new anti-infective drugs in the treatment of UTI. These modifications included a

clarification of the clinical definition of acute pyelonephritis, the deletion of recurrent UTI and UTI in women over 55 years of age as criteria for complicated UTI, the inclusion of subjects who developed UTI in the presence of an indwelling catheter (with catheter maintenance regimen specified), addition of the provision that a subject was considered a failure if discontinued after the on-therapy culture due to a colony count (admission pathogen isolated) of $ 10^4 cfu/mL, and clarification of the definitions of superinfection, reinfection, and microbiologic response (eradication, persistence, and persistence with acquisition of resistance).

STUDY POPULATION

Overview

Approximately 500 subjects, men and women who were 18 years of age or older and had a diagnosis of complicated UTI or acute pyelonephritis, were to be enrolled in this study to attain a sample size of 147 microbiologically evaluable subjects per treatment group for efficacy analysis. Enrollment could continue until sufficient numbers of microbiologically evaluable subjects with infections due to target pathogens had entered. Subjects were enrolled according to the inclusion/exclusion criteria summarized below:

Inclusion Criteria

- C Men and women, 18 years of age or older, who were appropriate candidates for oral therapy, and who had a diagnosis of complicated UTI or acute pyelonephritis were eligible for enrollment. Complicated UTI was defined as >5 urine white blood cells (WBCs) per high power field, $ 10^5 organisms per milliliter of at least one species of a uropathogen, the presence of some anatomical or functional abnormality, and any of the following symptoms: urgency, frequency, dysuria, fever (or history of fever), or hematuria. Examples of complicating factors included partial obstruction, stone, neurogenic bladder, enlarged prostate, and the presence of an indwelling catheter.
- C Subjects with an indwelling catheter had to be able to follow one of the catheter maintenance regimens specified in the protocol. Infections in men were considered complicated, however, men with prostatitis were excluded from the study.
- C Acute pyelonephritis was defined as >20 urine WBCs per low power field ($ 5 WBC per high power field), $ 10^5 organisms per milliliter of at least one species of a uropathogen, and two of the following: flank pain or costovertebral angle (CVA) tenderness, fever (or history of fever), WBC count greater than 15,000/mm, and a positive antibody coated bacteria test or WBC casts in urine. Subjects who were paraplegic or quadriplegic were not excluded for being asymptomatic.
- C Subjects who received previous antimicrobial therapy could be enrolled if the duration of therapy was 24 hours or less. If the previous therapy was greater than 24 hours and the subject had not improved or stabilized on that therapy, the subject could be enrolled in the study.
- C Women were required to be postmenopausal for at least one year, surgically sterile, or using an adequate form of birth control. Women of childbearing potential were required to have had a normal menstrual flow within one month before study entry and to have had a negative pregnancy test immediately before study entry.

Exclusion Criteria

- C Subjects with a history of allergic or serious adverse reaction to levofloxacin, or any other member of the quinolone of antimicrobial drugs.
- C Subjects with severe illness requiring administration of intravenous antimicrobial therapy.
- C Subjects who required a second systemic antimicrobial therapy.
- C Subjects who had used any investigational agent within 30 days or who had been previously treated under this protocol.
- C Subjects with infections caused by organisms determined at screening to be resistant to either study drug.
- C Subjects with complete obstruction of any portion of the urinary tract, prostatitis, or any disorder or disease that might interfere with the evaluation of the study drugs.

C Women who were pregnant or nursing, subjects with a calculated creatinine clearance of 50 mL/min or less, and subjects with a seizure disorder or unstable psychiatric conditions.

RANDOMIZATION AND BLINDING

All study personnel who evaluated subjects, and all sponsor monitors, statisticians, and other personnel who reviewed data, remained blinded during the course of the study.

DOSAGE AND ADMINISTRATION

Subjects were assigned randomly to receive either levofloxacin or ciprofloxacin. Subjects assigned to the levofloxacin treatment group received two 125 mg tablets of levofloxacin once daily and one placebo tablet to match ciprofloxacin 500 mg twice daily. Subjects assigned to the ciprofloxacin control group received one 500 mg tablet of ciprofloxacin twice daily and two placebo tablets to match levofloxacin 125 mg once daily. The total duration of therapy for both treatment groups was 10 days as clinically indicated.

COMPLIANCE

Compliance was estimated by counting unused study drug in the test medication containers returned by the subjects to the investigators.

CONCOMITANT THERAPY

The use of other medications during the study was to be kept to a minimum. Administration of nonstudy systemic antimicrobials was prohibited and aluminum-magnesium based antacids (e.g., Maalox ®) and mineral supplements or vitamins with iron or minerals were strongly discouraged because they may decrease the bioavailability of quinolones.

EFFICACY AND SAFETY EVALUATIONS

Efficacy evaluations included assessments of microbiologic response by pathogen (assessed as eradicated, persisted, persisted with acquisition of resistance, or unknown) and infection (assessed as eradicated, persisted, or unknown), evaluation of clinical signs and symptoms, and clinical response rates (assessed as cured, improved, failed, or unable to evaluate).

Microbiologic response in the group of subjects evaluable for microbiologic efficacy was the primary efficacy variable for this study. Clinical response was a secondary efficacy variable and was also based on the group of microbiologically evaluable subjects. Safety evaluations included the incidence of treatment-emergent adverse events, laboratory tests of hematology, blood chemistry, and urinalysis, and physical examinations including vital signs.

EVALUABILITY CRITERIA

Safety Evaluability

To be evaluable for safety analysis, subjects must have taken at least one dose of study medication and had some available postadmission safety information.

Microbiologic Efficacy

To be evaluable for microbiologic efficacy, subjects must not be classified by any of the following:

C Not evaluable for safety.

C Infection not bacteriologically proven (i.e. no pathogen identified in the admission cultures).

C Insufficient course of therapy. A subject did not take at least five days of therapy. If a subject was discontinued because he was judged a clinical failure and had received at least 48 hours of therapy, he was not considered unevaluable for this reason. And if the subject had a pathogen isolated at admission, the admission pathogen is presumed to persist in this situation.

C Effective concomitant therapy. A subject received an effective systemic antimicrobial between time of admission culture and the test-of-cure culture. (Subjects who received previous antimicrobial therapy could be enrolled if the previous therapy duration was 24 hours or less, or if greater than 24 hours, the subject failed to improve or stabilize on that therapy). A subject who received an effective systemic antimicrobial

because he was judged a clinical failure was not considered unevaluable for this reason.

C Inappropriate bacteriologic cultures.
I. Admission culture was greater than 48 hours prior to start of therapy or any time following initiation of therapy.
ii. Posttherapy culture was not within 5-12 days posttherapy. If a subject was discontinued due to clinical failure or considered a clinical failure upon the completion of therapy and the posttherapy culture was obtained on the last day of therapy, he was not considered unevaluable for this reason.
iii. Adequate microbiologic data were unevaluable. If a subject was a clinical failure and persistence of the pathogen isolated on admission was not confirmed by culture results, the subject was not considered unevaluable for this reason and the pathogen was presumed to persist in this situation.

C Lost to follow-up but provided safety information (no posttherapy evaluation).

C Other protocol violation.
I. A subject re-entered the study.
ii. A subject did not take at least 70% of assigned study drug. Number of assigned doses was not captured on the case record form; therefore, "70% of assigned study drug" was calculated by taking 70% of the number of days subject was on drug times the number of doses/day as outlined in the protocol.

To be eligible to enroll in the study, a subject should have had at least one organism identified by its quantity greater than or equal to 10^5 per milliliter in urine specimen, greater than five white blood cells per high power field, and any of the following symptoms: urgency, frequency, dysuria, fever (or history of fever) or hematuria. Because of these rigid inclusion criteria, which differentiate clinical from microbiologic evaluability, the clinical evaluability assessment became redundant. Hence, any subject evaluable for microbiologic efficacy in this study also represented subjects evaluable for clinical efficacy.

EFFICACY EVALUATIONS

Clinical

Clinical Signs and Symptoms

Clinical symptoms of complicated UTI or acute pyelonephritis including urgency, frequency, dysuria, chills, fever, CVA tenderness or flank pain, incontinence, nausea, or vomiting were graded as none, mild, moderate, or severe at admission, at the posttherapy visit (five to nine days posttherapy), and at long-term follow-up (four to six weeks following therapy). A subject's infection was retrospectively (prior to breaking the blind) classified by the medical monitor as severe if it met the following criteria:

Bacteremia or Presence of any one of the following clinical signs of septicemia:
- -Diastolic blood pressure < 60 mmHg
- -Altered mental status
- -Use of vasopressors or Presence of any three of the following signs/symptoms:
- -Moderate to severe CVA/flank pain
- -Oral temperature > $101.0^{o}F$
- -Chills
- -Nausea or vomiting
- -WBC> or = $15{,}000/mm^3$

All other infections were considered mild/moderate in severity.

Clinical Response Rating

At the posttherapy visit five to nine days after the end of therapy, the investigator assessed clinical response as cured, improved, failed, or unable to evaluate based on comparison to admission signs and symptoms. The definitions for these assessments are as follows:

Cured: Complete resolution of signs and symptoms associated with the active infection.

Improved: Incomplete resolution of signs and symptoms and no additional antimicrobial therapy required.

Failure: No response to therapy.
Unable to evaluate: Subject did not return for follow-up evaluation.

Microbiology
Urine Cultures
Urine specimens were obtained via clean catch or midstream collection, or by straight catheterization. Specimens were collected at admission, at the on-therapy visit (study day 3-5), at the posttherapy visit (five to nine days posttherapy) and at long-term follow-up (four to six weeks following therapy) for culture, susceptibility testing, and urinalysis.
Blood Culture
Two specimens for blood culture were obtained at admission if bacteremia was suspected. Cultures were repeated at the on-therapy visit and at the posttherapy visit if bacteremia was found at admission.
Susceptibility Testing
Susceptibility to levofloxacin and ciprofloxacin was determined for all pathogens at admission, on therapy (Study Day 3-5), at five to nine days posttherapy, and, if subject returned for the long-term follow-up, at four to six weeks posttherapy. Disk susceptibility testing was performed on all aerobic pathogens, and minimum inhibitory concentration (MIC) susceptibility was obtained on all aerobic and anaerobic pathogens. Disk susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) methods. The criteria for susceptibility to levofloxacin were based on inhibition zone diameters:

	MIC (µg/mL)	
Interpretation	Levofloxacin	Ciprofloxacin
Susceptible	≤2.0	≤1.0
Moderately susceptible	>2.0 and <8.0	>1.0 and <4.0
Resistant	≥8.0	≥4.0

Minimum inhibitory concentrations for both levofloxacin and ciprofloxacin were determined for all aerobic and anaerobic pathogens. Using a broth microdilution susceptibility assay for determination of MICs in accordance with NCCLS, the susceptibility criteria for levofloxacin were as follows:

	Inhibition Zone Diameter (mm)	
Interpretation	Levofloxacin	Ciprofloxacin
Susceptible	≥16	≥21
Moderately susceptible	13-15	16-20
Resistant	≤12	≤15

Susceptibility to levofloxacin and ciprofloxacin, was requested for all pathogens isolated throughout the study. When MIC values were not available, disks were used to determine susceptibility. Susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS). The criteria used were:

LEVOFLOXACIN

	MIC (µg/mL)	Disc Zone (mm)
Susceptible	≤2.0	≥16
Moderately Susceptible	>2.0 and <8.0	13-15
Resistant	≥8.0	≤12

CIPROFLOXACIN

	MIC (µg/mL)	Disc Zone (mm)
Susceptible	≤1.0	≥21
Moderately Susceptible	>1.0 and <4.0	16-20
Resistant	≥4.0	≤21

Microbiologic Response

Each organism isolated was assigned a pathogenic classification according to the following criteria:

Pathogen: Organism(s) ($ 10^5 cfu/mL) isolated from urine at admission and responsible for UTI.

Superinfection: Organism(s) other than that (those) isolated at admission, isolated while on-therapy through to and including the posttherapy culture from urine ($ 10^5 cfu/mL) or blood, or culture of a distant site, associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection, or requiring antimicrobial therapy.

Reinfection: Organism(s) other than that (those) isolated at admission, isolated from urine ($ 10^5 cfu/mL) or blood after the posttherapy visit, associated with emergence or worsening of clinical signs and symptoms and/or laboratory evidence of active infection, or requiring antimicrobial therapy.

Relapse: Reappearance of an organism ($ 10^5 cfu/mL) identical to that isolated at admission, at the long-term follow-up visit following eradication of the original admission pathogen at the posttherapy visit.

Colonizer: Organism, other than those classified above, isolated from urine ($ 10^4 cfu/mL), or culture of a distant site, not considered pathogenic (not associated with signs or symptoms of active infection) and not requiring antimicrobial therapy.

The microbiologic response at posttherapy for uropathogens isolated at admission was the primary efficacy variable and was determined by evaluating the posttherapy/early withdrawal culture results. A negative culture was considered valid if the subject was not receiving any effective concomitant antimicrobial treatment. Results were categorized as follows:

Eradicated: Eradication or reduction (<10^4 cfu/mL in urine) of the admission pathogen in a valid posttherapy/early withdrawal culture.

Persisted: Persistence of the admission pathogen ($ 10^4 cfu/mL in urine) as evidenced by isolation of the pathogen in the last obtained (on-therapy or posttherapy) culture. If a subject was discontinued due to clinical failure and persistence of the admission pathogen was not confirmed by culture results, or the subject was considered a clinical failure and no valid negative culture was obtained, the pathogen was presumed to persist.

Persisted with Acquisition of Resistance: Persistence of the admission pathogen ($ 10^4 cfu/mL in urine) as

evidenced by isolation of the pathogen in the last obtained (on-therapy or posttherapy) culture with documented acquisition of resistance.
Unknown: No posttherapy/early withdrawal culture results available due to subject lost-to-follow-up, no specimen available for culture, or culture not done when specimen was available. In the absence of clinical failure, the response was unknown if the culture was performed on therapy or if the culture was done while the subject was receiving an effective nonstudy antimicrobial agent and was negative (unless persistence was presumed for blood pathogens).

Organisms isolated in the blood at admission were assigned a microbiologic response similar to those given above (eradicated, persisted, persisted with acquisition of resistance, or unknown); however the specifications for quantity did not apply. In addition, eradication of blood pathogens was considered presumed if the eradication could not be confirmed by culture results but the subject was a clinical success.

In order for an infection to be considered documented as eradicated, each pathogen isolated at admission had to be documented as eradicated:

Eradicated: Eradication of all admission pathogens.
Persisted: Persistence, presumed persistence, or persistence with acquisition of resistance of at least one pathogen isolated at admission in the last obtained culture (on-therapy or posttherapy).
Unknown: No culture results available or unknown results for at least one pathogen isolated at admission.

The microbiologic response for the admission pathogen at the long-term follow-up (four to six weeks after the posttherapy visit) was based on microbiologic culture data and was assessed in subjects who had clinical success (cured or improved) at posttherapy.

Microbiologic response was assessed as eradicated, relapse, unknown, or not applicable.

- C A response of "unknown" included those subjects for whom no culture information was available (e.g., subject did not return for long-term follow-up visit), or subjects who received an effective concurrent antimicrobial between the posttherapy and long-term follow-up evaluations.
- C A response of "not applicable" was assigned in cases where the admission pathogen had persisted at posttherapy or the posttherapy clinical response was "failed".

The microbiologic response for the subject's infection at the long-term follow-up was assessed as eradicated, relapse, unknown, or not applicable, as based on eradication of all pathogens (including blood pathogens).

- C A response of "unknown"was assigned in cases where the outcome was unknown for at least one pathogen and no pathogen was a relapse.
- C An infection was assessed as "not applicable" if the response for at least one pathogen was not applicable.

Clinical Response
The secondary efficacy variable was clinical response, assessed by the investigator as cured, improved, failed, or unable to evaluate at the posttherapy visit five to nine days after the end of therapy. The clinical cure rate was evaluated by determining the percentage of microbiologically evaluable subjects who were cured and the clinical success rate was based on the percentage of microbiologically evaluable subjects who were cured or improved.

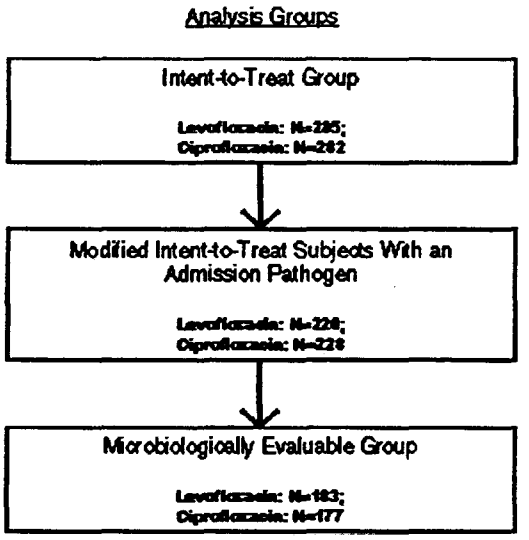
REMOVAL OF SUBJECTS FROM THE STUDY

Subjects could be discontinued from study therapy due to adverse events, significant protocol violation, intercurrent illness, treatment failure, a negative admission urine culture, or at the request of the subject. In addition, prior to the protocol amendment (March 8, 1994) subjects were to be discontinued due to isolation of a resistant pathogen. At the time of premature withdrawal of therapy, posttherapy evaluations including physical examination and vital signs, urine culture and susceptibility testing, and clinical laboratory tests were to be performed.

Sponsor's Analysis Populations

- C Intent-to-Treat — adheres strictly to randomization; thus subjects are included in the analysis regardless of whether or not an admission pathogen was isolated.
- C Modified Intent-to-Treat with an Admission Pathogen — which represents subjects in the intent-to-treat group who had a pathogen isolated at admission.
- C Microbiologically evaluable subjects - which represent subjects with complicated UTI or acute pyelonephritis according to the protocol-specified evaluability criteria

Statistical Reviewer's Note: In this study, the sponsor's "modified intent-to-treat with an admission pathogen" analysis group is, in fact, defined in the same way as DAIDP defines modified intent-to-treat. FDA analysis is based on patients considered microbiologically evaluable by FDA. In addition, for most analyses, results are presented separately for patients with complicated UTI and patients with acute pyelonephritis.



RESULTS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Five hundred sixty-seven subjects were enrolled in this study at 31 of 35 centers (three investigators did not enroll any subjects and data for 11 subjects enrolled by Dr. Maggiacomo were not included). The sponsor intent-to-treat group included 285 subjects who were randomized to the levofloxacin treatment group, and 282 subjects who were randomized to the ciprofloxacin treatment group, at the 31 centers. The study was prematurely terminated at Dr. Maggiacomo's site for administrative reasons. None of the 11 subjects enrolled at this study center reported serious adverse events and none were withdrawn from the study because of adverse events.

The demographic and baseline (admission) characteristics of the sponsor intent-to-treat group are summarized in Table 2 and were comparable between the levofloxacin and ciprofloxacin treatment groups.

Table 2. Demographic and Baseline Characteristics: Sponsor Intent-to-Treat Patients

(Study L91-058)

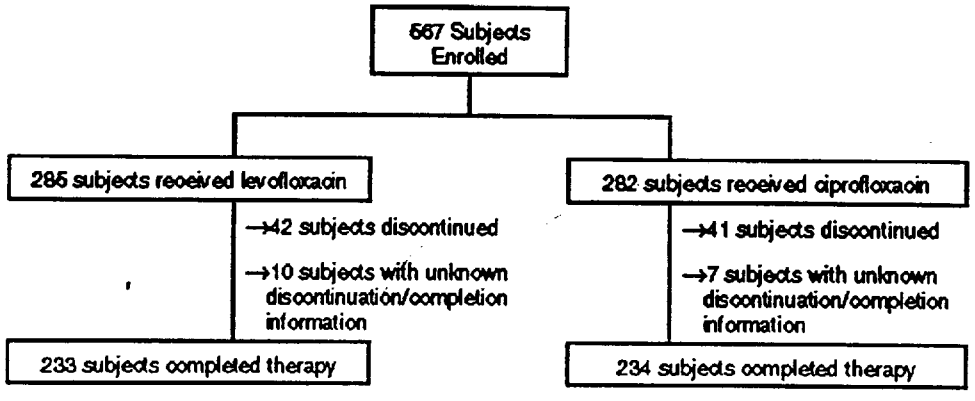
	Levofloxacin (N=285)		Ciprofloxacin (N=282)		Overall Total (N=567)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	117	(41.1)	112	(39.7)	229	(40.4)
Women	168	(58.9)	170	(60.3)	338	(59.6)
Race						
Caucasian	230	(80.7)	220	(78.0)	450	(79.4)
Black	34	(11.9)	44	(15.6)	78	(13.8)
Oriental	4	(1.4)	3	(1.1)	7	(1.2)
Hispanic	12	(4.2)	8	(2.8)	20	(3.5)
Other	5	(1.8)	7	(2.5)	12	(2.1)
Age (Years)						
≤45	116	(40.7)	127	(45.0)	243	(42.9)
46-64	66	(23.2)	66	(23.4)	132	(23.3)
≥65	103	(36.1)	89	(31.6)	192	(33.9)
N	285		282		567	
Mean±SD	51.7±21.9		49.7±20.5		50.7±21.3	
Range	[illegible]		[illegible]		[illegible]	
Weight (lbs)						
N	260		273		553	
Mean±SD	159.6±39.6		160.6±38.6		160.0±39.1	
Range	[illegible]		[illegible]		[illegible]	
Missing	5		9		14	
Height (Inches)						
N	254		249		503	
Mean±SD	66.3±4.01		66.2±4.00		66.2±4.00	
Range	[illegible]		[illegible]		[illegible]	
Missing	31		33		64	
Diagnosis						
Complicated UTI	197	(69.1)	188	(66.7)	385	(67.9)
Acute Pyelonephritis	69	(24.2)	80	(28.4)	149	(26.3)
Uncomplicated UTI	19	(6.7)	14	(5.0)	33	(5.8)
Severity						
Complicated UTI						
Severe	8	(4.1)	9	(4.8)	17	(4.4)
Mild/Moderate	189	(95.9)	179	(95.2)	368	(95.6)
Acute Pyelonephritis						
Severe	3	(4.3)	8	(10.0)	11	(7.4)
Mild/Moderate	66	(95.7)	72	(90.0)	138	(92.6)
Uncomplicated UTI						
Mild/Moderate	19	(100.0)	14	(100.0)	33	(100.0)

NOTE: Values represent number of subjects except as otherwise indicated.
UTI = urinary tract infection.

DISCONTINUATION/COMPLETION INFORMATION

Discontinuation information for the sponsor intent-to-treat group is provided in Figure 1.

Figure 1: Discontinuation/Completion Information: Intent-to-Treat Subjects (Study L91-058)



The reasons for premature discontinuation are summarized in Table 3.

Table 3. Reasons for Premature Discontinuation of Therapy: Sponsor Intent-to-Treat Subjects

(Study L91-058)

Reason	Levofloxacin (N=285) No.	(%)[a]	Ciprofloxacin (N=282) No.	(%)[a]
No Admission Pathogen	18	(6.5)	15	(5.6)
Adverse Event	10	(3.6)	16	(5.8)
Resistant Pathogen[b]	2	(0.7)	2	(0.7)
Clinical Failure	1	(0.4)	2	(0.7)
Personal Reason	0	(0.0)	1	(0.4)
Other	11[c]	(4.0)	5[d]	(1.8)
Total Discontinued	42	(15.3)	41	(14.9)
Total with Discontinuation/Completion Information	275		275	
Total with Unknown Discontinuation/Completion Information	10		7	

a Percentages based on total number with discontinuation/completion information.
b Subjects enrolled prior to the protocol amendment (March 8, 1994) were to be discontinued if a resistant pathogen was isolated at admission.
c Four subjects discontinued prematurely either due to subject error ([redacted] took only half of study medication) or study site error ([redacted]). Subject [redacted] received an effective concomitant antimicrobial. Subject [redacted] was enrolled in error (diagnosed with prostatitis). Two subjects were discontinued to allow administration of i.v. antibiotics ([redacted] had a positive blood culture and a high fever and [redacted] had a high fever and chills, received ampicillin and netilmicin, and was considered "too unstable" to participate in the protocol). Subject [redacted] had increased serum creatinine at admission (3.7 mg/dL; normal range: 0.8-1.6 mg/dL). Subject [redacted] had on-therapy urine culture with a colony count of >10 4 /mL (microbiologic failure). Subject [redacted] was discontinued from the study as the result of an erroneous admission colony count of <10 5 /mL (actual result was >10 5 /mL but lab reported wrong value in error).
d Two subjects were discontinued to allow administration of i.v. antibiotics ([redacted] developed an epidural abscess and was treated wit vancomycin and ceftazidime and [redacted] was started on gentamycin and nafcillin to treat bacteremia). Subject [redacted] withdrew on Day 8 in error. Subject [redacted] had trouble swallowing pills and only took the "small" ones (placebo) after Day 7. Subject [redacted] was discontinued from the study at her request.

DOSAGE INFORMATION

The extent of exposure to therapy is shown by treatment group in Table 4 for the sponsor intent-to-treat group.

Table 4. Extent of Exposure to Therapy: Sponsor Intent-to-Treat Subjects

(Study L91-058)

Extent of Therapy	Levofloxacin (N=286)	Ciprofloxacin (N=282)
Days on Therapy[a]		
Unknown	10	7
1	0	3
2	6	8
3	7	6
4	6	6
5	8	9
6	3	6
7	6	2
8	3	1
9	3	1
10	179	174
11	52	57
12	1	2
13	1	0
Mean±SD	9.4±2.1	9.3±2.4
Median	10	10
Number of Doses[b]		
Total with Dosing Information	275	276
Total with Unknown Dosing Information	10	6
Mean±SD	18.3±4.4	18.0±4.9
Median	20	20
Range	2-20	1-24

[a] The total planned duration of therapy for levofloxacin and ciprofloxacin was 10 days. Days on therapy was defined as (last day - first day) +1.

[b] Levofloxacin had a q24h dosing schedule and ciprofloxacin had a q12h dosing schedule. However, levofloxacin-treated subjects received study drug (levofloxacin or placebo) q12h to maintain double-blind dosing.

EFFICACY RESULTS

The total numbers of subjects evaluable at each study center for sponsor intent-to-treat and sponsor microbiologically evaluable analyses is shown in Table 5. One hundred eighty-three (64.2%) subjects in the levofloxacin treatment group and 177 (62.8%) subjects in the ciprofloxacin-treatment group were considered microbiologically evaluable by the sponsor. The primary reasons (subjects counted only once) for exclusion from the sponsor microbiologically evaluable group are summarized in Table 6. The main reason that subjects were not microbiologically evaluable was absence of bacteriologically proven infection.

Table 5. Number of Subjects by Sponsor Analysis Group and Center

(Study L91-058)

	Levofloxacin			Ciprofloxacin		
Investigator[a]	Intent-to-Treat	Microbiologic Efficacy		Intent-to-Treat	Microbiologic Efficacy	
Bernstein	6	6	(100.0)	4	2	(50.0)
Brunston	8	3	(37.5)	8	2	(25.0)
Bruce	19	11	(57.9)	19	10	(52.6)
Childs	48	36	(75.0)	48	40	(83.3)
Dennis	2	1	(50.0)	2	0	(0.0)
Duckett	6	1	(16.7)	6	2	(33.3)
Durden	16	10	(62.5)	15	9	(60.0)
Epstein	2	2	(100.0)	1	0	(0.0)
File	3	1	(33.3)	4	1	(25.0)
Foster	2	0	(0.0)	2	1	(50.0)
Gallis	8	7	(87.5)	7	4	(57.1)
Geckler	2	0	(0.0)	2	0	(0.0)
Irizarry	3	3	(100.0)	5	4	(80.0)
Israelski	2	0	(0.0)	2	1	(50.0)
Kern	12	2	(16.7)	12	2	(16.7)
Kimani	1	1	(100.0)	0	0	(.)
Lipsky	5	3	(60.0)	6	4	(66.7)
Martel	6	2	(33.3)	6	4	(60.0)
Martel	11	6	(54.5)	11	9	(81.8)
McCabe	4	2	(50.0)	4	2	(50.0)
Montgomerie	8	6	(75.0)	8	3	(37.5)
Nicolle	19	17	(89.5)	18	10	(55.6)
Pitman	20	19	(95.0)	20	16	(80.0)
Powers	1	1	(100.0)	1	1	(100.0)
Richard	28	24	(85.7)	29	25	(86.2)
Silverman	2	0	(0.0)	1	0	(0.0)
Smith	7	1	(14.3)	6	1	(16.7)
Stark	13	7	(53.8)	14	12	(85.7)
Steidle	6	3	(50.0)	6	3	(50.0)
Young	11	7	(63.6)	11	6	(54.5)
Zervos	4	1	(25.0)	5	3	(60.0)
Total	285	183	(64.2)	282	177	(62.8)

Numbers shown in parentheses are percentages for that category.
a Three investigators (Adducci, Ellis, and Meacham) did not enroll any subjects. The study was prematurely terminated at one site f administrative reasons and data for this investigator (Maggiacomo) are not included.

Table 6. Primary Reasons for Microbiologic NonEvaluability: Sponsor Intent-to-Treat Subjects

(Study L91-058)

Reasons	Levofloxacin (N=285)		Ciprofloxacin (N=282)	
Infection Not Bacteriologically Proven	64		63	
Inappropriate Bacteriologic Culture	20		24	
Insufficient Course of Therapy	8		15	
Effective Concomitant Therapy	6		6	
Unevaluable for Safety	3		3	
No Posttherapy Evaluation	2		1	
Other Protocol Violation	0		3[b]	
Total Unevaluable For Microbiologic Efficacy	102	(35.8%)	105	(37.2%)

[a] Subjects counted only once.
[b] Subject 509 had trouble swallowing pills and took only the 'small' ones (placebo) on Days 8 and 9. Subject 902 was asymptomatic. Subject 2202 was excluded in error; this subject should have been included as microbiologically evaluable.

The demographic and baseline characteristics of sponsor microbiologically evaluable subjects are presented in Table 7 and were similar to characteristics in the sponsor intent-to-treat population (Table 2).

Table 7. Demographic and Baseline Characteristics: Sponsor Microbiologically Evaluable Subjects

(Study L91-058)

	Levofloxacin (N=183)	Ciprofloxacin (N=177)
Sex		
Men	70	64
Women	113	113
Race		
Caucasian	148	141
Black	20	21
Oriental	3	3
Hispanic	9	6
Other	3	7
Age (Years)		
≤45	77	81
46-64	45	45
≥65	61	51
N	183	177
Mean±SD	51.0±22.1	48.1±20.3
Range	[redacted]	[redacted]
Weight (lbs)		
N	179	172
Mean±SD	150±40.4	160±40.9
Range	[redacted]	[redacted]
Missing	4	5
Height (in)		
N	164	161
Mean±SD	66.2±3.60	65.0±3.65
Range	[redacted]	[redacted]
Missing	19	16
Diagnosis		
Complicated UTI	126	113
Acute Pyelonephritis	51	58
Uncomplicated UTI	6	6
Severity		
Complicated UTI		
Severe	5	4
Mild/Moderate	121	109
Acute Pyelonephritis		
Severe	2	5
Mild/Moderate	49	53
Uncomplicated UTI		
Mild/Moderate	6	6

NOTE: Values represent numbers of subjects unless otherwise indicated.
UTI = urinary tract infection

Clinical Outcome

Sponsor Results

The clinical response to therapy (at the posttherapy visit) for sponsor microbiologically evaluable subjects with a diagnosis of either complicated UTI or acute pyelonephritis is summarized by treatment group and study center in Table 8a. Among subjects in the levofloxacin treatment group, 84.7% were cured and 7.3% were improved at the posttherapy visit (five to nine days after completion of therapy), compared with 81.9% and 8.8% in the ciprofloxacin treatment group. Fourteen (7.9%) levofloxacin-treated subjects and 16 (9.4%) ciprofloxacin-treated subjects failed treatment. The cure rates for the two treatment groups for all centers combined were considered therapeutically equivalent (95% confidence interval of [-11.0, 5.3]). Note: All confidence intervals in this study report are for the difference "ciprofloxacin minus levofloxacin", thus we are interested in the upper bound of the confidence interval for determining therapeutic equivalence.

FDA Results

Clinical response to therapy at the posttherapy visit is summarized by treatment group and study center for FDA microbiologically evaluable patients with a diagnosis of complicated UTI in Table 8b and for FDA

microbiologically evaluable patients with a diagnosis of acute pyelonephritis in Table 8c. In both cases, there is no statistically significant treatment difference and levofloxacin is considered therapeutically equivalent to ciprofloxacin [95% confidence interval of 104, 133(-18.1, 5.4) 76%, 82% for complicated UTI; 95% confidence interval of 56, 45 (-16.0, 13.2) 88%, 89% for acute pyelonephritis]. Notice that therapeutic equivalence is shown in these subgroups even though the study was not powered to look at complicated UTI and acute pyelonephritis separately.

Table 8a. Clinical Response Rate by Center: Sponsor Microbiologically Evaluable Subjects (Complicated Urinary Tract Infection and Acute Pyelonephritis Combined)

(Study L91-058)

	Levofloxacin							Ciprofloxacin						
Investigator	N	Cured		Improved		Failed		N	Cured		Improved		Failed	
Bernstein	6	6	(100.0)	0	(0.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	0	(0.0)
Brankston	3	2	(66.7)	0	(0.0)	1	(33.3)	1	1	(100.0)	0	(0.0)	0	(0.0)
Bruce	11	8	(72.7)	1	(9.1)	2	(18.2)	10	8	(80.0)	2	(20.0)	0	(0.0)
Childs	35	32	(91.4)	2	(5.7)	1	(2.9)	38	31	(81.6)	4	(10.5)	3	(7.9)
Dennis	1	0	(0.0)	1	(100.0)	0	(0.0)	0	0	(.)	0	(.)	0	(.)
Duckett	1	0	(0.0)	0	(0.0)	1	(100.0)	2	1	(50.0)	0	(0.0)	1	(50.0)
Durden	10	7	(70.0)	0	(0.0)	3	(30.0)	9	5	(55.6)	1	(11.1)	3	(33.3)
Epstein	2[1]	2	(100.0)	0	(0.0)	0	(0.0)	0	0	(.)	0	(.)	0	(.)
File	1	1	(100.0)	0	(0.0)	0	(0.0)	1	1	(100.0)	0	(0.0)	0	(0.0)
Foster	0	0	(.)	0	(.)	0	(.)	1	1	(100.0)	0	(0.0)	0	(0.0)
Gallis	5	4	(80.0)	1	(20.0)	0	(0.0)	3	3	(100.0)	0	(0.0)	0	(0.0)
Irizarry	3	2	(66.7)	0	(0.0)	1	(33.3)	4	4	(100.0)	0	(0.0)	0	(0.0)
Israelski	0	0	(.)	0	(.)	0	(.)	1	1	(100.0)	0	(0.0)	0	(0.0)
Kern	2	2	(100.0)	0	(0.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	0	(0.0)
Kimani	1	0	(0.0)	1	(100.0)	0	(0.0)	0	0	(.)	0	(.)	0	(.)
Lipsky	3	2	(66.7)	1	(33.3)	0	(0.0)	4	3	(75.0)	0	(0.0)	1	(25.0)
Markel	2	1	(50.0)	0	(0.0)	1	(50.0)	3	3	(100.0)	0	(0.0)	0	(0.0)
Martel	6	6	(100.0)	0	(0.0)	0	(0.0)	9	7	(77.8)	2	(22.2)	0	(0.0)
McCabe	2	2	(100.0)	0	(0.0)	0	(0.0)	2	1	(50.0)	1	(50.0)	0	(0.0)
Montgomerie	6	5	(83.3)	0	(0.0)	1	(16.7)	3	1	(33.3)	1	(33.3)	1	(33.3)
Nicolle	16	14	(87.5)	2	(12.5)	0	(0.0)	10	8	(80.0)	1	(10.0)	1	(10.0)
Pitman	18	15	(83.3)	3	(16.7)	0	(0.0)	16	14	(87.5)	1	(6.3)	1	(6.3)
Powers	1	1	(100.0)	0	(0.0)	0	(0.0)	1	1	(100.0)	0	(0.0)	0	(0.0)
Richard	24	24	(100.0)	0	(0.0)	0	(0.0)	25	25	(100.0)	0	(0.0)	0	(0.0)
Smith	0	0	(.)	0	(.)	0	(.)	1	1	(100.0)	0	(0.0)	0	(0.0)
Stark	7	6	(85.7)	1	(14.3)	0	(0.0)	11	11	(100.0)	0	(0.0)	0	(0.0)
Stalder	3	0	(0.0)	0	(0.0)	3	(100.0)	3	0	(0.0)	1	(33.3)	2	(66.7)
Young	7	7	(100.0)	0	(0.0)	0	(0.0)	6	3	(50.0)	1	(16.7)	2	(33.3)
Zervos	1	1	(100.0)	0	(0.0)	0	(0.0)	3	2	(66.7)	0	(0.0)	1	(33.3)
Combined*	73	57	(78.1)	5	(6.8)	11	(15.1)	72	54	(75.0)	7	(9.7)	11	(15.3)
Total	377	356	(94.7)	13	(7.3)	14	(7.9)	371	348	(91.9)	15	(3.8)	16	(9.4)

Numbers shown in parentheses are percentages for that category.

* Combined = centers that enrolled fewer than 10 microbiologically evaluable subjects in either treatment group: Bernstein, Brankston, Dennis, Duckett, Durden, Epstein, File, Foster, Gallis, Irizarry, Israelski, Kern, Kimani, Lipsky, Markel, Martel, McCabe, Montgomerie, Powers, Smith, Stark, Stalder, Young, and Zervos.

Table 8b. Clinical Response Rate by Center:
FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

	Levofloxacin				Ciprofloxacin			
Investigator	N[a]	Cure	Improve	Fail	N	Cure	Improve	Fail
Bruce	11	8 (73)	1 (9)	2 (18)	10	8 (80)	2 (20)	0 (0)
Childs	28	26 (93)	2 (7)	0 (0)	29	23 (79)	4 (14)	2 (7)
Pittmon	17	14 (82)	3 (18)	0 (0)	16	14 (88)	1 (6)	1 (6)
Other	57	45 (79)	6 (11)	6 (11)	49	34 (69)	5 (10)	10 (20)
Total	113	93 (82)	12 (11)	8 (7)	104	79 (76)	12 (12)	13 (13)

Numbers shown in parentheses are percentages for that category.
[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".

Table 8c. Clinical Response Rate by Center:
FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

	Levofloxacin				Ciprofloxacin			
Investigator	N[a]	Cure	Improve	Fail	N	Cure	Improve	Fail
Richard	21	21 (100)	0 (0)	0 (0)	23	23 (100)	0 (0)	0 (0)
Other	24	19 (79)	1 (4)	4 (17)	33	26 (79)	4 (12)	3 (9)
Total	45	40 (89)	1 (2)	4 (9)	56	49 (88)	4 (7)	3 (5)

Numbers shown in parentheses are percentages for that category.
[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".

To allow for a dichotomous analysis of clinical response, the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success". Among sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis, the clinical success rate was 92.1% for levofloxacin-treated subjects and 90.6% for ciprofloxacin-treated subjects, with a 95% confidence interval of [-7.6, 4.7] for the difference (ciprofloxacin minus levofloxacin) in success rates (See Table 9a). Clinical success rates were considered therapeutically equivalent for FDA microbiologically evaluable patients with complicated UTI (see Table 9b). Clinical success rates were not shown to be therapeutically equivalent in FDA microbiologically evaluable patients with acute pyelonephritis (see Table 9c), however the sponsor is not required to show this. The DAIDP "Points to Consider" document says simply that "if there is not a sufficient number of patients with pyelonephritis successfully treated with the investigative agent (minimum: 30 patients/arm/study), the listing (in the label) should not include pyelonephritis. No statistically significant treatment difference was detected between levofloxacin (91% success rate) and ciprofloxacin (95% success rate).

Table 9a. Clinical Success/Failure Rates and Confidence Intervals by Study Center: Sponsor Microbiologically Evaluable Subjects (Complicated UTI and Acute Pyelonephritis Combined)

(Study L91-058)

	Levofloxacin				Ciprofloxacin				95% Confidence Interval[b]	
Investigator	N	Success[a]		Failure[a]	N	Success[a]		Failure[a]		
Bernstein	6	6	(100.0)	0 (0.0)	2	2	(100.0)	0 (0.0)	(. ,	.)
Brankston	3	2	(66.7)	1 (33.3)	1	1	(100.0)	0 (0.0)	(. ,	.)
Bruce	11	9	(81.8)	2 (18.2)	10	10	(100.0)	0 (0.0)	(-9.6,	46.0)
Childs	35	34	(97.1)	1 (2.9)	38	35	(92.1)	3 (7.9)	(-16.7,	6.6)
Dennis	1	1	(100.0)	0 (0.0)	0	0	(.)	0 (.)	(. ,	.)
Duckett	1	0	(0.0)	1 (100.0)	2	1	(50.0)	1 (50.0)	(. ,	.)
Durden	10	7	(70.0)	3 (30.0)	9	6	(66.7)	3 (33.3)	(. ,	.)
Epstein	2	2	(100.0)	0 (0.0)	0	0	(.)	0 (.)	(. ,	.)
File	1	1	(100.0)	0 (0.0)	1	1	(100.0)	0 (0.0)	(. ,	.)
Foster	0	0	(.)	0 (.)	1	1	(100.0)	0 (0.0)	(. ,	.)
Gallis	5	5	(100.0)	0 (0.0)	3	3	(100.0)	0 (0.0)	(. ,	.)
Irizarry	3	2	(66.7)	1 (33.3)	4	4	(100.0)	0 (0.0)	(. ,	.)
Israelski	0	0	(.)	0 (.)	1	1	(100.0)	0 (0.0)	(. ,	.)
Kern	2	2	(100.0)	0 (0.0)	2	2	(100.0)	0 (0.0)	(. ,	.)
Kirmani	1	1	(100.0)	0 (0.0)	0	0	(.)	0 (.)	(. ,	.)
Lipsky	3	3	(100.0)	0 (0.0)	4	3	(75.0)	1 (25.0)	(. ,	.)
Markel	2	1	(50.0)	1 (50.0)	3	3	(100.0)	0 (0.0)	(. ,	.)
Martel	6	6	(100.0)	0 (0.0)	9	9	(100.0)	0 (0.0)	(. ,	.)
McCabe	2	2	(100.0)	0 (0.0)	2	2	(100.0)	0 (0.0)	(. ,	.)
Montgomerie	6	5	(83.3)	1 (16.7)	3	2	(66.7)	1 (33.3)	(. ,	.)
Nicolle	16	16	(100.0)	0 (0.0)	10	9	(90.0)	1 (10.0)	(-33.6,	13.6)
Pitman	18	18	(100.0)	0 (0.0)	16	15	(93.8)	1 (6.3)	(-21.2,	8.7)
Powers	1	1	(100.0)	0 (0.0)	1	1	(100.0)	0 (0.0)	(. ,	.)
Richard	24	24	(100.0)	0 (0.0)	25	25	(100.0)	0 (0.0)	(-2.1,	2.1)
Smith	0	0	(.)	0 (.)	1	1	(100.0)	0 (0.0)	(. ,	.)
Stark	7	7	(100.0)	0 (0.0)	11	11	(100.0)	0 (0.0)	(. ,	.)
Steidle	3	0	(0.0)	3 (100.0)	3	1	(33.3)	2 (66.7)	(. ,	.)
Young	7	7	(100.0)	0 (0.0)	6	4	(66.7)	2 (33.3)	(. ,	.)
Zervos	1	1	(100.0)	0 (0.0)	3	2	(66.7)	1 (33.3)	(. ,	.)
Combined[c]	73	62	(84.9)	11 (15.1)	72	61	(84.7)	11 (15.3)	(-12.6,	12.2)
Total	177	163	(92.1)	14 (7.9)	171	155	(90.6)	16 (9.4)	(-7.6,	4.7)

[a] Numbers shown in parentheses are percentages for that category.

[b] Two-sided 95% confidence intervals around the difference (ciprofloxacin minus levofloxacin) in clinical success rates(cured and improved) were calculated for study centers enrolling 10 or more microbiologically evaluable subjects in each treatment group.

[c] Combined = centers that enrolled fewer than 10 evaluable subjects in either treatment group: Bernstein, Brankston, Dennis, Duckett, Durden, Epstein, File, Foster, Gallis, Irizarry, Israelski, Kern, Kirmani, Lipsky, Markel, Martel, McCabe, Montgomerie, Powers, Smith, Stark, Steidle, Young, and Zervos.

Table 9b. Clinical Success/Failure Rates and Confidence Intervals By Study Center:
FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[c]
	N[a]	Success[b]	N	Success	
Bruce	11	9 (82)	10	10 (100)	(-14.2, 50.5)
Childs	28	28 (100)	29	27 (93)	(-19.6, 5.8)
Pittmon	17	17 (100)	16	15 (94)	(-24.2, 11.7)
Other	57	51 (89)	49	39 (80)	(-25.6, 5.8)
Total	113	105 (93)	104	91 (88)	(-14.3, 3.4)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]Clinical success is defined as either clinical cure or clinical improvement. Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in clinical success rate.

Table 9c. Clinical Success/Failure Rates and Confidence Intervals By Study Center:
FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[c]
	N[a]	Success[b]	N	Success	
Richard	21	21 (100)	23	23 (100)	N/A
Other	24	20 (83)	33	30 (91)	(-13.9, 29.0)
Total	45	41 (91)	56	53 (95)	(-8.7, 15.7)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]Clinical success is defined as either clinical cure or clinical improvement. Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in clinical success rate.

Clinical Response by Pathogen

Clinical response rates for sponsor microbiologically evaluable subjects infected with uropathogens of interest alone or in combination with other pathogens are shown in Table 10a. E. coli and K. pneumoniae were the most prevalent pathogens across the two treatment groups. Clinical success rates (cured + improved) for these two commonly isolated pathogens were similar in the two treatment groups (94.6% and 96.9%, respectively, for levofloxacin and 94.9% and 91.3%, respectively, for ciprofloxacin). Table 10b summarizes clinical response by pathogen for FDA microbiologically evaluable patients with complicated UTI and Table 10c summarizes clinical response by pathogen for FDA microbiologically evaluable patients with acute pyelonephritis. The FDA analyses include only those pathogens requested by the sponsor in their label.

Table 10a. Clinical Response Rates for Subjects with Pathogens of Primary Interest: Sponsor Microbiologically Evaluable Subjects (Complicated UTI and Acute Pyelonephritis Combined)

(Study L91-058)

	Levofloxacin				Ciprofloxacin			
Pathogen from Urine Culture	N*	Cured	Improved	Failed	N*	Cured	Improved	Failed
Escherichia coli	32	81 (88.0)	6 (6.5)	5 (5.4)	99	90 (90.9)	4 (4.0)	5 (5.1)
Klebsiella pneumoniae	32	30 (93.8)	1 (3.1)	1 (3.1)	23	17 (73.9)	4 (17.4)	2 (8.7)
Proteus mirabilis	14	12 (85.7)	1 (7.1)	1 (7.1)	5	5(100.0)	0 (0.0)	0 (0.0)
Pseudomonas aeruginosa	12	8 (66.7)	2 (16.7)	2 (16.7)	7	5 (71.4)	1 (14.3)	1 (14.3)
Streptococcus faecalis	9	7 (77.8)	1 (11.1)	1 (11.1)	11	5 (45.5)	3 (27.3)	3 (27.3)
Enterobacter cloacae	9	8 (88.9)	0 (0.0)	1 (11.1)	4	3 (75.0)	1 (25.0)	0 (0.0)
Enterobacter aerogenes	4	3 (75.0)	0 (0.0)	1 (25.0)	8	5 (62.5)	1 (12.5)	2 (25.0)
Staphylococcus saprophyticus	6	5 (83.3)	0 (0.0)	1 (16.7)	5	5(100.0)	0 (0.0)	0 (0.0)

Numbers shown in parentheses are percentages for that category.
* N≥5 in either treatment group.
* N = Number of subjects who had that pathogen alone or in combination with other pathogens.

Table 10b. Clinical Response for Subjects with Pathogens of Primary Interest: FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

	Levofloxacin				Ciprofloxacin			
Pathogen	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Citrobacter freundii	2	1 (50)	0 (0)	1 (50)	3	2 (67)	0 (0)	1 (33)
Enterobacter cloacae	8	7 (88)	0 (0)	1 (13)	4	3 (75)	1 (25)	0 (0)
Escherichia coli	49	41 (84)	5 (10)	3 (6)	52	45 (87)	4 (8)	3 (6)
Klebsiella oxytoca	4	2 (50)	2 (50)	0 (0)	4	2 (50)	2 (50)	0 (0)
Klebsiella pneumoniae	26	25 (96)	1 (4)	0 (0)	14	10 (71)	2 (14)	2 (14)
Proteus mirabilis	9	7 (78)	1 (11)	1 (11)	2	2 (100)	0 (0)	0 (0)
Pseudomonas aeruginosa	10	8 (80)	2 (20)	0 (0)	7	5 (71)	1 (14)	1 (14)
Staphylococcus saprophyticus	0	0 (-)	0 (-)	0 (-)	0	0 (-)	0 (-)	0 (-)
Streptococcus agalactiae	0	0 (-)	0 (-)	0 (-)	1	0 (0)	0 (0)	1 (100)
Enterococcus faecalis	6	6 (100)	0 (0)	0 (0)	10	5 (50)	2 (20)	3 (30)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that pathogen alone or in combination with other pathogens.

Table 10c. Clinical Response for Subjects with Pathogens of Primary Interest: FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

	Levofloxacin				Ciprofloxacin			
Pathogen	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Escherichia coli	31	28 (90)	1 (3)	2 (6)	40	37 (93)	1 (3)	2 (5)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that pathogen alone or in combination with other pathogens.

Four sponsor microbiologically evaluable subjects had pathogens isolated from blood; all four subjects were clinical cures. E. coli was isolated from one levofloxacin-treated subject [redacted] and two ciprofloxacin-treated subjects and K. pneumoniae was isolated in one ciprofloxacin-treated subject [redacted]

Clinical response to therapy is summarized by diagnosis for subjects who were sponsor and FDA microbiologically evaluable in Tables 11a and 11b, respectively. Among sponsor microbiologically evaluable subjects in the levofloxacin treatment group, clinical success (cured plus improved) was achieved by 92.1% of subjects with complicated UTI, 92.2% of subjects with acute pyelonephritis, and 100% of subjects with uncomplicated UTI. In ciprofloxacin-treated subjects, the proportions of subjects with clinical success were 88.5%, 94.8%, and 100%, respectively.

Table 11a. Clinical Response Rate by Diagnosis: Sponsor Microbiologically Evaluable Subjects

(Study L91-058)

	Levofloxacin				Ciprofloxacin			
Diagnosis	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Complicated UTI	126	104 (82.5)	12 (9.5)	10 (7.9)	113	89 (78.8)	11 (9.7)	13(11.5)
Acute Pyelonephritis	51	46 (90.2)	1 (2.0)	4 (7.8)	58	51 (87.9)	4 (6.9)	3 (5.2)
Uncomplicated UTI	6	5 (83.3)	1 (16.7)	0 (0.0)	6	5 (83.3)	1 (16.7)	0 (0.0)

Numbers shown in parentheses are percentages for that category.

Table 11b. Clinical Response by Diagnosis: FDA Microbiologically Evaluable Subjects

	Levofloxacin				Ciprofloxacin			
Diagnosis	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Complicated UTI	113	93 (82)	12 (11)	8 (7)	104	79 (76)	12 (12)	13 (13)
Acute Pyelonephritis	45	40 (89)	1 (2)	4 (9)	56	49 (88)	4 (7)	3 (5)
Uncomplicated UTI	25	21 (84)	1 (4)	3 (12)	19	18 (95)	1 (5)	0 (0)
Total	183	154 (84)	14 (8)	15 (8)	179	146 (82)	17 (10)	16 (9)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that diagnosis.

Table 12 shows the clinical response rates for the sponsor microbiologically evaluable subjects by diagnosis and severity. Among the subjects in the levofloxacin treatment group, the proportion who achieved clinical success (cured plus improved) ranged from 80.0% (severe complicated UTI) to 100% (severe pyelonephritis). In ciprofloxacin-treated subjects, the proportion who achieved clinical success ranged from 75.0% (severe complicated UTI) to 100% (mild/moderate uncomplicated UTI).

Table 12. Clinical Response Rate by Diagnosis and Severity of Infection:
Sponsor Microbiologically Evaluable Subjects

(Study L91-058)

	Levofloxacin				Ciprofloxacin			
	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Complicated UTI								
Severe	5	4 (80.0)	0 (0.0)	1 (20.0)	4	3 (75.0)	0 (0.0)	1 (25.0)
Mild/Moderate	121	100 (82.6)	12 (9.9)	9 (7.4)	109	86 (78.9)	11 (10.1)	12 (11.0)
Acute Pyelonephritis								
Severe	2	2 (100.0)	0 (0.0)	0 (0.0)	5	4 (80.0)	0 (0.0)	1 (20.0)
Mild/Moderate	49	44 (89.8)	1 (2.0)	4 (8.2)	53	47 (88.7)	4 (7.5)	2 (3.8)
Total Complicated UTI/ Acute Pyelonephritis								
Severe	7	6 (85.7)	0 (0.0)	1 (14.3)	9	7 (77.8)	0 (0.0)	2 (22.2)
Mild/Moderate	170	144 (84.7)	13 (7.6)	13 (7.6)	162	133 (82.1)	15 (9.3)	14 (8.6)
Uncomplicated UTI								
Mild/Moderate	6	5 (83.3)	1 (16.7)	0 (0.0)	6	5 (83.3)	1 (16.7)	0 (0.0)

Numbers shown in parentheses are percentages for that category.

Clinical Signs and Symptoms

The proportions of sponsor microbiologically evaluable subjects with resolution or improvement of clinical signs and symptoms of UTI at the posttherapy visit are presented in Table 13. In general, for both the levofloxacin and ciprofloxacin treatment groups, individual symptoms resolved or improved in the majority (approximately 85% or more) of subjects with the exception of incontinence which resolved or improved in approximately 55% of subjects in each treatment group.

Table 13. Proportion of Subjects with Resolution [a] or Improvement [b] of Clinical Signs and Symptoms of UTI Based on Posttherapy Clinical Assessment:
Sponsor Microbiologically Evaluable Subjects (Complicated UTI and Acute Pyelonephritis Combined)

(Study L91-058)

	Levofloxacin				Ciprofloxacin			
Signs and Symptoms	Resolved[c]	(%)	Improved[c]	(%)	Resolved[c]	(%)	Improved[c]	(%)
Dysuria	94/108	(87.0)	10/108	(9.3)	92/108	(85.2)	11/108	(10.2)
Frequency	100/115	(87.0)	8/115	(7.0)	98/123	(79.7)	16/123	(13.0)
Urgency	82/95	(86.3)	7/95	(7.4)	95/114	(83.3)	8/114	(7.0)
CVA/Flank Pain	54/61	(88.5)	5/61	(8.2)	58/ 75	(77.3)	10/75	(13.3)
Chills	34/34	(100.0)	0/34	(0.0)	40/ 44	(90.9)	1/44	(2.3)
Fever	35/36	(97.2)	0/36	(0.0)	49/ 54	(90.7)	0/54	(0.0)
Incontinence	19/36	(50.0)	2/36	(5.3)	12/ 33	(36.4)	6/33	(18.2)
Nausea	16/16	(100.0)	0/16	(0.0)	19/ 21	(90.5)	0/21	(0.0)
Vomiting	5/ 5	(100.0)	0/ 5	(0.0)	6/ 7	(85.7)	0/ 7	(0.0)

[a] Sign or symptom present at admission (mild, moderate, or severe) and absent (none) at posttherapy evaluation.
[b] Signs and symptoms were graded as none, mild, moderate, or severe. Improvement was defined as a decrease in severity category without complete resolution.
[c] Denominator represents number of subjects with that sign or symptom at admission.
UTI = urinary tract infection; CVA = costovertebral angle.

Microbiologic Results

In vitro susceptibility of all pathogens isolated at admission in the sponsor modified intent-to-treat subjects is represented in Table 14.

Table 14. In Vitro Susceptibility of All Pathogens Isolated at Admission: Sponsor Modified Intent-to-Treat Subjects with an Admission Pathogen

(Study L91-058)

	No. (%)[a] of Pathogens			
Susceptibility of Pathogen	Levofloxacin		Ciprofloxacin	
Susceptible	221	(93.2%)	228	(94.2%)
Moderately Susceptible	6	(2.5%)	6	(2.5%)
Resistant	10	(4.2%)	8	(3.3%)
Unknown	10		10	
Total No. Pathogens[b]	247		252	

[a] Percentages were based on numbers of pathogens with known susceptibilities. Pathogens were isolated from 220 subjects in the levofloxacin group and 228 subjects in the ciprofloxacin group.
[b] Includes information for pathogens isolated from urine or blood.

Microbiologic Eradication Rates by Subject

The microbiologic eradication rates at the posttherapy visit for subjects who were sponsor microbiologically evaluable are summarized by treatment group and study center in Table 15a. Among sponsor microbiologically evaluable subjects in the levofloxacin treatment group with a diagnosis of complicated UTI or acute pyelonephritis, the eradication rate was 92.7% compared with 93.0% in the ciprofloxacin group. The confidence interval was [-5.4, 6.0] for the difference (ciprofloxacin minus levofloxacin) in eradication rates. Microbiologic eradication rates are summarized by treatment group and study center for FDA microbiologically evaluable patients with either complicated UTI or acute pyelonephritis in Table 15b, for FDA microbiologically evaluable patients with complicated UTI in Table 15c, and for FDA microbiologically evaluable patients with acute pyelonephritis in Table 15d. In all 3 FDA analyses, no statistically significant treatment differences are detected and the two drugs are considered therapeutically equivalent.

Table 15a: Microbiologic Eradication Rates and Confidence Intervals by Study Center: Sponsor Microbiologically Evaluable Subjects (Complicated UTI and Acute Pyelonephritis Combined)

(Study L91-058)

	Levofloxacin				Ciprofloxacin				
Investigator	N	Eradicated[a,b]		Persisted[a]	N	Eradicated[a,b]		Persisted[a]	95% Confidence Interval[c]
Bernstein	6	6	(100.0)	0 (0.0)	2	2	(100.0)	0 (0.0)	(. , .)
Brankston	3	3	(100.0)	0 (0.0)	1	1	(100.0)	0 (0.0)	(. , .)
Bruce	11	8	(72.7)	3 (27.3)	10	10	(100.0)	0 (0.0)	(-4.0, 58.6)
Childs	36	36	(100.0)	0 (0.0)	38	36	(94.7)	2 (5.3)	(-13.8, 3.3)
Dennis	1	1	(100.0)	0 (0.0)	0	0	(.)	0 (.)	(. , .)
Duckett	1	0	(0.0)	1 (100.0)	2	1	(50.0)	1 (50.0)	(. , .)
Durden	10	8	(80.0)	2 (20.0)	9	8	(88.9)	1 (11.1)	(. , .)
Epstein	2	2	(100.0)	0 (0.0)	0	0	(.)	0 (.)	(. , .)
Fila	1	1	(100.0)	0 (0.0)	1	1	(100.0)	0 (0.0)	(. , .)
Foster	0	0	(.)	0 (.)	1	1	(100.0)	0 (0.0)	(. , .)
Gallis	6	6	(100.0)	0 (0.0)	3	3	(100.0)	0 (0.0)	(. , .)
Irizarry	3	3	(100.0)	0 (0.0)	4	4	(100.0)	0 (0.0)	(. , .)
Ismaelski	0	0	(.)	0 (.)	1	1	(100.0)	0 (0.0)	(. , .)
Kern	2	2	(100.0)	0 (0.0)	2	2	(100.0)	0 (0.0)	(. , .)
Kimani	1	0	(0.0)	1 (100.0)	0	0	(.)	0 (.)	(. , .)
Lipsky	3	3	(100.0)	0 (0.0)	4	3	(75.0)	1 (25.0)	(. , .)
Markel	2	2	(100.0)	0 (0.0)	3	3	(100.0)	0 (0.0)	(. , .)
Marsal	6	6	(100.0)	0 (0.0)	9	9	(100.0)	0 (0.0)	(. , .)
McCabe	2	2	(100.0)	0 (0.0)	2	1	(50.0)	1 (50.0)	(. , .)
Montgomerie	6	6	(100.0)	0 (0.0)	3	3	(100.0)	0 (0.0)	(. , .)
Nicolle	16	14	(87.5)	2 (12.5)	10	9	(90.0)	1 (10.0)	(-27.2, 32.2)
Pitman	18	17	(94.4)	1 (5.6)	16	16	(100.0)	0 (0.0)	(-8.2, 19.3)
Powers	1	1	(100.0)	0 (0.0)	1	1	(100.0)	0 (0.0)	(. , .)
Richard	24	24	(100.0)	0 (0.0)	25	25	(100.0)	0 (0.0)	(-2.1, 2.1)
Smith	0	0	(.)	0 (.)	1	1	(100.0)	0 (0.0)	(. , .)
Stark	7	7	(100.0)	0 (0.0)	11	11	(100.0)	0 (0.0)	(. , .)
Steidle	3	0	(0.0)	3 (100.0)	3	1	(33.3)	2 (66.7)	(. , .)
Young	7	7	(100.0)	0 (0.0)	6	4	(66.7)	2 (33.3)	(. , .)
Zervos	1	1	(100.0)	0 (0.0)	3	2	(66.7)	1 (33.3)	(. , .)
Combined[d]	73	66	(90.4)	7 (9.6)	72	63	(87.5)	9 (12.5)	(-13.8, 8.0)
Total	177	164	(92.7)	13 (7.3)	171	150	(93.6)	12 (7.6)	(-6.4, 6.6)

[a] Eradication of all pathogens isolated for a subject at admission.

[b] Numbers shown in parentheses are percentages for that category.

[c] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rates were calculated for study centers enrolling 10 or more microbiologically evaluable subjects in each treatment group.

[d] Combined = centers that enrolled fewer than 10 microbiologically evaluable subjects in either treatment group: Bernstein, Brankston, Dennis, Duckett, Durden, Epstein, Fila, Foster, Gallis, Irizarry, Ismaelski, Kern, Kimani, Lipsky, Markel, Marsal, McCabe, Montgomerie, Powers, Smith, Stark, Steidle, Young, and Zervos.

Table 15b. Microbiologic Eradication Rates and Confidence Intervals By Study Center:
FDA Microbiologically Evaluable Subjects (Complicated UTI and Acute Pyelonephritis Combined)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Bruce	11	8 (73)	10	10 (100)	(-8.6, 63.1)
Childs	34	34 (100)	35	33 (94)	(-16.3, 4.9)
Pittmon	17	16 (94)	16	16 (100)	(-11.4, 23.1)
Richard	21	21 (100)	23	23 (100)	N/A
Other	75	68 (91)	76	66 (87)	(-15.2, 7.6)
Total	158	147 (93)	160	148 (93)	(-6.9, 5.8)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (cipro minus levo) in microbiologic eradication rate.

Table 15c. Microbiologic Eradication Rates and Confidence Intervals By Study Center:
FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Bruce	11	8 (73)	10	10 (100)	(-8.6, 63.1)
Childs	28	28 (100)	29	28 (97)	(-13.6, 6.7)
Pittmon	17	16 (94)	16	16 (100)	(-11.4, 23.1)
Other	57	52 (91)	49	42 (86)	(-18.8, 6.1)
Total	113	104 (92)	104	96 (92)	(-7.8, 8.3)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (cipro minus levo) in microbiologic eradication rate.

Table 15d. Microbiologic Eradication Rates and Confidence Intervals By Study Center:
FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Investigator	Levofloxacin		Ciprofloxacin		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Richard	21	21 (100)	23	23 (100)	N/A
Other	24	22 (92)	33	29 (88)	(-23.1, 15.5)
Total	45	43 (96)	56	52 (93)	(-13.7, 8.3)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (cipro minus levo) in microbiologic eradication rate.

Microbiologic Eradication Rates by Pathogen

The microbiologic eradication rates achieved at the posttherapy visit for sponsor microbiologically evaluable subjects in each treatment group are summarized by pathogen category and pathogen (N $ 5 for either treatment group) in Table 16a (only includes pathogens isolated from urine). The overall microbiologic eradication rates by pathogen in subjects with complicated UTI or acute pyelonephritis in the levofloxacin and ciprofloxacin treatment groups were 93.4% and 92.4%, with a 95% confidence interval of [-6.5, 4.4], for the difference between treatments (ciprofloxacin minus levofloxacin), assuming independence of multiple pathogens and multiple strains within a subject.

Table 16b summarizes microbiologic eradication rates by pathogen and pathogen category for FDA microbiologically evaluable subjects with complicated UTI. Table 16c summarizes the same information for FDA microbiologically evaluable subjects with acute pyelonephritis. Note: Eradication rates for individual pathogens (in FDA analyses) are shown only for those pathogens requested by the sponsor in their label.

Table 16a: Microbiologic Eradication Rates Summarized by Pathogen Category and Pathogen: Sponsor Microbiologically Evaluable Subjects (Complicated UTI and Acute Pyelonephritis Combined)

(Study L91-058)

Urine Cultures: Pathogen Category/Pathogen	Levofloxacin N	Levofloxacin Eradicated[a]	Ciprofloxacin N	Ciprofloxacin Eradicated[a]	95% Confidence Interval[b]
Pathogen Category					
Gram positive aerobic pathogens	20	18 (90.0)	22	15 (68.2)	(-47.8, 4.2)
Gram negative aerobic pathogens	178	167 (93.8)	162	155 (95.7)	(-3.2, 6.9)
Total by pathogen	198	185 (93.4)	184	170 (92.4)	(-6.5, 4.4)
Total by subject[c]	177	164 (92.7)	171	159 (93.0)	(-6.4, 6.0)
Pathogen[d]					
Escherichia coli	92	88 (95.7)	99	96 (97.0)	(-4.6, 7.2)
Klebsiella pneumoniae	32	31 (96.9)	23	22 (95.7)	(-13.7, 11.2)
Streptococcus faecalis	9	8 (88.9)	11	6 (54.5)	
Proteus mirabilis	14	13 (92.9)	6	6 (100.0)	
Pseudomonas aeruginosa	12	7 (58.3)	7	7 (100.0)	
Enterobacter cloacae	9	9 (100.0)	4	4 (100.0)	
Enterobacter aerogenes	4	4 (100.0)	8	7 (87.5)	
Staphylococcus saprophyticus	6	6 (100.0)	5	5 (100.0)	

[a] Numbers shown in parentheses are percentages for that category.
[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rates was 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] N≥5 for either treatment group.

Table 16b. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Pathogen Category/Pathogen	Levofloxacin		Ciprofloxacin		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	10	9 (90)	12	7 (58)	(-74.4, 11.0)
Gram-negative aerobic pathogens	118	111 (94)	101	96 (95)	(-5.9, 7.9)
Total by pathogen	128	120 (94)	113	103 (91)	(-10.1, 4.9)
Total by subject	113	104 (92)	104	96 (92)	(-7.8, 8.3)
Pathogen					
Citrobacter freundii	2	2 (100)	3	2 (67)	-
Enterobacter cloacae	8	8 (100)	4	4 (100)	-
Escherichia coli	48	45 (94)	52	51 (98)	(-5.5, 14.1)
Klebsiella oxytoca	4	4 (100)	4	4 (100)	-
Klebsiella pneumoniae	26	26 (100)	14	13 (93)	(-26.1, 11.8)
Proteus mirabilis	9	8 (89)	2	2 (100)	-
Pseudomonas aeruginosa	10	7 (70)	7	7 (100)	-
Staphylococcus saprophyticus	0	0 (-)	0	0 (-)	-
Streptococcus agalactiae	0	0 (-)	1	1 (100)	-
Enterococcus faecalis	6	6 (100)	10	6 (60)	-

[a] Numbers shown in parentheses are percentages for that category.

[b] A two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Table 16c. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Pathogen Category/Pathogen	Levofloxacin		Ciprofloxacin		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	8	7 (88)	9	7 (78)	-
Gram-negative aerobic pathogens	41	40 (98)	51	49 (96)	(-10.8, 7.8)
Total by pathogen	49	47 (96)	60	56 (93)	(-12.8, 7.7)
Total by subject	45	43 (96)	56	52 (93)	(-13.7, 8.3)
Pathogen					
Escherichia coli	31	31 (100)	40	38 (95)	(-14.6, 4.6)

[a] Numbers shown in parentheses are percentages for that category.

[b] A two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Among microbiologically evaluable subjects, four pathogens were isolated from blood (E. coli in one levofloxacin-treated subject and two ciprofloxacin-treated subjects, and K. pneumoniae in one ciprofloxacin-treated subject). All four pathogens were eradicated at posttherapy.

Microbiologic Eradication Rates by Diagnosis and Severity of Infection

The posttherapy microbiologic eradication rates for sponsor microbiologically evaluable subjects in each treatment group are presented by diagnosis and severity of infection in Table 17. Subjects with complicated UTI had infection eradication rates of 91.3% and 92.9% after treatment with levofloxacin and ciprofloxacin, respectively, whereas subjects with acute pyelonephritis had infection eradication rates of 96.1% and 93.1%, respectively. For the combined group of subjects with complicated UTI or acute pyelonephritis, microbiologic eradication rates were >90% for mild/moderate infections.

Table 17: Microbiologic Eradication Rates Summarized by Diagnosis and Severity of Infection: Sponsor Microbiologically Evaluable Subjects

(Study L91-058)

	Levofloxacin			Ciprofloxacin		
	N	Eradicated[a]	Persisted[b]	N	Eradicated[a]	Persisted[b]
Complicated UTI						
Total Severe By Pathogen	7	5 (71.4)	2 (28.6)	5	4 (80.0)	1 (20.0)
Total Severe By Subject	5	3 (60.0)	2 (40.0)	4	3 (75.0)	1 (25.0)
Total Mild/Moderate By Pathogen	135	126 (93.3)	9[c] (6.7)	117	108 (92.3)	9 (7.7)
Total Mild/Moderate By Subject	121	112 (92.6)	9 (7.4)	109	102 (93.6)	7 (6.4)
Total Complicated UTI By Pathogen	142	131 (92.3)	11[c] (7.7)	122	112 (91.8)	10 (8.2)
Total Complicated UTI By Subject	126	115 (91.3)	11 (8.7)	113	105 (92.9)	8 (7.1)
Acute Pyelonephritis						
Total Severe By Pathogen	2	2 (100.0)	0 (0.0)	5	4 (80.0)	1 (20.0)
Total Severe By Subject	2	2 (100.0)	0 (0.0)	5	4 (80.0)	1 (20.0)
Total Mild/Moderate By Pathogen	54	52 (96.3)	2 (3.7)	57	54 (94.7)	3 (5.3)
Total Mild/Moderate By Subject	49	47 (95.9)	2 (4.1)	63	60 (94.3)	3 (5.7)
Total Acute Pyelonephritis By Pathogen	56	54 (96.4)	2 (3.6)	62	58 (93.5)	4 (6.5)
Total Acute Pyelonephritis By Subject	51	49 (96.1)	2 (3.9)	58	54 (93.1)	4 (6.9)
Complicated UTI/Acute Pyelonephritis Combined						
Total Severe By Pathogen	9	7 (77.8)	2 (22.2)	10	8 (80.0)	2 (20.0)
Total Severe By Subject	7	5 (71.4)	2 (28.6)	9	7 (77.8)	2 (22.2)
Total Mild/Moderate By Pathogen	189	178 (94.2)	11[c] (5.8)	174	162 (93.1)	12 (6.9)
Total Mild/Moderate By Subject	170	159 (93.5)	11 (6.5)	162	152 (93.8)	10 (6.2)
Total Complicated UTI/Pyelo By Pathogen	198	185 (93.4)	13[c] (6.6)	184	170 (92.4)	14 (7.6)
Total Complicated UTI/Pyelo By Subject	177	164 (92.7)	13 (7.3)	171	159 (93.0)	12 (7.0)
Uncomplicated UTI						
Total Mild/Moderate By Pathogen	6	5 (83.3)	1 (16.7)	6	6 (100.0)	0 (0.0)
Total Mild/Moderate By Subject	6	5 (83.3)	1 (16.7)	6	6 (100.0)	0 (0.0)
Total Uncomplicated UTI By Pathogen	6	5 (83.3)	1 (16.7)	6	6 (100.0)	0 (0.0)
Total Uncomplicated UTI By Subject	6	5 (83.3)	1 (16.7)	6	6 (100.0)	0 (0.0)

Numbers shown in parentheses are percentages for that category.

[a] Eradication rates by subject reflect eradication of all pathogens isolated for a subject at admission.

[b] Categories of 'persisted' and 'unknown' combined to create persisted column.

[c] One subject (1602) in the levofloxacin group is erroneously miscategorized as having an unknown microbiologic response for this admission pathogen (*E coli*). The pathogen was, in fact, eradicated.

UTI = urinary tract infection; Pyelo = acute pyelonephritis.

Superinfection

In the sponsor microbiologically evaluable group, eight levofloxacin-treated subjects and six ciprofloxacin-treated subjects developed superinfections (See Table 18) . Of the 12 isolates with known susceptibility information, three were susceptible (or moderately susceptible) to both study drugs and nine were resistant to both study drugs.

Table 18: List of Subjects With Superinfections: Sponsor Microbiologically Evaluable Subjects

(Study L91-058)

Subject Number	Period	Pathogen	Type of Specimen	Susceptibility	
				Levofloxacin	Ciprofloxacin
Levofloxacin					
	Posttherapy	*Staphylococcus aureus*	Skin & Skin Tissue/ Exudate Culture	Unknown	Unknown
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Pseudomonas aeruginosa*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Unknown	Unknown
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Klebsiella pneumoniae*	Urine	Susceptible	Susceptible
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	On Therapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
Ciprofloxacin					
	Posttherapy	*Streptococcus agalactiae*	Urine	Susceptible	Susceptible
	Posttherapy	*Enterococcus*	Urine	Susceptible	Moderate
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Unknown
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant

Microbiologic Response at Long-Term Follow-Up

Of the 255 sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis for whom data were available at the long-term follow-up and for whom their long-term response was neither "unknown" nor "not applicable", 18 (14.3%) of 126 levofloxacin-treated subjects and 13 (10.1%) of 129 ciprofloxacin-treated subjects had a microbiologic relapse. In most cases the pathogens isolated from relapsed subjects were still susceptible to both levofloxacin and ciprofloxacin. Among sponsor microbiologically evaluable subjects, reinfections (i.e., an infection in which an organism other than the original admission pathogen was isolated) were seen in nine levofloxacin-treated subjects and 12 ciprofloxacin-treated subjects. In most cases, the isolates were found to be susceptible to both study drugs.

Summary of Key Efficacy Results

Clinical success rates and microbiologic eradication rates for patients with an admission pathogen are summarized for the levofloxacin and ciprofloxacin treatment groups for various sponsor analysis groups in Table 19. There was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response (See Table 20).

Table 19: Summary of Sponsor Key Efficacy Results: Clinical and Microbiologic Response Rates at Posttherapy for Subjects With Complicated UTI or Acute Pyelonephritis

(Study L91-058)

Response/Group	Levofloxacin Clinical Success or Microbiologic Eradication Rates[a]		Ciprofloxacin Clinical Success or Microbiologic Eradication Rates[a]		95% Confidence Interval[b]
Clinical Response					
Microbiologically Evaluable					
Complicated UTI	116/126	(92.1)	100/113	(88.5)	
Acute Pyelonephritis	47/ 51	(92.2)	55/ 58	(94.8)	
Complicated UTI/Acute Pyelonephritis	163/177	(92.1)	155/171	(90.6)	(-7.6, 4.7)
Intent-to-Treat					
Complicated UTI	171/197	(86.8)	164/188	(87.2)	
Acute Pyelonephritis	62/ 69	(89.9)	74/ 80	(92.5)	
Complicated UTI/Acute Pyelonephritis	233/266	(87.6)	238/268	(88.8)	(-4.4, 6.9)
Microbiologic Response					
Microbiologically Evaluable					
Complicated UTI	115/126	(91.3)	105/113	(92.9)	
Acute Pyelonephritis	49/ 51	(96.1)	54/ 58	(93.1)	
Complicated UTI/Acute Pyelonephritis	164/177	(92.7)	159/171	(93.0)	(-5.4, 6.0)
Modified Intent-to-Treat With an Admission Pathogen					
Complicated UTI	124/152	(81.6)	123/149	(82.6)	
Acute Pyelonephritis	50/ 57	(87.7)	61/ 70	(87.1)	
Complicated UTI/Acute Pyelonephritis	174/209	(83.3)	184/219	(84.0)	(-6.5, 8.0)

[a] Denominator for clinical success rate = cured + improved + failed + unable to evaluate. Denominator for microbiologic eradication rate = eradication + persistence + unknown.
[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in clinical success or microbiologic eradication rates.
NOTE: All microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a given subject at admission.
UTI = urinary tract infection.

Table 20: Summary of Sponsor Key Efficacy Results: Cross-Tabulation of Microbiologic Response Versus Clinical Response at Posttherapy for Microbiologically Evaluable Subjects With Complicated UTI or Acute Pyelonephritis

(Study L91-058)

	Clinical Response									
	Levofloxacin					Ciprofloxacin				
Microbiologic Response	N	Cured		Improved	Failed	N	Cured		Improved	Failed
Complicated UTI										
Eradicated	115	101	(87.8)	11 (9.6)	3 (2.6)	105	89	(84.8)	10 (9.5)	6 (5.7)
Persisted	11	3	(27.3)	1 (9.1)	7 (63.6)	8	0	(0.0)	1 (12.5)	7 (87.5)
Acute Pyelonephritis										
Eradicated	49	46	(93.9)	0 (0.0)	3 (6.1)	64	61	(94.4)	3 (4.6)	0 (0.0)
Persisted	2	0	(0.0)	1 (50.0)	1 (50.0)	4	0	(0.0)	1 (25.0)	3 (75.0)
Complicated UTI Acute Pyelonephritis										
Eradicated	164	147	(89.6)	11 (6.7)	6 (3.7)	169	140	(88.1)	13 (8.2)	6 (3.8)
Persisted	13	3	(23.1)	2 (15.4)	8 (61.5)	12	0	(0.0)	2 (16.7)	10 (83.3)

NOTE: All microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a given subject at admission.
UTI = urinary tract infection.

SAFETY RESULTS

Table 21 summarizes the incidence of adverse events by body system. The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal (GI) system and consisted primarily of nausea, diarrhea, and abdominal pain. The incidence of GI system adverse events was statistically significantly higher in the ciprofloxacin group (19.4%) than in the levofloxacin group (12.4%) with a 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) of [0.7, 13.1]. Although not statistically significant, the incidence of female reproductive system adverse events was also greater in ciprofloxacin-treated subjects (9.5%) than in levofloxacin-treated subjects (4.8%); these events consisted primarily of vaginitis. In addition, skin and appendages disorders were reported by a higher proportion of ciprofloxacin-treated subjects (5.0% vs. 2.5%) and vision disorders were reported by a higher proportion of levofloxacin-treated subjects (1.8% vs. 0.0%); this difference for vision disorders was statistically significant with a confidence interval of [-3.5, -0.1].

Table 21: Incidence of Adverse Events Summarized by Body System: Subjects Evaluable For Safety

(Study L91-058)

Body System	Levofloxacin (N=282) No.	(%)	Ciprofloxacin (N=279) No.	(%)	95% Confidence Interval[a]
Gastrointestinal System Disorders	35	(12.4)	54	(19.4)	(0.7, 13.1)
Central & Peripheral Nervous System Disorders	22	(7.8)	17	(6.1)	(-6.1, 2.7)
Body as a Whole--General Disorders	17	(6.0)	12	(4.3)	(-5.5, 2.1)
Psychiatric Disorders	10	(3.5)	10	(3.6)	(-3.2, 3.3)
Reproductive Disorders, Female[b]	8	(4.8)	16	(9.5)	(-1.1, 10.4)
Skin and Appendages Disorders	7	(2.5)	14	(5.0)	(-0.8, 5.9)
Respiratory System Disorders	6	(2.1)	6	(2.2)	(-2.5, 2.5)
Urinary System Disorders	6	(2.1)	1	(0.4)	(-3.8, 0.2)
Musculo-Skeletal System Disorders	5	(1.8)	2	(0.7)	(-3.1, 1.0)
Vision Disorders	5	(1.8)	0	(0.0)	(-3.5, -0.1)
Reproductive Disorders, Male	3	(2.5)	1	(0.9)	(-5.5, 2.2)
Neoplasms	2	(0.7)	3	(1.1)	(-1.4, 2.1)
Resistance Mechanism Disorders	2	(0.7)	7	(2.5)	(-0.5, 4.1)
Hearing and Vestibular Disorders	1	(0.4)	1	(0.4)	(-1.2, 1.2)
Special Senses Other, Disorders	1	(0.4)	0	(0.0)	(-1.2, 0.5)
Myo Endo Pericardial & Valve Disorders	1	(0.4)	1	(0.4)	(-1.2, 1.2)
Heart Rate and Rhythm Disorders	1	(0.4)	1	(0.4)	(-1.2, 1.2)
Vascular (Extracardiac) Disorders	1	(0.4)	3	(1.1)	(-0.9, 2.3)
Autonomic Nervous System Disorders	0	(0.0)	3	(1.1)	(-0.3, 2.5)
Liver and Biliary System Disorders	0	(0.0)	1	(0.4)	(-0.5, 1.2)
Metabolic and Nutritional Disorders	0	(0.0)	1	(0.4)	(-0.5, 1.2)
Endocrine Disorders	0	(0.0)	1	(0.4)	(-0.5, 1.2)
White Cell and Resistance Disorders	0	(0.0)	2	(0.7)	(-0.5, 1.9)
Total With Adverse Events (%)	94	(33.3)	165	(37.6)	(-3.8, 12.4)

[a] Two-sided 95% confidence interval around the difference between treatments (ciprofloxacin minus levofloxacin) in incidence of adverse events.

[b] Percentages calculated from the total number of women in each treatment group. The total number of women who received levofloxacin was 166 and the total number of women who received ciprofloxacin was 169.

Adverse events (primary terms) reported for at least 2.0% of subjects in either treatment group are presented in Table 22. In the levofloxacin group, no single adverse event was reported in $ 5% of subjects. Consistent with the higher percentage of gastrointestinal adverse events reported by ciprofloxacin-treated subjects as compared with levofloxacin-treated subjects, several specific gastrointestinal complaints were more common in the ciprofloxacin group (e.g., nausea, diarrhea, and abdominal pain) than in the levofloxacin group. A similar percentage of subjects in each group reported flatulence, vomiting, and dyspepsia.

Table 22: Incidence of Frequently Reported ($ 2.0%) Adverse Events
Summarized by Body System and Primary Term: Subjects Evaluable for Safety

(Study L91-058)

Body System/ Primary Term	Levofloxacin (N=282) No. Subjects	%	Ciprofloxacin (N=279) No. Subjects	%
All Body Systems	94	33.3	105	37.6
Central & Peripheral Nervous System Disorders	22	7.8	17	6.1
Headache	10	3.5	11	3.9
Dizziness	6	2.1	5	1.8
Gastrointestinal System Disorders	35	12.4	54	19.4
Nausea	12	4.3	23	8.2
Diarrhea	9	3.2	18	6.5
Flatulence	6	2.1	5	1.8
Vomiting	6	2.1	5	1.8
Abdominal Pain	4	1.4	12	4.3
Dyspepsia	4	1.4	7	2.5
Reproductive Disorders, Female[b]	8	4.8	16	9.5
Vaginitis	8	4.8	12	7.1

[a] Primary term reported by ≥2.0% of subjects in either treatment group.
[b] Percentages calculated from the total number of women in each treatment group. The total number of women who received levofloxacin was 165 and the total number of women who received ciprofloxacin was 169.

The majority of adverse events were assessed as mild or moderate in severity. Ten subjects in each treatment group reported one or more adverse events of marked severity (Table 23). Most of the marked adverse events were considered by the investigator as unrelated or remotely related to the study drug. None of the levofloxacin-treated subjects had marked drug-related (probably or definitely related to study drug) adverse events whereas marked drug-related adverse events were reported by two subjects in the ciprofloxacin group (diarrhea and vaginitis in one subject and abdominal pain and nausea in the second subject). Of the 20 subjects with marked adverse events, there was one subject who died (410 in the levofloxacin treatment group) and seven subjects who discontinued study drug treatment (two subjects in the levofloxacin treatment group and five subjects in the ciprofloxacin treatment group). Of these seven subjects who discontinued, the adverse event was considered serious or potentially serious in one levofloxacin-treated subject and three ciprofloxacin-treated subjects. Five additional subjects who did not discontinue the study (all in levofloxacin group) had marked adverse events that were considered serious or potentially serious. Eleven (3.9%) subjects in the levofloxacin treatment group and 15 (5.4%) subjects in the ciprofloxacin treatment group had adverse events considered by the investigator to be drug-related. Drug-related adverse events reported by $ 1.0% of levofloxacin-treated subjects were vaginitis (1.2%) and dizziness (1.1%). Drug-related adverse events reported by $ 1.0% of ciprofloxacin-treated subjects were vaginitis (3.6%), nausea (1.8%), and diarrhea (1.1%).

Table 23: Subjects With Adverse Events of Marked Severity

(Study L91-058)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship To Drug[a]
Levofloxacin				
	21	F	Agitation	Possible
			Pain	Possible
	63	F	Abdominal Pain	None
			Metastatic Adenocarcinoma of Pancreas[b]	None
			GI Hemorrhage[b]	None
			Intestinal Obstruction	None
			Nausea	None
			Vomiting	None
	61	M	Pseudomembranous Colitis[c]	None
	60	M	Convulsions[d]	Remote
			Mental Deficiency[d]	Remote
	66	M	Edema	Remote
	76	M	Myocardial Infarction[b]	None
			Urinary Retention[c]	None
	67	F	Retinal Detachment[c]	None
	66	M	Paralysis	Remote
	24	F	Pain	None
	75	F	Fracture Pathological[b,c]	None
Ciprofloxacin				
	23	F	Headache	Possible
	35	F	Moniliasis[c]	Remote
	66	F	Granulocytopenia[f]	Possible
	77	F	Diarrhea[c]	Probable
			Vaginitis	Definite
	43	F	Abdominal Pain	Probable
			Nausea	Probable
	61	F	Back Pain	None
	76	M	Neoplasm (Unspecified)	None
	48	M	Sepsis[b]	Remote
	62	F	Hepatic Function Abnormal	Possible
			Jaundice	Possible
	31	F	Headache	Remote

[a] Based on investigator's assessment.
[b] Fractured right elbow.
[c] Subject discontinued due to this adverse event. (See Table 28)
[d] Subject also had a markedly abnormal laboratory value. (See Table 33)
[e] Serious or potentially serious adverse event. (See Table 29)
[f] Subject subsequently died due to progression of her serious adverse event.

Discontinuations Due to Adverse Events

Twenty-six (4.6%) of the 561 subjects evaluable for safety discontinued the study drug due to adverse events, including 10 (3.5%) of the 282 subjects evaluable for safety in the levofloxacin treatment group and 16 (5.7%) of the 279 subjects evaluable for safety in the ciprofloxacin treatment group. A summary of discontinuations due to adverse events appears in Table 24.

Table 24: Subjects Who Discontinued Therapy Due to Adverse Events

(Study L91-058)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Study Day Of Onset[a]	Severity	Relationship to Study Drug[b]	Duration Of Therapy (Days)
Levofloxacin							
	29	M	Dizziness	1	Moderate	Probable	2
			Fatigue	1	Moderate	Probable	
	73	F	Nausea	3	Moderate	Remote	5
			Vomiting	3	Moderate	Remote	
	60	M	Convulsions[c]	4	Marked	Remote	5
			Mental Deficiency[c]	4	Marked	Remote	
	72	F	Dizziness	2	Moderate	Probable	2
			Muscle Weakness	2	Moderate	Probable	
			Nervousness	2	Moderate	Probable	
			Tremor	2	Moderate	Probable	
	53	F	Diarrhea	6	Moderate	Possible	7
	43	M	Abdominal Pain	2	Mild	Remote	2
			Anxiety	2	Mild	Remote	
			Asthenia	2	Mild	Remote	
			Headache	2	Mild	Remote	
			Maculopapular Rash	2	Mild	Remote	
	35	M	Abdominal Pain	2	Moderate	Probable	3
			Dizziness	2	Moderate	Probable	
			Insomnia	2	Moderate	Probable	
			Rash	2	Moderate	Probable	
	86	M	Paralysis	3	Marked	Remote	6
	73	F	Abdominal Pain	4	Moderate	Possible	7
			Diarrhea	4	Moderate	Possible	
	75	F	Palpitation	4	Mild	Possible	3
Ciprofloxacin							
	35	F	Chest Pain[c]	6	Moderate	Remote	6
			Dyspnea[c]	6	Moderate	Remote	
			Moniliasis[c]	7	Marked	Remote	
	88	F	Granulocytopenia[c]	2	Marked	Possible	5
	77	F	Diarrhea	6	Marked	Probable	6
	43	F	Abdominal Pain	2	Marked	Probable	3
			Nausea	3	Marked	Probable	
	27	F	Confusion	4	Mild	Possible	5
			Headache	5	Mild	Possible	
	33	M	Urticaria	1	Mild	Possible	1
	40	F	Nausea	2	Moderate	Possible	5
			Dizziness	4	Mild	Possible	
			Pruritus	4	Moderate	Possible	
	22	F	Diarrhea	4	Moderate	Possible	5
	29	M	Rash	1	Moderate	Possible	2
	48	M	Sepsis[c]	1	Marked	Remote	1
	65	F	Palpitation	1	Moderate	Possible	2
	41	M	Dizziness	1	Moderate	Possible	4
			Malaise	1	Moderate	Possible	
	77	F	Nausea	1	Moderate	Probable	1
	56	M	Cerebrovascular Disorder[c]	4	Moderate	None	4
	71	M	Eructation	3	Moderate	Possible	3
			Nausea	3	Moderate	Possible	
			Vomiting	3	Moderate	Possible	
	85	F	Asthenia	2	Moderate	Possible	2
			Dyspepsia	2	Moderate	Possible	
			Nausea	2	Moderate	Possible	
			Sweating Increased	2	Moderate	Possible	

a Relative to start of therapy (Day 1).
b Based on investigator's assessment.
c Transient ischemic attack.
‡ Serious or potentially serious adverse event.
** Subject also had a markedly abnormal laboratory value.

Serious or Potentially Serious Adverse Events, Including Deaths

Fifteen (5.3%) subjects in the levofloxacin treatment group and eight (2.9%) subjects in the ciprofloxacin treatment group reported a serious or potentially serious adverse event during therapy or up to approximately one month after the end of study drug administration (Table 25).

Three levofloxacin-treated subjects) subsequently died (approximately three weeks to three months after the end of study drug administration) from complications related to their serious adverse events. The investigators considered the deaths of these subjects to be remotely related or unrelated to study drug treatment. Of the 23 subjects with serious or potentially serious adverse events, five subjects withdrew from the study because of their adverse event. In all but two cases, the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug; one levofloxacin-treated subject ([redacted]-cerebrovascular disorder-transient ischemic attacks), and one ciprofloxacin-treated subject ([redacted] granulocytopenia) had events that were considered possibly related to the study drug.

Table 25: Subjects With Serious or Potentially Serious Adverse Events

(Study L91-058)

Subject Number	Age	Sex	Adverse Event	Day of Onset[a]	Severity	Relationship To Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	63	F	GI Hemorrhage	20 (10 PT)	Marked	None	10
			Intestinal Ulceration	21 (11 PT)	Moderate	None	
			Metastatic Adenocarcinoma of Pancreas	24 (14 PT)	Marked	None	
	68	M	Cerebrovascular Disorder[c]	13 (3 PT)	Moderate	Possible	10
	61	M	Pseudomembranous Colitis	22 (14 PT)	Marked	None	8
	60	M	Convulsions	4	Marked	Remote	5
			Mental Deficiency	4	Marked	Remote	
	64	M	Respiratory Insufficiency[d]	31 (21 PT)	–	Remote	10
			Cholelithiasis[e]	21 (11 PT)	–	Remote	
	76	M	Myocardial Infarction	31 (21 PT)	Marked	None	10
			Urinary Retention	41 (31 PT)	Marked	None	
	48	F	MS Aggravated	14 (3 PT)	Moderate	None	11
	68	F	Neoplasm Malignant Aggravated[f]	25 (14 PT)	–	None	11
	67	F	Dyspnea	27 (16 PT)	Moderate	Remote	11
			Edema	27 (16 PT)	Moderate	Remote	
			Cardiac Failure[g]	27 (16 PT)	–	Remote	
	67	F	Retinal Detachment	19 (8 PT)	Marked	None	11
	73	M	Hematuria	23 (13 PT)	Moderate	None	10
			Renal Carcinoma[h]	23 (13 PT)	–	Remote	
	76	F	Syncope	24 (14 PT)	Moderate	None	10
			Arrhythmia[i]	24 (14 PT)	–	Remote	
			Peripheral Ischemia[c]	24 (14 PT)	–	Remote	
	35	M	Vomiting[j]	18 (8 PT)	Moderate	None	10
	75	F	Fracture Pathological[k]	11 (1 PT)	Marked	None	10
	51	M	Pulmonary Carcinoma[l]	14 (11 PT)	–	Remote	3
Ciprofloxacin							
	64	F	Skin Neoplasm Malignant (SCC)	29 (19 PT)	Mild	None	10
	74	F	Skin Neoplasm Malignant (SCC)	9	Moderate	None	10
	35	F	Chest Pain	6	Moderate	Remote	6
			Dyspnea	6	Moderate	Remote	
			Moniliasis	7 (1 PT)	Marked	Remote	
	60	F	Abscess	7	Moderate	None	7
	68	F	Granulocytopenia	2	Marked	Possible	5
	48	M	Sepsis	1	Marked	Remote	1
	56	M	Cerebrovascular Disorder[c]	4	Moderate	None	4
			Chest Pain	15 (11 PT)	Moderate	None	
	72	F	Angina Pectoris[f]	32 (22 PT)	Moderate	None	10

[a] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy relative to the last day of study drug administration.

[b] Based on investigator's assessment.

[c] Transient ischemic attack.

[d] This serious adverse event occurred after the scheduled posttherapy visit and therefore does not appear on the case report form or in the data base for this individual study report. However, this event was collected as part of the RJWPRI serious adverse event reporting data base and therefore is reflected in the data base for the NDA Integrated Safety Summary.

[e] This adverse event does not appear in the individual study report data base but was captured as serious in the RWJPRI serious adverse event reporting data base. It is therefore reflected as serious in the data base for the NDA Integrated Safety Summary.

[f] This serious adverse event, which appears as non-serious in the individual study report data base, was captured as serious in the RWJPRI serious adverse event reporting data base; it is therefore reflected as serious in the data base for the NDA Integrated Safety Summary.

[g] Fractured right elbow.

[h] An IND safety report was filed with the FDA for this subject.

[i] Subject subsequently died due to progression of the serious adverse event.

* Subject discontinued due to this adverse event.
** Subject also had markedly abnormal laboratory value.
NOTE: SCC=squamous cell carcinoma.

Clinical Laboratory Tests

There were no clinically significant mean changes from baseline for any laboratory analyte in the levofloxacin-treated or ciprofloxacin-treated group, with comparable results in both groups. A summary of markedly abnormal laboratory values after therapy start in subjects with admission data available is shown in Table 26. A list of subjects experiencing marked treatment-emergent abnormalities is presented in Table 27.

Table 26. Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

(Study L91-058)

Laboratory Test	Levofloxacin		Ciprofloxacin	
	Proportion*	%	Proportion	%
Blood Chemistry				
Elevated Glucose	1/254	0.4	3/247	1.2
Decreased Glucose	4/254	1.6	4/247	1.6
Decreased Potassium	0/257	0.0	1/250	0.4
Elevated LDH	1/257	0.4	0/250	0.0
Elevated Uric Acid	1/260	0.4	0/255	0.0
Elevated Creatinine	0/260	0.0	1/255	0.4
Elevated Alkaline Phosphatase	1/258	0.4	0/253	0.0
Elevated SGOT	1/260	0.4	3/255	1.2
Elevated SGPT	2/260	0.8	2/255	0.8
Hematology				
Decreased Neutrophils	0/250	0.0	1/244	0.4
Decreased Lymphocytes	3/250	1.2	0/244	0.0

*Numerator = number of subjects with a treatment-emergent markedly abnormal test value and denominator = number of subjects evaluable (i.e., admission and posttherapy data available) for that analyte.

Table 27: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

(Study L91-058)

Subject Number	Age	Sex	Lab Test[a] (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[b]	Duration of Therapy (Days)
Levofloxacin							
	23	M	SGPT (>75 IU/L)	27.00	67.00	20 (9 PT)	11
	35	F	Lymphocytes (<1.0 x 10^9/µL)	1.95	0.25	15 (5 PT)	10
	27	F	Glucose (<70 or >200 mg/dL)	66.00	43.00	15 (5 PT)	10
	78	F	Uric Acid (>10.0 mg/dL)	6.7	11.70	15 (5 PT)	10
	73	F	Lymphocytes (<1.0 x 10^9/µL)	1.69	0.91	5 (1 PT)	5
	25	F	Glucose (<70 or >200 mg/dL)	94.00	682.00	19 (9 PT)	11
	23	M	Glucose (<70 or >200 mg/dL)	102.00	68.00	19 (9 PT)	11
	82	M	Alkaline Phosphatase (>250 IU/L) SGOT (>75 IU/L) SGPT (>75 IU/L)	124.00 29.00 23.00	365.00[c] 91.00[c] 67.00[c]	1[c] 1[c] 1[c]	10
	33	M	Glucose (<70 or >200 mg/dL)	337.00	64.00	15 (5 PT)	10
	74	M	Glucose (<70 or >200 mg/dL)	113.00	68.00	15 (5 PT)	10
	74	M	Lactic Dehydrogenase (>600 IU/L) Lymphocytes (<1.0 x 10^9/µL)	785.00 1.35	946.00 0.88	21 (10 PT) 21 (10 PT)	11
Ciprofloxacin							
	34	M	Potassium (<3.0 or >5.0 mEq/L)	4.20	2.60	15 (5 PT)	10
	45	M	Glucose (<70 or >200 mg/dL)	122.00	68.00	20 (9 PT)	11
	43	M	SGOT (>75 IU/L)	163.00	334.00	15 (5 PT)	10
	88	F	Neutrophils (<1.0 x 10^9/µL)	2.94	0.78	5 (1 PT)	5
	79	F	Creatinine (>1.5 mg/dL)	1.00	1.80	15 (5 PT)	11
	63	F	Glucose (<70 or >200 mg/dL)	95.00	69.00	15 (5 PT)	10
	53	F	SGOT (>75 IU/L) SGPT (>75 IU/L)	41.00 72.00	123.00 179.00	17 (7 PT) 17 (7 PT)	10
	71	M	Glucose (<70 or >200 mg/dL)	122.00	66.00	15 (5 PT)	10
	45	F	SGOT (>75 IU/L) SGPT (>75 IU/L)	41.00 21.00	99.00 65.00	5 (1 PT) 5 (1 PT)	5
	40	M	Glucose (<70 or >200 mg/dL)	164.00	277.00	23 (11 PT)	12
	62	M	Glucose (<70 or >200 mg/dL)	105.00	69.00	15 (5 PT)	10
	68	F	Glucose (<70 or >200 mg/dL)	166.00	307.00	19 (9 PT)	11
	71	F	Glucose (<70 or >200 mg/dL)	110.00	224.00	15 (5 PT)	10

a Only range given in table.
b Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy, relative to the last day of study drug administration.
c Abnormal values represent repeat admission tests performed 1½ hours after the admission value on Day 1; see narrative for additional explanation.
* Subject discontinued due to adverse event.
‡ Subject also had serious or potentially serious adverse event.

SUMMARY AND DISCUSSION

For the sponsor microbiologically evaluable group, subjects with complicated UTI had infection eradication rates of 91.3% and 92.9% after treatment with levofloxacin and ciprofloxacin, respectively, and subjects with acute pyelonephritis had infection eradication rates of 96.1% and 93.1%, respectively. In subjects with a diagnosis of complicated UTI or acute pyelonephritis, levofloxacin treatment resulted in 95.7% eradication of E. coli from urine and 96.9% eradication of K. pneumoniae from urine versus 97.0% and 95.7% eradication in the ciprofloxacin treatment group. When the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success", levofloxacin treatment resulted in 92.1% clinical success compared to 90.6% for ciprofloxacin subjects with a 95% confidence interval for the difference of [-7.6, 4.7]. Among all pathogens isolated at admission, 17 pathogens were ultimately identified as resistant to levofloxacin versus 22 for ciprofloxacin. In addition, four of

the 22 ciprofloxacin-resistant pathogens were fully susceptible to levofloxacin.

The overall incidence of adverse events in the levofloxacin and ciprofloxacin treatment groups was very similar, 33.3% and 37.6%, respectively. Gastrointestinal system (GI) adverse events were the most common adverse events in both treatment groups and were reported by a statistically significantly higher proportion of ciprofloxacin-treated subjects (19.4%) than levofloxacin-treated subjects (12.4%). The majority of adverse events were assessed as mild or moderate in severity. Eleven (3.9%) subjects in the levofloxacin treatment group and 15 (5.4%) subjects in the ciprofloxacin treatment group had adverse events considered by the investigator to be drug-related. Fifteen (5.3%) subjects in the levofloxacin treatment group and eight (2.9%) subjects in the ciprofloxacin group reported serious or potentially serious adverse events, most of which were unrelated or remotely related to the study drug. Three levofloxacin-treated subjects died approximately three weeks to three months after the end of study drug administration. These deaths were considered by the investigators to be unrelated or remotely related to study drug.

CONCLUSIONS

Levofloxacin was safe, well-tolerated and effective in the treatment of subjects with complicated urinary tract infections or acute pyelonephritis. Microbiologic eradication rates in the levofloxacin treatment group were therapeutically equivalent to those observed in the ciprofloxacin group in both the sponsor analysis (sponsor microbiologically evaluable patients with either complicated UTI or acute pyelonephritis) and FDA analyses (FDA microbiologically evaluable patients with complicated UTI and FDA microbiologically evaluable patients with acute pyelonephritis). Moreover, clinical cure rates were therapeutically equivalent to those of ciprofloxacin for both sponsor and FDA analyses (same patient groups as in the previous sentence).

Microbiologic eradication rates in microbiologically evaluable subjects (from this study alone) support the use of levofloxacin for the treatment of complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. However, the numbers of patients with other organisms were too low (in this study) to support the use of levofloxacin for the treatment of complicated UTI due to other organisms.

Because 100 percent of 31 acute pyelonephritis patients were eradicated of E. coli, this study (alone) supports the use of levofloxacin for acute pyelonephritis due to *E. coli*.

STUDY L91-059

TITLE

A multi-center, randomized, unblinded study to compare the safety and efficacy of oral levofloxacin with that of lomefloxacin HCL in the treatment of complicated urinary tract infections in adults.

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OBJECTIVES

The objective of this study was to compare the safety and efficacy of 250 mg of levofloxacin administered orally once daily for seven to 10 days with that of 400 mg of lomefloxacin administered orally once daily for 14 days in the treatment of complicated UTI or acute pyelonephritis due to susceptible organisms in adults.

STUDY DESIGN

The schedule of assessments are described in Table 1. The study design was similar to study L91-058.

Table 1: Schedule of Assessments

(Study L91-059)

Assessment/Procedure	Admission (Day 1)	During Therapy (Days 3-5)	Posttherapy (5-9 days PT)[a]	Long-Term Follow-Up (4-6 weeks PT)
Pertinent Medical History	X			
Pregnancy Test[b]	X		X	
Study Drug Administration	X———	———X[c]		
Efficacy Evaluations: (see Section III.H.2.)				
Clinical:				
-Clinical Signs and Symptoms	X		X	X
-Clinical Response Rating			X	
Microbiologic:				
-Urine Culture	X	X	X	X
-Susceptibility Test	X	X	X	X
-Blood Culture	X[d]	X[e]	X[e]	
Safety Assessments: (see Section III.H.4.)				
Adverse Events		X	X	
Clinical Laboratory Tests:				
-Hematology	X		X	
-Chemistry	X		X	
-Urinalysis	X	X	X	X
Pertinent Physical Examination (including Vital Signs)	X		X	

[a] Or upon early withdrawal.
[b] Performed on all women of childbearing potential.
[c] Levofloxacin was to be administered for 7 to 10 days and lomefloxacin was to be administered for 14 days.
[d] Performed only if indicated (if bacteremia suspected).
[e] Performed if positive at admission.
PT=Posttherapy

STUDY POPULATION

Approximately 600 subjects, men and women who were 18 years of age or older and had a diagnosis of complicated UTI or acute pyelonephritis, were to be enrolled in this study to attain a sample size of at least 147 microbiologically evaluable subjects per treatment group for efficacy analysis.

MAIN DIFFERENCES BETWEEN STUDY L91-058 AND L91-059

CHARACTERISTIC	STUDY L91-058	STUDY L91-059
Blinding	Double blinded	Unblinded
Planned number of subjects	600 subjects	500 subjects

Analyses Planned

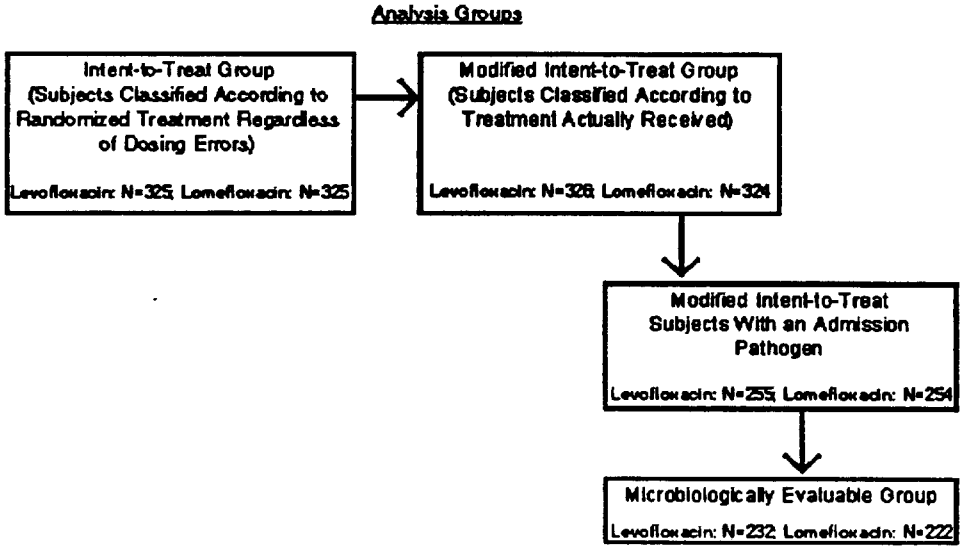
Approximately 600 subjects were to be enrolled into the study to provide 294 microbiologically evaluable subjects, a minimum of 147 subjects per treatment group. Assuming infection eradication rates of 89% for lomefloxacin and 85% for levofloxacin and a significance level of 2.5%, 147 microbiologically evaluable subjects per treatment group were required to demonstrate, with 80% power, that the difference (lomefloxacin minus levofloxacin) in infection eradication rates was less than 15%.

Sponsor's Analysis Populations

The analysis groups were:

- Intent-to-Treat — adheres strictly to randomization; thus subjects are included in their assigned treatment group regardless of any dosing or dispensing errors.
- Modified Intent-to-Treat — takes drug dispensing errors into account by grouping subjects according to the drug actually received. These two approaches (modified intent-to-treat and intent-to-treat) classified only three subjects differently; two were randomized to treatment with lomefloxacin but received levofloxacin and one was randomized to treatment with levofloxacin but received lomefloxacin (*note: DAIDP would consider this an "intent-to-treat" analysis where dispensing errors are taken into account*).
- Modified Intent-to-Treat with an Admission Pathogen — which represents those subjects in the modified intent-to-treat group who had a pathogen isolated at admission (*note: DAIDP terms this "modified intent-to-treat"*).
- Microbiologically evaluable subjects -- which represent subjects with complicated UTI or acute pyelonephritis according to the protocol-specified evaluability criteria.

The relationship between these groups is represented below:



RESULTS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Six hundred fifty subjects were enrolled in this study at 29 of the 30 centers. The sponsor intent-to-treat group included 325 subjects who were randomized to the levofloxacin treatment group and 325 subjects who were randomized to the lomefloxacin treatment group. The demographic and baseline characteristics for the sponsor modified intent-to-treat group are summarized in Table 2 and were comparable between the levofloxacin and lomefloxacin groups.

Table 2. Demographic and Baseline Characteristics: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

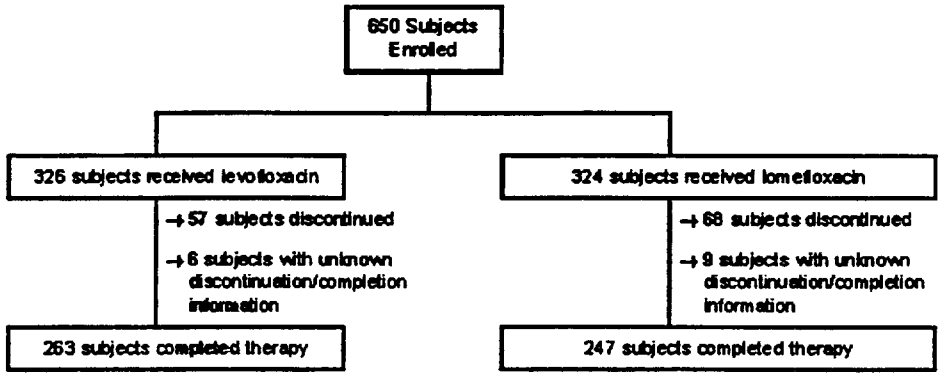
	Levofloxacin (N=326)		Lomefloxacin (N=324)		Overall Total (N=650)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	124	(38.0)	105	(32.4)	229	(35.2)
Women	202	(62.0)	219	(67.6)	421	(64.8)
Race						
Caucasian	239	(73.3)	234	(72.2)	473	(72.8)
Black	75	(23.0)	71	(21.9)	146	(22.5)
Oriental	1	(0.3)	0	(0.0)	1	(0.2)
Hispanic	10	(3.1)	18	(5.6)	28	(4.3)
Other	1	(0.3)	1	(0.3)	2	(0.3)
Age (Years)						
≤45	64	(19.6)	73	(22.5)	137	(21.1)
46-64	76	(23.3)	94	(29.0)	170	(26.2)
≥65	186	(57.1)	157	(48.5)	343	(52.8)
N	326		324		650	
Mean±SD	62.5±17.3		59.9±17.0		61.2±17.2	
Range	[redacted]		[redacted]		[redacted]	
Weight (lbs)						
N	311		314		625	
Mean±SD	167.2±35.0		169.6±37.7		168.4±36.4	
Range	[redacted]		[redacted]		[redacted]	
Missing	15		10		25	
Height (inches)						
N	292		299		591	
Mean±SD	66.0±4.42		65.7±4.02		65.8±4.22	
Range	[redacted]		[redacted]		[redacted]	
Missing	34		25		59	
Diagnosis						
Complicated UTI	232	(71.2)	230	(71.0)	462	(71.1)
Acute Pyelonephritis	55	(16.9)	56	(17.3)	111	(17.1)
Uncomplicated UTI	39	(12.0)	38	(11.7)	77	(11.8)
Severity						
Complicated UTI						
Severe	10	(4.3)	5	(2.2)	15	(3.2)
Mild/Moderate	222	(95.7)	225	(97.8)	447	(96.8)
Acute Pyelonephritis						
Severe	4	(7.3)	3	(5.4)	7	(6.3)
Mild/Moderate	51	(92.7)	53	(94.6)	104	(93.7)
Uncomplicated UTI						
Severe	0	(0.0)	1	(2.6)	1	(1.3)
Mild/Moderate	39	(100.0)	37	(97.4)	76	(98.7)

NOTE: Values represent number of subjects except as otherwise indicated.
UTI = Urinary tract infection.

DISCONTINUATION/COMPLETION INFORMATION

Discontinuation information for the sponsor modified intent-to-treat group is provided in Figure 1.

Figure 1: Discontinuation/Completion Information: Modified Intent-to-Treat Subjects (Study L91-059)



The reasons for premature discontinuation are summarized in Table 3.

Table 3: Reasons for Premature Discontinuation of Therapy: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

	Levofloxacin (N=326)		Lomefloxacin (N=324)	
Reason	No.	(%)[a]	No.	(%)[a]
No Admission Pathogen	41	(12.8)	38	(12.1)
Adverse Event	9	(2.8)	18	(5.7)
Resistant Pathogen[b]	3	(0.9)	6	(1.9)
Clinical Failure	0	(0.0)	4	(1.3)
Other	4[c]	(1.3)	2[d]	(0.6)
Total Discontinued	57	(17.8)	68	(21.6)
Total with Discontinuation/Completion Information	320		315	
Total with Unknown Discontinuation/Completion Information	6		9	

[a] Percentages based on total number with discontinuation/completion information.

[b] Subjects enrolled prior to the second protocol amendment (March 8, 1994) were to be discontinued if a resistant pathogen was isolated at admission.

[c] Subject [redacted] was discontinued after receiving amoxicillin for treatment of an adverse event (eye abnormality - pterygium excision). Subject [redacted] received two doses of levofloxacin and was dropped from the study per the investigator's decision because he was found to have a history of seizures and was taking phenytoin. Subject [redacted] was discontinued after receiving three doses because of a lab error (no urine culture and sensitivity testing done on admission). Subject [redacted] took one dose of levofloxacin and was then dropped from the study when she was discharged from the hospital and study drug was not sent with her.

[d] Subject [redacted] was asymptomatic at admission and was withdrawn by the investigator at the request of RWJPRI after receiving four doses of lomefloxacin. Subject [redacted] was withdrawn after receiving five doses because her admission urine specimen was contaminated and an infecting pathogen could not be identified.

DOSAGE INFORMATION

The extent of exposure to therapy is shown by treatment group in Table 4 for the sponsor modified intent-to-treat group.

Table 4: Extent of Exposure to Therapy: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

Extent of Therapy	Levofloxacin (N=326)	Lomefloxacin (N=324)
Days on Therapy*		
Unknown	6	8
1	2	2
2	8	4
3	4	11
4	17	15
5	12	13
6	5	6
7	4	5
8	4	3
9	3	4
10	256	6
11	1	1
12	2	1
13	0	3
14	0	236
15	2	5
16	0	1
Mean±SD	9.1±2.3	12.0±3.8
Median	10	14
Number of Doses		
Total with Dosing Information	321	316
Total Unknown Dosing Information	5	8
Mean±SD	9.0±2.4	12.1±3.8
Median	10	14
Range	[redacted]	[redacted]

NOTE: The scheduled dosages were levofloxacin 250mg po q24h for 7-10 days and lomefloxacin 400mg po q24h for 14 days.

*Days on therapy was defined as (last day - first day) + 1.

EFFICACY RESULTS

The total number of subjects evaluable by the sponsor for microbiologic efficacy at each study center is shown in Table 5. Two hundred thirty-two (71.2%) subjects in the levofloxacin group and 222 (68.5%) in the lomefloxacin group were microbiologically evaluable. The primary reasons (subjects counted only once) for exclusion from the microbiologically evaluable group are summarized in Table 6. The main reasons that subjects in both treatment groups were not evaluable was absence of bacteriologically proven infection.

Table 5. Number of Subjects by Sponsor Analysis Group and Center

(Study L91-059)

	Levofloxacin			Lomefloxacin		
Investigator*	Modified Intent-to Treat	Microbiologic Efficacy		Modified Intent-to Treat	Microbiologic Efficacy	
Bakule	12	8	(66.7)	12	9	(75.0)
Coburn	7	1	(14.3)	8	2	(25.0)
Collins	6	3	(50.0)	6	1	(16.7)
Cox	40	37	(92.5)	39	37	(94.9)
Deebele	24	16	(66.7)	24	13	(54.2)
Feris	29	17	(58.6)	28	12	(42.9)
Fuselier	0	0	(.)	1	1	(100.0)
Green	2	1	(50.0)	2	2	(100.0)
Griffin	4	3	(75.0)	6	3	(50.0)
Jemsek	8	3	(37.5)	7	1	(14.3)
Kane	4	3	(75.0)	2	1	(50.0)
Keeler	3	2	(66.7)	2	2	(100.0)
King	30	27	(90.0)	31	25	(80.6)
Klimberg	62	54	(87.1)	62	52	(83.9)
Koper	2	2	(100.0)	2	2	(100.0)
Leatherman	1	0	(0.0)	2	1	(50.0)
Malek	22	16	(72.7)	21	14	(66.7)
May	3	3	(100.0)	3	3	(100.0)
Mccrone	4	2	(50.0)	2	2	(100.0)
Rajter	2	1	(50.0)	5	1	(20.0)
Reid	9	4	(44.4)	8	5	(62.5)
Sarshik	10	9	(90.0)	10	9	(90.0)
Serfer	2	1	(50.0)	3	2	(66.7)
Tuttle	8	6	(75.0)	7	6	(85.7)
Urich	2	0	(0.0)	2	1	(50.0)
Valenzuela	10	4	(40.0)	10	3	(30.0)
Witt	0	0	(.)	1	1	(100.0)
Witten	12	3	(25.0)	9	3	(33.3)
Zinner	8	6	(75.0)	9	8	(88.9)
Total	**326**	**232**	**(71.2)**	**324**	**222**	**(68.5)**

Numbers shown in parentheses are percentages for that category.
*One investigator (Finnerty) did not enroll any subjects.

Table 6: Primary Reasons for Microbiologic NonEvaluability: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

Reasons	Levofloxacin (N=326)		Lomefloxacin (N=324)	
Infection Not Bacteriologically Proven	70		70	
Inappropriate Bacteriologic Culture	11		11	
Insufficient Course of Therapy	6		13	
No Posttherapy Evaluation	3		5	
Effective Concomitant Therapy	2		1	
Other Protocol Violation	1[b]		0	
Unevaluable for Safety	1		2	
Total Unevaluable For Microbiologic Efficacy	94	(28.8%)	102	(31.5%)

*Subjects counted only once.
[b]Subject [redacted] took 125 mg of levofloxacin twice daily and not 250 mg once daily as prescribed.

Demographic and Baseline Characteristics

The demographic and baseline characteristics for sponsor microbiologically evaluable subjects are shown in Table 7 and were comparable to those previously described for the sponsor modified intent-to-treat group.

Table 7: Demographic and Baseline Characteristics: Sponsor Microbiologically Evaluable Subjects

(Study L91-059)

	Levofloxacin (N=232)	Lomefloxacin (N=222)
Sex		
Men	88	73
Women	144	149
Race		
Caucasian	171	164
Black	54	51
Oriental	1	0
Hispanic	6	7
Age (Years)		
≤45	41	40
46-64	52	64
≥65	139	118
N	232	222
Mean±SD	63.6±17.1	[redacted]
Range	[redacted]	[redacted]
Weight (lbs)		
N	224	217
Mean±SD	168±33.9	169±36.8
Range	[redacted]	[redacted]
Missing	8	5
Height (inches)		
N	210	204
Mean±SD	66.0±4.32	65.8±3.89
Range	[redacted]	[redacted]
Missing	22	18
Diagnosis		
Complicated UTI	171	165
Acute Pyelonephritis	38	39
Uncomplicated UTI	23	18
Severity		
Complicated UTI		
Severe	6	4
Mild/Moderate	165	161
Acute Pyelonephritis		
Severe	4	2
Mild/Moderate	34	37
Uncomplicated UTI		
Mild/Moderate	23	18

NOTE: Values represent numbers of subjects unless otherwise indicated.
UTI = urinary tract infection.

Clinical Outcome

Sponsor Results

The clinical response to therapy for subjects with complicated UTI or acute pyelonephritis who were sponsor microbiologically evaluable is summarized by treatment group and study center in Table 8a. Among sponsor microbiologically evaluable subjects in the levofloxacin treatment group, 86.6% were cured and 6.7% were improved at the posttherapy visit (five to nine days after completion of therapy), compared with 81.9% and 7.8% in the lomefloxacin group. Fourteen (6.7%) subjects in the levofloxacin treatment group and 21(10.3%) subjects in the lomefloxacin treatment group failed treatment.

FDA Results

Clinical response to therapy at the posttherapy visit is summarized by treatment group and study center for FDA microbiologically evaluable patients with a diagnosis of complicated UTI in Table 8b and for FDA microbiologically evaluable patients with a diagnosis of acute pyelonephritis in Table 8c. In both cases, there is no statistically

significant treatment difference and levofloxacin is considered therapeutically equivalent to lomefloxacin (95% confidence interval of $_{158,169}(-9.6, 7.5)_{84\%,85\%}$ for complicated UTI; 95% confidence interval of $_{36,35}(-34.9, 2.6)_{76\%,94\%}$ for acute pyelonephritis). Notice that therapeutic equivalence is shown in these subgroups even though the study was not powered to look at complicated UTI and acute pyelonephritis separately.

Note: All confidence intervals in this study report are for the difference "lomefloxacin minus levofloxacin", thus we are interested in the upper bound of the confidence interval for determining therapeutic equivalence.

Table 8a. Clinical Response Rate by Study Center:
Sponsor Microbiologically Evaluable Subjects (Complicated UTI or Acute Pyelonephritis)

(Study L91-059)

	Levofloxacin						Lomefloxacin					
Investigator	N	Cured		Improved		Failed	N	Cured		Improved		Failed
Bakula	8	7	(87.5)	1	(12.5)	0 (0.0)	9	9	(100.0)	0	(0.0)	0 (0.0)
Coburn	1	1	(100.0)	0	(0.0)	0 (0.0)	2	1	(50.0)	0	(0.0)	1 (50.0)
Cox	37	36	(97.3)	0	(0.0)	1 (2.7)	37	35	(94.6)	0	(0.0)	2 (5.4)
Deabate	13	12	(92.3)	1	(7.7)	0 (0.0)	10	10	(100.0)	0	(0.0)	0 (0.0)
Faris	13	12	(92.3)	1	(7.7)	0 (0.0)	8	7	(87.5)	1	(12.5)	0 (0.0)
Fusselier	0	0	(.)	0	(.)	0 (.)	1	1	(100.0)	0	(0.0)	0 (0.0)
Green	1	1	(100.0)	0	(0.0)	0 (0.0)	2	2	(100.0)	0	(0.0)	0 (0.0)
Griffin	3	2	(66.7)	1	(33.3)	0 (0.0)	3	1	(33.3)	2	(66.7)	0 (0.0)
Jemsek	1	1	(100.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	1	(100.0)	0 (0.0)
Kane	3	2	(66.7)	0	(0.0)	1 (33.3)	1	1	(100.0)	0	(0.0)	0 (0.0)
Keeler	2	2	(100.0)	0	(0.0)	0 (0.0)	2	2	(100.0)	0	(0.0)	0 (0.0)
King	25	24	(96.0)	0	(0.0)	1 (4.0)	23	18	(78.3)	1	(4.3)	4 (17.4)
Kimberg	50	43	(86.0)	3	(6.0)	4 (8.0)	50	43	(86.0)	4	(8.0)	3 (6.0)
Koper	1	1	(100.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	1 (100.0)
Leatherman	0	0	(.)	0	(.)	0 (.)	1	1	(100.0)	0	(0.0)	0 (0.0)
Malek	13	10	(76.9)	1	(7.7)	2 (15.4)	11	9	(81.8)	1	(9.1)	1 (9.1)
May	3	2	(66.7)	0	(0.0)	1 (33.3)	3	1	(33.3)	1	(33.3)	1 (33.3)
Moorone	1	1	(100.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	1 (100.0)
Rajfer	1	1	(100.0)	0	(0.0)	0 (0.0)	1	1	(100.0)	0	(0.0)	0 (0.0)
Reid	4	3	(75.0)	1	(25.0)	0 (0.0)	5	4	(80.0)	0	(0.0)	1 (20.0)
Sarshik	9	6	(66.7)	3	(33.3)	0 (0.0)	9	7	(77.8)	2	(22.2)	0 (0.0)
Serfer	1	1	(100.0)	0	(0.0)	0 (0.0)	1	1	(100.0)	0	(0.0)	0 (0.0)
Tuttle	6	4	(66.7)	1	(16.7)	1 (16.7)	6	3	(50.0)	0	(0.0)	3 (50.0)
Urich	0	0	(.)	0	(.)	0 (.)	1	0	(0.0)	0	(0.0)	1 (100.0)
Valenzuela	4	4	(100.0)	0	(0.0)	0 (0.0)	3	3	(100.0)	0	(0.0)	0 (0.0)
Wilt	0	0	(.)	0	(.)	0 (.)	1	0	(0.0)	0	(0.0)	1 (100.0)
Witten	3	2	(66.7)	0	(0.0)	1 (33.3)	3	1	(33.3)	1	(33.3)	1 (33.3)
Zinner	6	3	(50.0)	1	(16.7)	2 (33.3)	8	5	(75.0)	2	(25.0)	0 (0.0)
Combined*	71	55	(78.9)	9	(12.7)	6 (8.5)	73	52	(71.2)	10	(13.7)	11 (15.1)
Total	283	181	(86.5)	14	(5.7)	14 (5.7)	284	167	(81.9)	16	(7.8)	21 (10.3)

Numbers shown in parentheses are percentages for that category.

*Combined = centers that enrolled fewer than 10 evaluable subjects in either treatment group: Bakula, Coburn, Faris, Fusselier, Green, Griffen, Jemsek, Kane, Keeler, Koper, Leatherman, May, McCrone, Rajfer, Reid, Sarshik, Serfer, Tuttle, Urich, Valenzuela, Wilt, Witten, and Zinner.

Table 16b. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Pathogen Category/Pathogen	Levofloxacin		Ciprofloxacin		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	10	9 (90)	12	7 (58)	(-74.4, 11.0)
Gram-negative aerobic pathogens	118	111 (94)	101	96 (95)	(-5.9, 7.9)
Total by pathogen	128	120 (94)	113	103 (91)	(-10.1, 4.9)
Total by subject	113	104 (92)	104	96 (92)	(-7.8, 8.3)
Pathogen					
Citrobacter freundii	2	2 (100)	3	2 (67)	-
Enterobacter cloacae	8	8 (100)	4	4 (100)	-
Escherichia coli	48	45 (94)	52	51 (98)	(-5.5, 14.1)
Klebsiella oxytoca	4	4 (100)	4	4 (100)	-
Klebsiella pneumoniae	26	26 (100)	14	13 (93)	(-26.1, 11.8)
Proteus mirabilis	9	8 (89)	2	2 (100)	-
Pseudomonas aeruginosa	10	7 (70)	7	7 (100)	-
Staphylococcus saprophyticus	0	0 (-)	0	0 (-)	-
Streptococcus agalactiae	0	0 (-)	1	1 (100)	-
Enterococcus faecalis	6	6 (100)	10	6 (60)	-

[a] Numbers shown in parentheses are percentages for that category.

[b] A two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Table 16c. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Pathogen Category/Pathogen	Levofloxacin		Ciprofloxacin		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	8	7 (88)	9	7 (78)	-
Gram-negative aerobic pathogens	41	40 (98)	51	49 (96)	(-10.8, 7.8)
Total by pathogen	49	47 (96)	60	56 (93)	(-12.8, 7.7)
Total by subject	45	43 (96)	56	52 (93)	(-13.7, 8.3)
Pathogen					
Escherichia coli	31	31 (100)	40	38 (95)	(-14.6, 4.6)

[a] Numbers shown in parentheses are percentages for that category.

[b] A two-sided confidence interval for the difference (ciprofloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Among microbiologically evaluable subjects, four pathogens were isolated from blood (E. coli in one levofloxacin-treated subject and two ciprofloxacin-treated subjects, and K. pneumoniae in one ciprofloxacin-treated subject). All four pathogens were eradicated at posttherapy.

Microbiologic Eradication Rates by Diagnosis and Severity of Infection

The posttherapy microbiologic eradication rates for sponsor microbiologically evaluable subjects in each treatment group are presented by diagnosis and severity of infection in Table 17. Subjects with complicated UTI had infection eradication rates of 91.3% and 92.9% after treatment with levofloxacin and ciprofloxacin, respectively, whereas subjects with acute pyelonephritis had infection eradication rates of 96.1% and 93.1%, respectively. For the combined group of subjects with complicated UTI or acute pyelonephritis, microbiologic eradication rates were >90% for mild/moderate infections.

Table 17: Microbiologic Eradication Rates Summarized by Diagnosis and Severity of Infection: Sponsor Microbiologically Evaluable Subjects

(Study L91-058)

	Levofloxacin				Ciprofloxacin			
	N	Eradicated[a]	Persisted[b]		N	Eradicated[a]	Persisted[b]	
Complicated UTI								
Total Severe By Pathogen	7	5 (71.4)	2	(28.6)	5	4 (80.0)	1	(20.0)
Total Severe By Subject	5	3 (60.0)	2	(40.0)	4	3 (75.0)	1	(25.0)
Total Mild/Moderate By Pathogen	135	126 (93.3)	9[c]	(6.7)	117	108 (92.3)	9	(7.7)
Total Mild/Moderate By Subject	121	112 (92.6)	9	(7.4)	109	102 (93.6)	7	(6.4)
Total Complicated UTI By Pathogen	142	131 (92.3)	11[c]	(7.7)	122	112 (91.8)	10	(8.2)
Total Complicated UTI By Subject	126	115 (91.3)	11	(8.7)	113	105 (92.9)	8	(7.1)
Acute Pyelonephritis								
Total Severe By Pathogen	2	2 (100.0)	0	(0.0)	5	4 (80.0)	1	(20.0)
Total Severe By Subject	2	2 (100.0)	0	(0.0)	5	4 (80.0)	1	(20.0)
Total Mild/Moderate By Pathogen	54	52 (96.3)	2	(3.7)	57	54 (94.7)	3	(5.3)
Total Mild/Moderate By Subject	49	47 (95.9)	2	(4.1)	53	50 (94.3)	3	(5.7)
Total Acute Pyelonephritis By Pathogen	56	54 (96.4)	2	(3.6)	62	58 (93.5)	4	(6.5)
Total Acute Pyelonephritis By Subject	51	49 (96.1)	2	(3.9)	58	54 (93.1)	4	(6.9)
Complicated UTI/Acute Pyelonephritis Combined								
Total Severe By Pathogen	9	7 (77.8)	2	(22.2)	10	8 (80.0)	2	(20.0)
Total Severe By Subject	7	5 (71.4)	2	(28.6)	9	7 (77.8)	2	(22.2)
Total Mild/Moderate By Pathogen	189	178 (94.2)	11[c]	(5.8)	174	162 (93.1)	12	(6.9)
Total Mild/Moderate By Subject	170	159 (93.5)	11	(6.5)	162	152 (93.8)	10	(6.2)
Total Complicated UTI/Pyelo By Pathogen	198	185 (93.4)	13[c]	(6.6)	184	170 (92.4)	14	(7.6)
Total Complicated UTI/Pyelo By Subject	177	164 (92.7)	13	(7.3)	171	159 (93.0)	12	(7.0)
Uncomplicated UTI								
Total Mild/Moderate By Pathogen	6	5 (83.3)	1	(16.7)	6	6 (100.0)	0	(0.0)
Total Mild/Moderate By Subject	6	5 (83.3)	1	(16.7)	6	6 (100.0)	0	(0.0)
Total Uncomplicated UTI By Pathogen	6	5 (83.3)	1	(16.7)	6	6 (100.0)	0	(0.0)
Total Uncomplicated UTI By Subject	6	5 (83.3)	1	(16.7)	6	6 (100.0)	0	(0.0)

Numbers shown in parentheses are percentages for that category.

[a] Eradication rates by subject reflect eradication of all pathogens isolated for a subject at admission.

[b] Categories of 'persisted' and 'unknown' combined to create persisted column.

[c] One subject (1602) in the levofloxacin group is erroneously miscategorized as having an unknown microbiologic response for this admission pathogen (*E coli*). The pathogen was, in fact, eradicated.

UTI = urinary tract infection; Pyelo = acute pyelonephritis.

Superinfection

In the sponsor microbiologically evaluable group, eight levofloxacin-treated subjects and six ciprofloxacin-treated subjects developed superinfections (See Table 18) . Of the 12 isolates with known susceptibility information, three were susceptible (or moderately susceptible) to both study drugs and nine were resistant to both study drugs.

Table 18: List of Subjects With Superinfections: Sponsor Microbiologically Evaluable Subjects

(Study L91-058)

Subject Number	Period	Pathogen	Type of Specimen	Susceptibility	
				Levofloxacin	Ciprofloxacin
Levofloxacin					
	Posttherapy	*Staphylococcus aureus*	Skin & Skin Tissue/ Exudate Culture	Unknown	Unknown
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Pseudomonas aeruginosa*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Unknown	Unknown
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Klebsiella pneumoniae*	Urine	Susceptible	Susceptible
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	On Therapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
Ciprofloxacin					
	Posttherapy	*Streptococcus agalactiae*	Urine	Susceptible	Susceptible
	Posttherapy	*Enterococcus*	Urine	Susceptible	Moderate
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Unknown
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant

Microbiologic Response at Long-Term Follow-Up

Of the 255 sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis for whom data were available at the long-term follow-up and for whom their long-term response was neither "unknown" nor "not applicable", 18 (14.3%) of 126 levofloxacin-treated subjects and 13 (10.1%) of 129 ciprofloxacin-treated subjects had a microbiologic relapse. In most cases the pathogens isolated from relapsed subjects were still susceptible to both levofloxacin and ciprofloxacin. Among sponsor microbiologically evaluable subjects, reinfections (i.e., an infection in which an organism other than the original admission pathogen was isolated) were seen in nine levofloxacin-treated subjects and 12 ciprofloxacin-treated subjects. In most cases, the isolates were found to be susceptible to both study drugs.

Summary of Key Efficacy Results

Clinical success rates and microbiologic eradication rates for patients with an admission pathogen are summarized for the levofloxacin and ciprofloxacin treatment groups for various sponsor analysis groups in Table 19. There was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response (See Table 20).

Table 19: Summary of Sponsor Key Efficacy Results: Clinical and Microbiologic Response Rates at Posttherapy for Subjects With Complicated UTI or Acute Pyelonephritis

(Study L91-058)

Response/Group	Levofloxacin: Clinical Success or Microbiologic Eradication Rates[a]		Ciprofloxacin: Clinical Success or Microbiologic Eradication Rates[a]		95% Confidence Interval[b]
Clinical Response					
Microbiologically Evaluable					
Complicated UTI	116/126	(92.1)	100/113	(88.5)	
Acute Pyelonephritis	47/ 51	(92.2)	55/ 58	(94.8)	
Complicated UTI/Acute Pyelonephritis	163/177	(92.1)	155/171	(90.6)	(-7.6, 4.7)
Intent-to-Treat					
Complicated UTI	171/197	(86.8)	164/186	(87.2)	
Acute Pyelonephritis	62/ 69	(89.9)	74/ 80	(92.5)	
Complicated UTI/Acute Pyelonephritis	233/266	(87.6)	238/268	(88.8)	(-4.4, 6.9)
Microbiologic Response					
Microbiologically Evaluable					
Complicated UTI	115/126	(91.3)	105/113	(92.9)	
Acute Pyelonephritis	49/ 51	(96.1)	54/ 58	(93.1)	
Complicated UTI/Acute Pyelonephritis	164/177	(92.7)	159/171	(93.0)	(-5.4, 6.0)
Modified Intent-to-Treat With an Admission Pathogen					
Complicated UTI	124/152	(81.6)	123/149	(82.6)	
Acute Pyelonephritis	50/ 57	(87.7)	61/ 70	(87.1)	
Complicated UTI/Acute Pyelonephritis	174/209	(83.3)	184/219	(84.0)	(-6.5, 8.0)

[a] Denominator for clinical success rate = cured + improved + failed + unable to evaluate. Denominator for microbiologic eradication rate = eradication + persistence + unknown.
[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in clinical success or microbiologic eradication rates.
NOTE: All microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a given subject at admission.
UTI = urinary tract infection.

Table 20: Summary of Sponsor Key Efficacy Results: Cross-Tabulation of Microbiologic Response Versus Clinical Response at Posttherapy for Microbiologically Evaluable Subjects With Complicated UTI or Acute Pyelonephritis

(Study L91-058)

	Clinical Response									
	Levofloxacin					Ciprofloxacin				
Microbiologic Response	N	Cured		Improved	Failed	N	Cured		Improved	Failed
Complicated UTI										
Eradicated	115	101	(87.8)	11 (9.6)	3 (2.6)	105	89	(84.8)	10 (9.5)	6 (5.7)
Persisted	11	3	(27.3)	1 (9.1)	7 (63.6)	8	0	(0.0)	1 (12.5)	7 (87.5)
Acute Pyelonephritis										
Eradicated	49	46	(93.9)	0 (0.0)	3 (6.1)	54	51	(94.4)	3 (5.6)	0 (0.0)
Persisted	2	0	(0.0)	1 (50.0)	1 (50.0)	4	0	(0.0)	1 (25.0)	3 (75.0)
Complicated UTI/ Acute Pyelonephritis										
Eradicated	164	147	(89.6)	11 (6.7)	6 (3.7)	159	140	(88.1)	13 (8.2)	6 (3.8)
Persisted	13	3	(23.1)	2 (15.4)	8 (61.5)	12	0	(0.0)	2 (16.7)	10 (83.3)

NOTE: All microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a given subject at admission.
UTI = urinary tract infection.

SAFETY RESULTS

Table 21 summarizes the incidence of adverse events by body system. The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal (GI) system and consisted primarily of nausea, diarrhea, and abdominal pain. The incidence of GI system adverse events was statistically significantly higher in the ciprofloxacin group (19.4%) than in the levofloxacin group (12.4%) with a 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) of [0.7, 13.1]. Although not statistically significant, the incidence of female reproductive system adverse events was also greater in ciprofloxacin-treated subjects (9.5%) than in levofloxacin-treated subjects (4.8%); these events consisted primarily of vaginitis. In addition, skin and appendages disorders were reported by a higher proportion of ciprofloxacin-treated subjects (5.0% vs. 2.5%) and vision disorders were reported by a higher proportion of levofloxacin-treated subjects (1.8% vs. 0.0%); this difference for vision disorders was statistically significant with a confidence interval of [-3.5, -0.1].

Table 21: Incidence of Adverse Events Summarized by Body System: Subjects Evaluable For Safety

(Study L91-058)

	Levofloxacin (N=282)		Ciprofloxacin (N=279)		
Body System	No.	(%)	No.	(%)	95% Confidence Interval[a]
Gastrointestinal System Disorders	35	(12.4)	54	(19.4)	(0.7, 13.1)
Central & Peripheral Nervous System Disorders	22	(7.8)	17	(6.1)	(-5.1, 2.7)
Body as a Whole--General Disorders	17	(6.0)	12	(4.3)	(-5.5, 2.1)
Psychiatric Disorders	10	(3.5)	10	(3.6)	(-3.2, 3.3)
Reproductive Disorders, Female[b]	8	(4.8)	16	(9.5)	(-1.1, 10.4)
Skin and Appendages Disorders	7	(2.5)	14	(5.0)	(-0.8, 5.9)
Respiratory System Disorders	6	(2.1)	6	(2.2)	(-2.5, 2.5)
Urinary System Disorders	6	(2.1)	1	(0.4)	(-3.8, 0.2)
Musculo-Skeletal System Disorders	5	(1.8)	2	(0.7)	(-3.1, 1.0)
Vision Disorders	5	(1.8)	0	(0.0)	(-3.5, -0.1)
Reproductive Disorders, Male	3	(2.5)	1	(0.9)	(-5.5, 2.2)
Neoplasms	2	(0.7)	3	(1.1)	(-1.4, 2.1)
Resistance Mechanism Disorders	2	(0.7)	7	(2.5)	(-0.5, 4.1)
Hearing and Vestibular Disorders	1	(0.4)	1	(0.4)	(-1.2, 1.2)
Special Senses Other, Disorders	1	(0.4)	0	(0.0)	(-1.2, 0.5)
Myo Endo Pericardial & Valve Disorders	1	(0.4)	1	(0.4)	(-1.2, 1.2)
Heart Rate and Rhythm Disorders	1	(0.4)	1	(0.4)	(-1.2, 1.2)
Vascular (Extracardiac) Disorders	1	(0.4)	3	(1.1)	(-0.9, 2.3)
Autonomic Nervous System Disorders	0	(0.0)	3	(1.1)	(-0.3, 2.5)
Liver and Biliary System Disorders	0	(0.0)	1	(0.4)	(-0.5, 1.2)
Metabolic and Nutritional Disorders	0	(0.0)	1	(0.4)	(-0.5, 1.2)
Endocrine Disorders	0	(0.0)	1	(0.4)	(-0.5, 1.2)
White Cell and Resistance Disorders	0	(0.0)	2	(0.7)	(-0.5, 1.9)
Total With Adverse Events (%)	94	(33.3)	165	(37.5)	(-3.8, 12.4)

[a] Two-sided 95% confidence interval around the difference between treatments (ciprofloxacin minus levofloxacin) in incidence of adverse events.

[b] Percentages calculated from the total number of women in each treatment group. The total number of women who received levofloxacin was 166 and the total number of women who received ciprofloxacin was 169.

Adverse events (primary terms) reported for at least 2.0% of subjects in either treatment group are presented in Table 22. In the levofloxacin group, no single adverse event was reported in $ 5% of subjects. Consistent with the higher percentage of gastrointestinal adverse events reported by ciprofloxacin-treated subjects as compared with levofloxacin-treated subjects, several specific gastrointestinal complaints were more common in the ciprofloxacin group (e.g., nausea, diarrhea, and abdominal pain) than in the levofloxacin group. A similar percentage of subjects in each group reported flatulence, vomiting, and dyspepsia.

Table 22: Incidence of Frequently Reported ($ 2.0%) Adverse Events
Summarized by Body System and Primary Term: Subjects Evaluable for Safety

(Study L91-058)

Body System/ Primary Term	Levofloxacin (N=282) No. Subjects	%	Ciprofloxacin (N=279) No. Subjects	%
All Body Systems	94	33.3	105	37.6
Central & Peripheral Nervous System Disorders	22	7.8	17	6.1
Headache	10	3.5	11	3.9
Dizziness	6	2.1	5	1.8
Gastrointestinal System Disorders	35	12.4	54	19.4
Nausea	12	4.3	23	8.2
Diarrhea	9	3.2	18	6.5
Flatulence	6	2.1	5	1.8
Vomiting	6	2.1	5	1.8
Abdominal Pain	4	1.4	12	4.3
Dyspepsia	4	1.4	7	2.5
Reproductive Disorders, Female[b]	8	4.8	16	9.5
Vaginitis	8	4.8	12	7.1

[a] Primary term reported by ≥2.0% of subjects in either treatment group.
[b] Percentages calculated from the total number of women in each treatment group. The total number of women who received levofloxacin was 165 and the total number of women who received ciprofloxacin was 162.

The majority of adverse events were assessed as mild or moderate in severity. Ten subjects in each treatment group reported one or more adverse events of marked severity (Table 23). Most of the marked adverse events were considered by the investigator as unrelated or remotely related to the study drug. None of the levofloxacin-treated subjects had marked drug-related (probably or definitely related to study drug) adverse events whereas marked drug-related adverse events were reported by two subjects in the ciprofloxacin group (diarrhea and vaginitis in one subject and abdominal pain and nausea in the second subject). Of the 20 subjects with marked adverse events, there was one subject who died (410 in the levofloxacin treatment group) and seven subjects who discontinued study drug treatment (two subjects in the levofloxacin treatment group and five subjects in the ciprofloxacin treatment group). Of these seven subjects who discontinued, the adverse event was considered serious or potentially serious in one levofloxacin-treated subject and three ciprofloxacin-treated subjects. Five additional subjects who did not discontinue the study (all in levofloxacin group) had marked adverse events that were considered serious or potentially serious. Eleven (3.9%) subjects in the levofloxacin treatment group and 15 (5.4%) subjects in the ciprofloxacin treatment group had adverse events considered by the investigator to be drug-related. Drug-related adverse events reported by $ 1.0% of levofloxacin-treated subjects were vaginitis (1.2%) and dizziness (1.1%). Drug-related adverse events reported by $ 1.0% of ciprofloxacin-treated subjects were vaginitis (3.6%), nausea (1.8%), and diarrhea (1.1%).

Table 23: Subjects With Adverse Events of Marked Severity

(Study L91-058)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship To Drug*
Levofloxacin				
	21	F	Agitation	Possible
			Pain	Possible
	63	F	Abdominal Pain	None
			Metastatic Adenocarcinoma of Pancreas[†]	None
			GI Hemorrhage[§]	None
			Intestinal Obstruction	None
			Nausea	None
			Vomiting	None
	61	M	Pseudomembranous Colitis[‡]	None
	60	M	Convulsions[§]	Remote
			Mental Deficiency[§]	Remote
	66	M	Edema	Remote
	76	M	Myocardial Infarction[§]	None
			Urinary Retention[#]	None
	67	F	Retinal Detachment[#]	None
	66	M	Paralysis	Remote
	24	F	Pain	None
	75	F	Fracture Pathological[^§]	None
Ciprofloxacin				
	23	F	Headache	Possible
	35	F	Moniliasis[‡]	Remote
	68	F	Granulocytopenia[§]	Possible
	77	F	Diarrhea[‡]	Probable
			Vaginitis	Definite
	43	F	Abdominal Pain	Probable
			Nausea	Probable
	61	F	Back Pain	None
	76	M	Neoplasm (Unspecified)	None
	46	M	Sepsis[§]	Remote
	62	F	Hepatic Function Abnormal	Possible
			Jaundice	Possible
	31	F	Headache	Remote

* Based on investigator's assessment.
^ Fractured right elbow.
# Subject discontinued due to this adverse event. (See Table 28)
Subject also had a markedly abnormal laboratory value. (See Table 33)
§ Serious or potentially serious adverse event. (See Table 29)
† Subject subsequently died due to progression of her serious adverse events.

Discontinuations Due to Adverse Events

Twenty-six (4.6%) of the 561 subjects evaluable for safety discontinued the study drug due to adverse events, including 10 (3.5%) of the 282 subjects evaluable for safety in the levofloxacin treatment group and 16 (5.7%) of the 279 subjects evaluable for safety in the ciprofloxacin treatment group. A summary of discontinuations due to adverse events appears in Table 24.

Table 24: Subjects Who Discontinued Therapy Due to Adverse Events

(Study L91-058)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Study Day Of Onset[a]	Severity	Relationship to Study Drug[b]	Duration Of Therapy (Days)
Levofloxacin							
	29	M	Dizziness	1	Moderate	Probable	2
			Fatigue	1	Moderate	Probable	
	73	F	Nausea	3	Moderate	Remote	5
			Vomiting	3	Moderate	Remote	
	60	M	Convulsions[‡]	4	Marked	Remote	5
			Mental Deficiency[‡]	4	Marked	Remote	
	72	F	Dizziness	2	Moderate	Probable	2
			Muscle Weakness	2	Moderate	Probable	
			Nervousness	2	Moderate	Probable	
			Tremor	2	Moderate	Probable	
	53	F	Diarrhea	6	Moderate	Possible	7
	43	M	Abdominal Pain	2	Mild	Remote	2
			Anxiety	2	Mild	Remote	
			Asthenia	2	Mild	Remote	
			Headache	2	Mild	Remote	
			Maculopapular Rash	2	Mild	Remote	
	35	M	Abdominal Pain	2	Moderate	Probable	3
			Dizziness	2	Moderate	Probable	
			Insomnia	2	Moderate	Probable	
			Rash	2	Moderate	Probable	
	66	M	Paralysis	3	Marked	Remote	6
	73	F	Abdominal Pain	4	Moderate	Possible	7
			Diarrhea	4	Moderate	Possible	
	75	F	Palpitation	4	Mild	Possible	3
Ciprofloxacin							
	35	F	Chest Pain[‡]	6	Moderate	Remote	6
			Dyspnea[‡]	6	Moderate	Remote	
			Moniliasis[‡]	7	Marked	Remote	
	88	F	Granulocytopenia[‡]	2	Marked	Possible	5
	77	F	Diarrhea	6	Marked	Probable	6
	43	F	Abdominal Pain	2	Marked	Probable	3
			Nausea	3	Marked	Probable	
	27	F	Confusion	4	Mild	Possible	5
			Headache	5	Mild	Possible	
	33	M	Urticaria	1	Mild	Possible	1
	40	F	Nausea	2	Moderate	Possible	5
			Dizziness	4	Mild	Possible	
			Pruritus	4	Moderate	Possible	
	22	F	Diarrhea	4	Moderate	Possible	5
	29	M	Rash	1	Moderate	Possible	2
	48	M	Sepsis[‡]	1	Marked	Remote	1
	65	F	Palpitation	1	Moderate	Possible	2
	41	M	Dizziness	1	Moderate	Possible	4
			Malaise	1	Moderate	Possible	
	77	F	Nausea	1	Moderate	Probable	1
	56	M	Cerebrovascular Disorder[‡c]	4	Moderate	None	4
	71	M	Eructation	3	Moderate	Possible	3
			Nausea	3	Moderate	Possible	
			Vomiting	3	Moderate	Possible	
	65	F	Asthenia	2	Moderate	Possible	2
			Dyspepsia	2	Moderate	Possible	
			Nausea	2	Moderate	Possible	
			Sweating Increased	2	Moderate	Possible	

a Relative to start of therapy (Day 1).
b Based on investigator's assessment.
c Transient ischemic attack.
‡ Serious or potentially serious adverse event.
** Subject also had a markedly abnormal laboratory value.

Serious or Potentially Serious Adverse Events, Including Deaths

Fifteen (5.3%) subjects in the levofloxacin treatment group and eight (2.9%) subjects in the ciprofloxacin treatment group reported a serious or potentially serious adverse event during therapy or up to approximately one month after the end of study drug administration (Table 25).

Three levofloxacin-treated subjects) subsequently died (approximately three weeks to three months after the end of study drug administration) from complications related to their serious adverse events. The investigators considered the deaths of these subjects to be remotely related or unrelated to study drug treatment. Of the 23 subjects with serious or potentially serious adverse events, five subjects withdrew from the study because of their adverse event. In all but two cases, the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug; one levofloxacin-treated subject ([redacted]-cerebrovascular disorder-transient ischemic attacks), and one ciprofloxacin-treated subject ([redacted] granulocytopenia) had events that were considered possibly related to the study drug.

Table 25: Subjects With Serious or Potentially Serious Adverse Events

(Study L91-058)

Subject Number	Age	Sex	Adverse Event	Day of Onset[a]	Severity	Relationship To Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	63	F	GI Hemorrhage	20 (10 PT)	Marked	None	10
			Intestinal Ulceration	21 (11 PT)	Moderate	None	
			Metastatic Adenocarcinoma of Pancreas	24 (14 PT)	Marked	None	
	68	M	Cerebrovascular Disorder[c]	13 (3 PT)	Moderate	Possible	10
	61	M	Pseudomembranous Colitis	22 (14 PT)	Marked	None	8
	60	M	Convulsions	4	Marked	Remote	6
			Mental Deficiency	4	Marked	Remote	
	64	M	Respiratory Insufficiency[d]	31 (21 PT)	–	Remote	10
			Cholelithiasis[d]	21 (11 PT)	–	Remote	
	76	M	Myocardial Infarction	31 (21 PT)	Marked	None	10
			Urinary Retention	41 (31 PT)	Marked	None	
	48	F	MS Aggravated	14 (3 PT)	Moderate	None	11
	68	F	Neoplasm Malignant Aggravated[e]	25 (14 PT)	–	None	11
	67	F	Dyspnea	27 (16 PT)	Moderate	Remote	11
			Edema	27 (16 PT)	Moderate	Remote	
			Cardiac Failure[e]	27 (16 PT)	–	Remote	
	67	F	Retinal Detachment	19 (8 PT)	Marked	None	11
	73	M	Hematuria	23 (13 PT)	Moderate	None	10
			Renal Carcinoma[e]	23 (13 PT)	–	Remote	
	76	F	Syncope	24 (14 PT)	Moderate	None	10
			Arrhythmia[e]	24 (14 PT)	–	Remote	
			Peripheral Ischemia[e]	24 (14 PT)	–	Remote	
	36	M	Vomiting[f]	18 (8 PT)	Moderate	None	10
	76	F	Fracture Pathological[g]	11 (1 PT)	Marked	None	10
	51	M	Pulmonary Carcinoma[h]	14 (11 PT)	–	Remote	3
Ciprofloxacin							
	64	F	Skin Neoplasm Malignant (SCC)	29 (19 PT)	Mild	None	10
	74	F	Skin Neoplasm Malignant (SCC)	9	Moderate	None	10
	35	F	Chest Pain	6	Moderate	Remote	6
			Dyspnea	6	Moderate	Remote	
			Moniliasis	7 (1 PT)	Marked	Remote	
	60	F	Abscess	7	Moderate	None	7
*	68	F	Granulocytopenia	2	Marked	Possible	5
	46	M	Sepsis	1	Marked	Remote	1
	55	M	Cerebrovascular Disorder[c]	4	Moderate	None	4
			Chest Pain	15 (11 PT)	Moderate	None	
	72	F	Angina Pectoris[i]	32 (22 PT)	Moderate	None	10

[a] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy relative to the last day of study drug administration.
[b] Based on investigator's assessment.
[c] Transient ischemic attack.
[d] This serious adverse event occurred after the scheduled posttherapy visit and therefore does not appear on the case report form or in the data base for this individual study report. However, this event was collected as part of the RJWPRI serious adverse event reporting data base and therefore is reflected in the data base for the NDA Integrated Safety Summary.
[e] This adverse event does not appear in the individual study report data base but was captured as serious in the RWJPRI serious adverse event reporting data base. It is therefore reflected as serious in the data base for the NDA Integrated Safety Summary.
[f] This serious adverse event, which appears as non-serious in the individual study report data base, was captured as serious in the RWJPRI serious adverse event reporting data base; it is therefore reflected as serious in the data base for the NDA Integrated Safety Summary.
[g] Fractured right elbow.
[h] An IND safety report was filed with the FDA for this subject.
[i] Subject subsequently died due to progression of the serious adverse event.

* Subject discontinued due to this adverse event.
** Subject also had markedly abnormal laboratory value.
NOTE: SCC=squamous cell carcinoma.

Clinical Laboratory Tests

There were no clinically significant mean changes from baseline for any laboratory analyte in the levofloxacin-treated or ciprofloxacin-treated group, with comparable results in both groups. A summary of markedly abnormal laboratory values after therapy start in subjects with admission data available is shown in Table 26. A list of subjects experiencing marked treatment-emergent abnormalities is presented in Table 27.

Table 26. Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

(Study L91-058)

	Levofloxacin		Ciprofloxacin	
Laboratory Test	Proportion*	%	Proportion*	%
Blood Chemistry				
Elevated Glucose	1/254	0.4	3/247	1.2
Decreased Glucose	4/254	1.6	4/247	1.6
Decreased Potassium	0/257	0.0	1/250	0.4
Elevated LDH	1/257	0.4	0/250	0.0
Elevated Uric Acid	1/260	0.4	0/255	0.0
Elevated Creatinine	0/260	0.0	1/255	0.4
Elevated Alkaline Phosphatase	1/258	0.4	0/253	0.0
Elevated SGOT	1/260	0.4	3/255	1.2
Elevated SGPT	2/260	0.8	2/255	0.8
Hematology				
Decreased Neutrophils	0/250	0.0	1/244	0.4
Decreased Lymphocytes	3/250	1.2	0/244	0.0

* Numerator = number of subjects with a treatment-emergent markedly abnormal test value and denominator = number of subjects evaluable (i.e., admission and posttherapy data available) for that analyte.

Table 27: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

(Study L91-058)

Subject Number	Age	Sex	Lab Test[a] (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[b]	Duration of Therapy (Days)
Levofloxacin							
	23	M	SGPT (>75 IU/L)	27.00	87.00	20 (9 PT)	11
	35	F	Lymphocytes (<1.0 x 10^9/µL)	1.95	0.25	15 (5 PT)	10
	27	F	Glucose (<70 or >200 mg/dL)	86.00	43.00	15 (5 PT)	10
	78	F	Urib Acid (>10.0 mg/dL)	6.7	11.70	15 (5 PT)	10
	73	F	Lymphocytes (<1.0 x 10^9/µL)	1.59	0.91	6 (1 PT)	6
	25	F	Glucose (<70 or >200 mg/dL)	94.00	382.00	19 (9 PT)	11
	23	M	Glucose (<70 or >200 mg/dL)	102.00	68.00	19 (9 PT)	11
	82	M	Alkaline Phosphatase (>250 IU/L) SGOT (>75 IU/L) SGPT (>75 IU/L)	124.00 29.00 23.00	365.00[c] 91.00[c] 87.00[c]	1[c] 1[c] 1[c]	10
	33	M	Glucose (<70 or >200 mg/dL)	337.00	64.00	15 (5 PT)	10
	74	M	Glucose (<70 or >200 mg/dL)	113.00	68.00	15 (5 PT)	10
	74	M	Lactic Dehydrogenase (>500 IU/L) Lymphocytes (<1.0 x 10^9/µL)	785.00 1.35	946.00 0.88	21 (10 PT) 21 (10 PT)	11
Ciprofloxacin							
	34	M	Potassium (<3.0 or >5.0 mEq/L)	4.20	2.60	15 (5 PT)	10
	45	M	Glucose (<70 or >200 mg/dL)	122.00	68.00	20 (9 PT)	11
	43	M	SGOT (>75 IU/L)	163.00	334.00	15 (5 PT)	10
	88	F	Neutrophils (<1.0 x 10^9/µL)	2.94	0.78	6 (1 PT)	6
	79	F	Creatinine (>1.5 mg/dL)	1.00	1.80	15 (5 PT)	11
	63	F	Glucose (<70 or >200 mg/dL)	95.00	59.00	15 (5 PT)	10
	53	F	SGOT (>75 IU/L) SGPT (>75 IU/L)	41.00 72.00	123.00 179.00	17 (7 PT) 17 (7 PT)	10
	71	M	Glucose (<70 or >200 mg/dL)	122.00	66.00	15 (5 PT)	10
	45	F	SGOT (>75 IU/L) SGPT (>75 IU/L)	41.00 21.00	99.00 45.00	6 (1 PT) 6 (1 PT)	6
	40	M	Glucose (<70 or >200 mg/dL)	164.00	277.00	23 (11 PT)	12
	62	M	Glucose (<70 or >200 mg/dL)	106.00	69.00	15 (5 PT)	10
	68	F	Glucose (<70 or >200 mg/dL)	166.00	307.00	19 (9 PT)	11
	71	F	Glucose (<70 or >200 mg/dL)	110.00	224.00	15 (5 PT)	10

a Only range given in table.
b Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy, relative to the last day of study drug administration.
c Abnormal values represent repeat admission tests performed 1½ hours after the admission value on Day 1; see narrative for additional explanation.
* Subject discontinued due to adverse event.
‡ Subject also had serious or potentially serious adverse event.

SUMMARY AND DISCUSSION

For the sponsor microbiologically evaluable group, subjects with complicated UTI had infection eradication rates of 91.3% and 92.9% after treatment with levofloxacin and ciprofloxacin, respectively, and subjects with acute pyelonephritis had infection eradication rates of 96.1% and 93.1%, respectively. In subjects with a diagnosis of complicated UTI or acute pyelonephritis, levofloxacin treatment resulted in 95.7% eradication of E. coli from urine and 96.9% eradication of K. pneumoniae from urine versus 97.0% and 95.7% eradication in the ciprofloxacin treatment group. When the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success", levofloxacin treatment resulted in 92.1% clinical success compared to 90.6% for ciprofloxacin subjects with a 95% confidence interval for the difference of [-7.6, 4.7]. Among all pathogens isolated at admission, 17 pathogens were ultimately identified as resistant to levofloxacin versus 22 for ciprofloxacin. In addition, four of

the 22 ciprofloxacin-resistant pathogens were fully susceptible to levofloxacin.

The overall incidence of adverse events in the levofloxacin and ciprofloxacin treatment groups was very similar, 33.3% and 37.6%, respectively. Gastrointestinal system (GI) adverse events were the most common adverse events in both treatment groups and were reported by a statistically significantly higher proportion of ciprofloxacin-treated subjects (19.4%) than levofloxacin-treated subjects (12.4%). The majority of adverse events were assessed as mild or moderate in severity. Eleven (3.9%) subjects in the levofloxacin treatment group and 15 (5.4%) subjects in the ciprofloxacin treatment group had adverse events considered by the investigator to be drug-related. Fifteen (5.3%) subjects in the levofloxacin treatment group and eight (2.9%) subjects in the ciprofloxacin group reported serious or potentially serious adverse events, most of which were unrelated or remotely related to the study drug. Three levofloxacin-treated subjects died approximately three weeks to three months after the end of study drug administration. These deaths were considered by the investigators to be unrelated or remotely related to study drug.

CONCLUSIONS

Levofloxacin was safe, well-tolerated and effective in the treatment of subjects with complicated urinary tract infections or acute pyelonephritis. Microbiologic eradication rates in the levofloxacin treatment group were therapeutically equivalent to those observed in the ciprofloxacin group in both the sponsor analysis (sponsor microbiologically evaluable patients with either complicated UTI or acute pyelonephritis) and FDA analyses (FDA microbiologically evaluable patients with complicated UTI and FDA microbiologically evaluable patients with acute pyelonephritis). Moreover, clinical cure rates were therapeutically equivalent to those of ciprofloxacin for both sponsor and FDA analyses (same patient groups as in the previous sentence).

Microbiologic eradication rates in microbiologically evaluable subjects (from this study alone) support the use of levofloxacin for the treatment of complicated urinary tract infections due to Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa. However, the numbers of patients with other organisms were too low (in this study) to support the use of levofloxacin for the treatment of complicated UTI due to other organisms.

Because 100 percent of 31 acute pyelonephritis patients were eradicated of E. coli, this study (alone) supports the use of levofloxacin for acute pyelonephritis due to E. coli.

STUDY L91-059

TITLE

A multi-center, randomized, unblinded study to compare the safety and efficacy of oral levofloxacin with that of lomefloxacin HCL in the treatment of complicated urinary tract infections in adults.

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OBJECTIVES

The objective of this study was to compare the safety and efficacy of 250 mg of levofloxacin administered orally once daily for seven to 10 days with that of 400 mg of lomefloxacin administered orally once daily for 14 days in the treatment of complicated UTI or acute pyelonephritis due to susceptible organisms in adults.

STUDY DESIGN

The schedule of assessments are described in Table 1. The study design was similar to study L91-058.

Table 1: Schedule of Assessments

(Study L91-059)

Assessment/Procedure	Admission (Day 1)	During Therapy (Days 3-5)	Posttherapy (5-9 days PT)[a]	Long-Term Follow-Up (4-6 weeks PT)
Pertinent Medical History	X			
Pregnancy Test[b]	X		X	
Study Drug Administration	X	——— X[c]		
Efficacy Evaluations: (see Section III.H.2.)				
Clinical:				
-Clinical Signs and Symptoms	X		X	X
-Clinical Response Rating			X	
Microbiologic:				
-Urine Culture	X	X	X	X
-Susceptibility Test	X	X	X	X
-Blood Culture	X[d]	X[e]	X[e]	
Safety Assessments: (see Section III.H.4.)				
Adverse Events		X	X	
Clinical Laboratory Tests:				
-Hematology	X		X	
-Chemistry	X		X	
-Urinalysis	X	X	X	X
Pertinent Physical Examination (including Vital Signs)	X		X	

[a] Or upon early withdrawal.
[b] Performed on all women of childbearing potential.
[c] Levofloxacin was to be administered for 7 to 10 days and lomefloxacin was to be administered for 14 days.
[d] Performed only if indicated (if bacteremia suspected).
[e] Performed if positive at admission.
PT=Posttherapy

STUDY POPULATION

Approximately 600 subjects, men and women who were 18 years of age or older and had a diagnosis of complicated UTI or acute pyelonephritis, were to be enrolled in this study to attain a sample size of at least 147 microbiologically evaluable subjects per treatment group for efficacy analysis.

MAIN DIFFERENCES BETWEEN STUDY L91-058 AND L91-059

CHARACTERISTIC	STUDY L91-058	STUDY L91-059
Blinding	Double blinded	Unblinded
Planned number of subjects	600 subjects	500 subjects

Analyses Planned

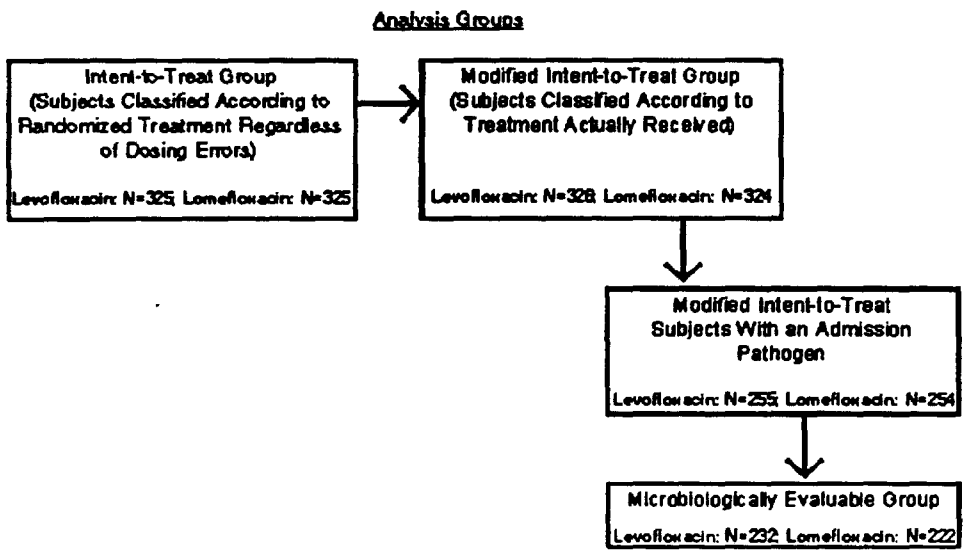
Approximately 600 subjects were to be enrolled into the study to provide 294 microbiologically evaluable subjects, a minimum of 147 subjects per treatment group. Assuming infection eradication rates of 89% for lomefloxacin and 85% for levofloxacin and a significance level of 2.5%, 147 microbiologically evaluable subjects per treatment group were required to demonstrate, with 80% power, that the difference (lomefloxacin minus levofloxacin) in infection eradication rates was less than 15%.

Sponsor's Analysis Populations

The analysis groups were:

- Intent-to-Treat — adheres strictly to randomization; thus subjects are included in their assigned treatment group regardless of any dosing or dispensing errors.
- Modified Intent-to-Treat — takes drug dispensing errors into account by grouping subjects according to the drug actually received. These two approaches (modified intent-to-treat and intent-to-treat) classified only three subjects differently; two were randomized to treatment with lomefloxacin but received levofloxacin and one was randomized to treatment with levofloxacin but received lomefloxacin (*note: DAIDP would consider this an "intent-to-treat" analysis where dispensing errors are taken into account*).
- Modified Intent-to-Treat with an Admission Pathogen — which represents those subjects in the modified intent-to-treat group who had a pathogen isolated at admission (*note: DAIDP terms this "modified intent-to-treat"*).
- Microbiologically evaluable subjects -- which represent subjects with complicated UTI or acute pyelonephritis according to the protocol-specified evaluability criteria.

The relationship between these groups is represented below:



RESULTS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Six hundred fifty subjects were enrolled in this study at 29 of the 30 centers. The sponsor intent-to-treat group included 325 subjects who were randomized to the levofloxacin treatment group and 325 subjects who were randomized to the lomefloxacin treatment group. The demographic and baseline characteristics for the sponsor modified intent-to-treat group are summarized in Table 2 and were comparable between the levofloxacin and lomefloxacin groups.

Table 2. Demographic and Baseline Characteristics: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

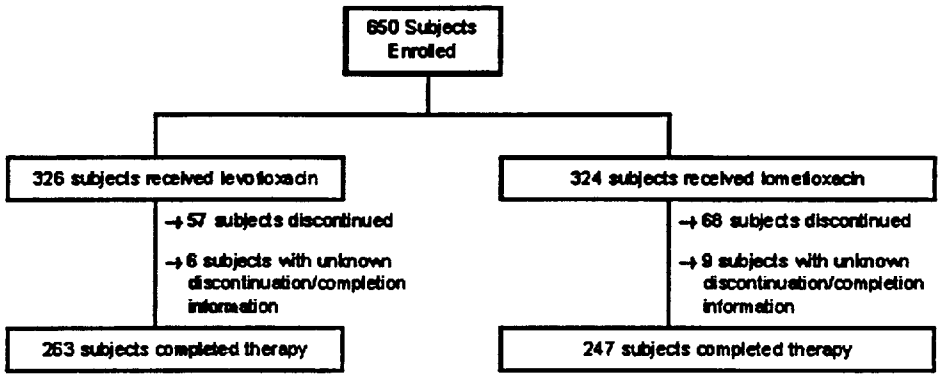
	Levofloxacin (N=326)		Lomefloxacin (N=324)		Overall Total (N=650)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	124	(38.0)	105	(32.4)	229	(35.2)
Women	202	(62.0)	219	(67.6)	421	(64.8)
Race						
Caucasian	239	(73.3)	234	(72.2)	473	(72.8)
Black	75	(23.0)	71	(21.9)	146	(22.5)
Oriental	1	(0.3)	0	(0.0)	1	(0.2)
Hispanic	10	(3.1)	18	(5.6)	28	(4.3)
Other	1	(0.3)	1	(0.3)	2	(0.3)
Age (Years)						
≤45	64	(19.6)	73	(22.5)	137	(21.1)
46-64	76	(23.3)	94	(29.0)	170	(26.2)
≥65	186	(57.1)	157	(48.5)	343	(52.8)
N	326		324		650	
Mean±SD	62.5±17.3		59.9±17.0		61.2±17.2	
Range	[redacted]		[redacted]		[redacted]	
Weight (lbs)						
N	311		314		625	
Mean±SD	167.2±35.0		169.6±37.7		168.4±36.4	
Range	[redacted]		[redacted]		[redacted]	
Missing	15		10		25	
Height (Inches)						
N	292		299		591	
Mean±SD	66.0±4.42		65.7±4.02		65.8±4.22	
Range	[redacted]		[redacted]		[redacted]	
Missing	34		25		59	
Diagnosis						
Complicated UTI	232	(71.2)	230	(71.0)	462	(71.1)
Acute Pyelonephritis	55	(16.9)	56	(17.3)	111	(17.1)
Uncomplicated UTI	39	(12.0)	38	(11.7)	77	(11.8)
Severity						
Complicated UTI						
Severe	10	(4.3)	5	(2.2)	15	(3.2)
Mild/Moderate	222	(95.7)	225	(97.8)	447	(96.8)
Acute Pyelonephritis						
Severe	4	(7.3)	3	(5.4)	7	(6.3)
Mild/Moderate	51	(92.7)	53	(94.6)	104	(93.7)
Uncomplicated UTI						
Severe	0	(0.0)	1	(2.6)	1	(1.3)
Mild/Moderate	39	(100.0)	37	(97.4)	76	(98.7)

NOTE: Values represent number of subjects except as otherwise indicated.
UTI = Urinary tract infection.

DISCONTINUATION/COMPLETION INFORMATION

Discontinuation information for the sponsor modified intent-to-treat group is provided in Figure 1.

Figure 1: Discontinuation/Completion Information: Modified Intent-to-Treat Subjects (Study L91-059)



The reasons for premature discontinuation are summarized in Table 3.

Table 3: Reasons for Premature Discontinuation of Therapy: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

Reason	Levofloxacin (N=326) No.	(%)*	Lomefloxacin (N=324) No.	(%)*
No Admission Pathogen	41	(12.8)	38	(12.1)
Adverse Event	9	(2.8)	18	(5.7)
Resistant Pathogen[b]	3	(0.9)	6	(1.9)
Clinical Failure	0	(0.0)	4	(1.3)
Other	4[c]	(1.3)	2[d]	(0.6)
Total Discontinued	57	(17.8)	68	(21.6)
Total with Discontinuation/Completion Information	320		315	
Total with Unknown Discontinuation/Completion Information	6		9	

* Percentages based on total number with discontinuation/completion information.

[b] Subjects enrolled prior to the second protocol amendment (March 8, 1994) were to be discontinued if a resistant pathogen was isolated at admission.

[c] Subject [redacted] was discontinued after receiving amoxicillin for treatment of an adverse event (eye abnormality - pterygium excision). Subject [redacted] received two doses of levofloxacin and was dropped from the study per the investigator's decision because he was found to have a history of seizures and was taking phenytoin. Subject [redacted] was discontinued after receiving three doses because of a lab error (no urine culture and sensitivity testing done on admission). Subject [redacted] took one dose of levofloxacin and was then dropped from the study when she was discharged from the hospital and study drug was not sent with her.

[d] Subject [redacted] was asymptomatic at admission and was withdrawn by the investigator at the request of RWJPRI after receiving four doses of lomefloxacin. Subject [redacted] was withdrawn after receiving five doses because her admission urine specimen was contaminated and an infecting pathogen could not be identified.

DOSAGE INFORMATION

The extent of exposure to therapy is shown by treatment group in Table 4 for the sponsor modified intent-to-treat group.

Table 4: Extent of Exposure to Therapy: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

Extent of Therapy	Levofloxacin (N=326)	Lomefloxacin (N=324)
Days on Therapy*		
Unknown	6	8
1	2	2
2	8	4
3	4	11
4	17	15
5	12	13
6	5	6
7	4	5
8	4	3
9	3	4
10	256	6
11	1	1
12	2	1
13	0	3
14	0	236
15	2	5
16	0	1
Mean±SD	9.1±2.3	12.0±3.8
Median	10	14
Number of Doses		
Total with Dosing Information	321	316
Total Unknown Dosing Information	5	8
Mean±SD	9.0±2.4	12.1±3.8
Median	10	14
Range	[redacted]	[redacted]

NOTE: The scheduled dosages were levofloxacin 250mg po q24h for 7-10 days and lomefloxacin 400mg po q24h for 14 days.

*Days on therapy was defined as (last day - first day) + 1.

EFFICACY RESULTS

The total number of subjects evaluable by the sponsor for microbiologic efficacy at each study center is shown in Table 5. Two hundred thirty-two (71.2%) subjects in the levofloxacin group and 222 (68.5%) in the lomefloxacin group were microbiologically evaluable. The primary reasons (subjects counted only once) for exclusion from the microbiologically evaluable group are summarized in Table 6. The main reasons that subjects in both treatment groups were not evaluable was absence of bacteriologically proven infection.

Table 5. Number of Subjects by Sponsor Analysis Group and Center

(Study L91-059)

Investigator*	Levofloxacin			Lomefloxacin		
	Modified Intent-to Treat	Microbiologic Efficacy		Modified Intent-to Treat	Microbiologic Efficacy	
Bakule	12	8	(66.7)	12	9	(75.0)
Coburn	7	1	(14.3)	8	2	(25.0)
Collins	6	3	(50.0)	6	1	(16.7)
Cox	40	37	(92.5)	39	37	(94.9)
Deebate	24	16	(66.7)	24	13	(54.2)
Faris	29	17	(58.6)	28	12	(42.9)
Fuselier	0	0	(.)	1	1	(100.0)
Green	2	1	(50.0)	2	2	(100.0)
Griffin	4	3	(75.0)	6	3	(50.0)
Jemsek	8	3	(37.5)	7	1	(14.3)
Kane	4	3	(75.0)	2	1	(50.0)
Keeler	3	2	(66.7)	2	2	(100.0)
King	30	27	(90.0)	31	25	(80.6)
Klimberg	62	54	(87.1)	62	52	(83.9)
Koper	2	2	(100.0)	2	2	(100.0)
Leatherman	1	0	(0.0)	2	1	(50.0)
Malek	22	16	(72.7)	21	14	(66.7)
May	3	3	(100.0)	3	3	(100.0)
Mccrone	4	2	(50.0)	2	2	(100.0)
Rajfer	2	1	(50.0)	5	1	(20.0)
Reid	9	4	(44.4)	8	5	(62.5)
Sarshik	10	9	(90.0)	10	9	(90.0)
Serfer	2	1	(50.0)	3	2	(66.7)
Tuttle	8	6	(75.0)	7	6	(85.7)
Urich	2	0	(0.0)	2	1	(50.0)
Valenzuela	10	4	(40.0)	10	3	(30.0)
Witt	0	0	(.)	1	1	(100.0)
Witten	12	3	(25.0)	9	3	(33.3)
Zinner	8	6	(75.0)	9	8	(88.9)
Total	**326**	**232**	**(71.2)**	**324**	**222**	**(68.5)**

Numbers shown in parentheses are percentages for that category.
*One investigator (Finnerty) did not enroll any subjects.

Table 6: Primary Reasons for Microbiologic NonEvaluability: Sponsor Modified Intent-to-Treat Subjects

(Study L91-059)

Reasons	Levofloxacin (N=326)		Lomefloxacin (N=324)	
Infection Not Bacteriologically Proven	70		70	
Inappropriate Bacteriologic Culture	11		11	
Insufficient Course of Therapy	6		13	
No Posttherapy Evaluation	3		5	
Effective Concomitant Therapy	2		1	
Other Protocol Violation	1[b]		0	
Unevaluable for Safety	1		2	
Total Unevaluable For Microbiologic Efficacy	94	(28.8%)	102	(31.5%)

*Subjects counted only once.
[b]Subject [redacted] took 125 mg of levofloxacin twice daily and not 250 mg once daily as prescribed.

Demographic and Baseline Characteristics

The demographic and baseline characteristics for sponsor microbiologically evaluable subjects are shown in Table 7 and were comparable to those previously described for the sponsor modified intent-to-treat group.

Table 7: Demographic and Baseline Characteristics: Sponsor Microbiologically Evaluable Subjects

(Study L91-059)

	Levofloxacin (N=232)	Lomefloxacin (N=222)
Sex		
Men	88	73
Women	144	149
Race		
Caucasian	171	164
Black	54	51
Oriental	1	0
Hispanic	6	7
Age (Years)		
≤45	41	40
46-64	52	64
≥65	139	118
N	232	222
Mean±SD	63.6±17.1	61.9±16.0
Range	[redacted]	[redacted]
Weight (lbs)		
N	224	217
Mean±SD	168±33.9	169±36.8
Range	[redacted]	[redacted]
Missing	8	5
Height (inches)		
N	210	204
Mean±SD	66.0±4.32	65.6±3.89
Range	[redacted]	[redacted]
Missing	22	18
Diagnosis		
Complicated UTI	171	165
Acute Pyelonephritis	38	39
Uncomplicated UTI	23	18
Severity		
Complicated UTI		
Severe	6	4
Mild/Moderate	165	161
Acute Pyelonephritis		
Severe	4	2
Mild/Moderate	34	37
Uncomplicated UTI		
Mild/Moderate	23	18

NOTE: Values represent numbers of subjects unless otherwise indicated.
UTI = urinary tract infection.

Clinical Outcome

Sponsor Results

The clinical response to therapy for subjects with complicated UTI or acute pyelonephritis who were sponsor microbiologically evaluable is summarized by treatment group and study center in Table 8a. Among sponsor microbiologically evaluable subjects in the levofloxacin treatment group, 86.6% were cured and 6.7% were improved at the posttherapy visit (five to nine days after completion of therapy), compared with 81.9% and 7.8% in the lomefloxacin group. Fourteen (6.7%) subjects in the levofloxacin treatment group and 21(10.3%) subjects in the lomefloxacin treatment group failed treatment.

FDA Results

Clinical response to therapy at the posttherapy visit is summarized by treatment group and study center for FDA microbiologically evaluable patients with a diagnosis of complicated UTI in Table 8b and for FDA microbiologically evaluable patients with a diagnosis of acute pyelonephritis in Table 8c. In both cases, there is no statistically

significant treatment difference and levofloxacin is considered therapeutically equivalent to lomefloxacin (95% confidence interval of $_{158,169}(-9.6, 7.5)_{84\%,85\%}$ for complicated UTI; 95% confidence interval of $_{36,33}(-34.9, 2.6)_{78\%,94\%}$ for acute pyelonephritis). Notice that therapeutic equivalence is shown in these subgroups even though the study was not powered to look at complicated UTI and acute pyelonephritis separately.

Note: All confidence intervals in this study report are for the difference "lomefloxacin minus levofloxacin", thus we are interested in the upper bound of the confidence interval for determining therapeutic equivalence.

Table 8a. Clinical Response Rate by Study Center:
Sponsor Microbiologically Evaluable Subjects (Complicated UTI or Acute Pyelonephritis)

(Study L91-059)

	Levofloxacin						Lomefloxacin					
Investigator	N	Cured		Improved		Failed	N	Cured		Improved		Failed
Baluda	8	7	(87.5)	1	(12.5)	0 (0.0)	9	9	(100.0)	0	(0.0)	0 (0.0)
Coburn	1	1	(100.0)	0	(0.0)	0 (0.0)	2	1	(50.0)	0	(0.0)	1 (50.0)
Cox	37	36	(97.3)	0	(0.0)	1 (2.7)	37	35	(94.6)	0	(0.0)	2 (5.4)
Deabate	13	12	(92.3)	1	(7.7)	0 (0.0)	10	10	(100.0)	0	(0.0)	0 (0.0)
Faris	13	12	(92.3)	1	(7.7)	0 (0.0)	8	7	(87.5)	1	(12.5)	0 (0.0)
Fuselier	0	0	(.)	0	(.)	0 (.)	1	1	(100.0)	0	(0.0)	0 (0.0)
Green	1	1	(100.0)	0	(0.0)	0 (0.0)	2	2	(100.0)	0	(0.0)	0 (0.0)
Griffin	3	2	(66.7)	1	(33.3)	0 (0.0)	3	1	(33.3)	2	(66.7)	0 (0.0)
Jemsek	1	1	(100.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	1	(100.0)	0 (0.0)
Kane	3	2	(66.7)	0	(0.0)	1 (33.3)	1	1	(100.0)	0	(0.0)	0 (0.0)
Keeler	2	2	(100.0)	0	(0.0)	0 (0.0)	2	2	(100.0)	0	(0.0)	0 (0.0)
King	25	24	(96.0)	0	(0.0)	1 (4.0)	23	18	(78.3)	1	(4.3)	4 (17.4)
Kimberg	50	43	(86.0)	3	(6.0)	4 (8.0)	50	43	(86.0)	4	(8.0)	3 (6.0)
Koper	1	1	(100.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	1 (100.0)
Leatherman	0	0	(.)	0	(.)	0 (.)	1	1	(100.0)	0	(0.0)	0 (0.0)
Mask	13	10	(76.9)	1	(7.7)	2 (15.4)	11	9	(81.8)	1	(9.1)	1 (9.1)
May	3	2	(66.7)	0	(0.0)	1 (33.3)	3	1	(33.3)	1	(33.3)	1 (33.3)
Moorre	1	1	(100.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	1 (100.0)
Rajfer	1	1	(100.0)	0	(0.0)	0 (0.0)	1	1	(100.0)	0	(0.0)	0 (0.0)
Reid	4	3	(75.0)	1	(25.0)	0 (0.0)	5	4	(80.0)	0	(0.0)	1 (20.0)
Sarshik	9	6	(66.7)	3	(33.3)	0 (0.0)	9	7	(77.8)	2	(22.2)	0 (0.0)
Sarter	1	1	(100.0)	0	(0.0)	0 (0.0)	1	1	(100.0)	0	(0.0)	0 (0.0)
Tuttle	6	4	(66.7)	1	(16.7)	1 (16.7)	6	3	(50.0)	0	(0.0)	3 (50.0)
Urich	0	0	(.)	0	(.)	0 (.)	1	0	(0.0)	0	(0.0)	1 (100.0)
Valenzuela	4	4	(100.0)	0	(0.0)	0 (0.0)	3	3	(100.0)	0	(0.0)	0 (0.0)
Wilt	0	0	(.)	0	(.)	0 (.)	1	0	(0.0)	0	(0.0)	1 (100.0)
Witten	3	2	(66.7)	0	(0.0)	1 (33.3)	3	1	(33.3)	1	(33.3)	1 (33.3)
Zinner	6	3	(50.0)	1	(16.7)	2 (33.3)	8	6	(75.0)	2	(25.0)	0 (0.0)
Combined*	71	55	(78.9)	9	(12.7)	6 (8.5)	73	52	(71.2)	10	(13.7)	11 (15.1)
Total	283	181	(86.5)	14	(6.7)	14 (6.7)	284	167	(81.9)	16	(7.8)	21 (10.3)

Numbers shown in parentheses are percentages for that category.

*Combined = centers that enrolled fewer than 10 evaluable subjects in either treatment group: Baluda, Coburn, Faris, Fuselier, Green, Griffen, Jemsek, Kane, Keeler, Koper, Leatherman, May, McCrone, Rajfer, Reid, Sarshik, Sarter, Tuttle, Urich, Valenzuela, Wilt, Witten, and Zinner.

Table 8b. Clinical Response Rate by Center:
FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

	Levofloxacin				Lomefloxacin			
Investigator	N[a]	Cure	Improve	Fail	N	Cure	Improve	Fail
Cox	37	36 (97)	0 (0)	1 (3)	37	35 (95)	0 (0)	2 (5)
King	24	23 (96)	0 (0)	1 (4)	22	17 (77)	1 (5)	4 (18)
Klimberg	42	36 (86)	3 (7)	3 (7)	38	34 (89)	3 (8)	1 (3)
Other	66	48 (73)	11 (17)	7 (11)	61	46 (75)	5 (8)	10 (16)
Total	169	143 (85)	14 (8)	12 (7)	158	132 (84)	9 (6)	17 (11)

Numbers shown in parentheses are percentages for that category.
[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".

Table 8c. Clinical Response Rate by Center:
FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

	Levofloxacin				Lomefloxacin			
Investigator	N[a]	Cure	Improve	Fail	N	Cure	Improve	Fail
Other	33	31 (94)	0 (0)	2 (6)	36	28 (78)	6 (17)	2 (6)
Total	33	31 (94)	0 (0)	2 (6)	36	28 (78)	6 (17)	2 (6)

Numbers shown in parentheses are percentages for that category.
[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other". (Note: No investigators enrolled 10 or more patients per treatment group with acute pyelonephritis who were considered evaluable by FDA.)

To allow for a dichotomous analysis of clinical response, the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success." Among sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis, levofloxacin treatment resulted in 93.3% clinical success while lomefloxacin treatment resulted in 89.7% clinical success, with a 95% confidence interval of [-9.2, 2.0] for the difference (lomefloxacin minus levofloxacin) in success rates (See Table 9a). *Clinical success rates were considered therapeutically equivalent for FDA microbiologically evaluable patients with complicated UTI (see Table 9b). Clinical success rates were not shown to be therapeutically equivalent in FDA microbiologically evaluable patients with acute pyelonephritis (see Table 9c), however the sponsor is not required to show this. The DAIDP "Points to Consider" document says simply that "if there is not a sufficient number of patients with pyelonephritis successfully treated with the investigative agent (minimum: 30 patients/arm/study), the listing (*in the label*) should not include pyelonephritis. No statistically significant treatment difference was detected between levofloxacin (94% success rate) and lomefloxacin (94% success rate), which in fact had the same observed success rates.*

Table 9a. Clinical Success/Failure Rates and Confidence Intervals by Study Center: Sponsor Microbiologically Evaluable Subjects (Complicated UTI or Acute Pyelonephritis)

(Study L91-059)

	Levofloxacin			Lomefloxacin			
Investigator	N	Success[a]	Failure[a]	N	Success[a]	Failure[a]	95% Confidence Interval[b]
Baluja	8	8 (100.0)	0 (0.0)	9	9 (100.0)	0 (0.0)	(., .)
Coburn	1	1 (100.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	(., .)
Cox	37	36 (97.3)	1 (2.7)	37	35 (94.6)	2 (5.4)	(-13.0, 7.6)
Dasbach	13	13 (100.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	(-5.0, 5.0)
Faris	13	13 (100.0)	0 (0.0)	8	8 (100.0)	0 (0.0)	(., .)
Fuselier	0	0 (.)	0 (.)	1	1 (100.0)	0 (0.0)	(., .)
Green	1	1 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(., .)
Griffin	3	3 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(., .)
Jamsek	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(., .)
Kane	3	2 (66.7)	1 (33.3)	1	1 (100.0)	0 (0.0)	(., .)
Keeler	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(., .)
King	25	24 (96.0)	1 (4.0)	23	19 (82.6)	4 (17.4)	(-32.9, 6.1)
Klimberg	50	46 (92.0)	4 (8.0)	50	47 (94.0)	3 (6.0)	(-9.0, 13.0)
Koper	1	1 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	(., .)
Leatherman	0	0 (.)	0 (.)	1	1 (100.0)	0 (0.0)	(., .)
Malek	13	11 (84.6)	2 (15.4)	11	10 (90.9)	1 (9.1)	(-24.2, 36.8)
May	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)	(., .)
McCrone	1	1 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	(., .)
Rajfer	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(., .)
Reid	4	4 (100.0)	0 (0.0)	5	4 (80.0)	1 (20.0)	(., .)
Sarshik	9	9 (100.0)	0 (0.0)	9	9 (100.0)	0 (0.0)	(., .)
Sarter	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(., .)
Tuttle	6	5 (83.3)	1 (16.7)	6	3 (50.0)	3 (50.0)	(., .)
Urich	0	0 (.)	0 (.)	1	0 (0.0)	1 (100.0)	(., .)
Valenzuela	4	4 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(., .)
Wilt	0	0 (.)	0 (.)	1	0 (0.0)	1 (100.0)	(., .)
Witten	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)	(., .)
Zinner	6	4 (66.7)	2 (33.3)	8	8 (100.0)	0 (0.0)	(., .)
Combined[c]	71	65 (91.5)	6 (8.5)	73	62 (84.9)	11 (15.1)	(-17.8, 4.5)
Total	289	195 (93.3)	14 (6.7)	284	183 (89.7)	21 (10.3)	(-9.2, 2.9)

[a] Numbers shown in parentheses are percentages for that category.

[b] Two-sided 95% confidence interval around the difference (lomefloxacin minus levofloxacin) in clinical success (cured and improved) rates were calculated for study centers enrolling 10 or more microbiologically evaluable subjects in each treatment group.

[c] Combined = centers that enrolled fewer than 10 evaluable subjects in either treatment group: Baluja, Coburn, Faris, Fuselier, Green, Griffen, Jamsek, Kane, Keeler, Koper, Leatherman, May, McCrone, Rajfer, Reid, Sarshik, Sarter, Tuttle, Urich, Valenzuela, Wilt, Witten, and Zinner.

Table 9b. Clinical Success/Failure Rates and Confidence Intervals By Study Center: FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Investigator	Levofloxacin		Lomefloxacin		95% Confidence Interval[c]
	N[a]	Success[b]	N	Success	
Cox	37	36 (97)	37	35 (95)	(-14.4, 9.0)
King	24	23 (96)	22	18 (82)	(-36.4, 8.3)
Klimberg	42	39 (93)	38	37 (97)	(-7.3, 16.3)
Other	66	59 (89)	61	51 (84)	(-19.3, 7.7)
Total	169	157 (93)	158	141 (89)	(-10.5, 3.1)

[a] Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".

[b] Clinical success is defined as either clinical cure or clinical improvement. Numbers shown in parentheses are percentages for that category.

[c] Two-sided confidence interval for the difference (lomefloxacin minus levofloxacin) in clinical success rate.

Table 9c. Clinical Success/Failure Rates and Confidence Intervals By Study Center:
FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Investigator	Levofloxacin		Lomefloxacin		95% Confidence Interval[c]
	N[a]	Success[b]	N	Success	
Other	33	31 (94)	36	34 (94)	(-13.5, 14.5)
Total	33	31 (94)	36	34 (94)	(-13.5, 14.5)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other". (Note: No investigators enrolled 10 or more patients per treatment group with acute pyelonephritis considered evaluable by FDA.)
[b]Clinical success is defined as either clinical cure or clinical improvement. Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (lomefloxacin minus levofloxacin) in clinical success rate.

Clinical Response by Pathogen

Clinical response rates for sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis and infected with uropathogens of interest alone or in combination with other pathogens are shown in Table 10a. *E. coli* and *K. pneumoniae* were the most prevalent pathogens in both treatment groups.

Table 10b summarizes clinical response by pathogen for FDA microbiologically evaluable patients with complicated UTI and Table 10c summarizes clinical response by pathogen for FDA microbiologically evaluable patients with acute pyelonephritis. The FDA analyses include only those pathogens requested by the sponsor in their label.

Table 10a. Clinical Response Rates for Subjects with Pathogens of Primary Interest: Sponsor Microbiologically Evaluable Subjects (Complicated UTI or Acute Pyelonephritis)

(Study L91-059)

Pathogen from Urine Culture	Levofloxacin N*	Cured	Improved	Failed	Lomefloxacin N*	Cured	Improved	Failed
Escherichia coli	119	107 (89.9)	7 (5.9)	5 (4.2)	118	103 (87.3)	10 (8.5)	5 (4.2)
Klebsiella pneumoniae	31	28 (90.3)	1 (3.2)	2 (6.5)	25	20 (80.0)	0 (0.0)	5 (20.0)
Proteus mirabilis	11	9 (81.8)	2 (18.2)	0 (0.0)	9	7 (77.8)	1 (11.1)	1 (11.1)
Pseudomonas aeruginosa	9	8 (88.9)	1 (11.1)	0 (0.0)	6	4 (66.7)	0 (0.0)	2 (33.3)
Streptococcus faecalis	8	4 (50.0)	1 (12.5)	3 (37.5)	8	7 (87.5)	0 (0.0)	1 (12.5)
Enterobacter cloacae	7	6 (85.7)	0 (0.0)	1 (14.3)	6	4 (66.7)	0 (0.0)	2 (33.3)
Citrobacter freundii	6	4 (66.7)	0 (0.0)	2 (33.3)	4	3 (75.0)	1 (25.0)	0 (0.0)
Enterobacter aerogenes	2	2 (100.0)	0 (0.0)	0 (0.0)	6	4 (66.7)	2 (33.3)	0 (0.0)
Total By Subject	209	181 (86.6)	14 (6.7)	14 (6.7)	204	167 (81.9)	16 (7.8)	21 (10.3)

Numbers shown in parentheses are percentages for that category.
* Na5 in either treatment group.
* N = number of subjects who had that pathogen alone or in combination with other pathogens.

Table 10b. Clinical Response for Subjects with Pathogens of Primary Interest: FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Pathogen	Levofloxacin N[a]	Cure	Improve	Fail	Lomefloxacin N[a]	Cure	Improve	Fail
Citrobacter freundii	5	3 (60)	0 (0)	2 (40)	4	3 (75)	1 (25)	0 (0)
Enterobacter cloacae	5	5 (100)	0 (0)	0 (0)	6	4 (67)	0 (0)	2 (33)
Escherichia coli	92	80 (87)	7 (8)	5 (5)	78	72 (92)	4 (5)	2 (3)
Klebsiella oxytoca	2	1 (50)	1 (50)	0 (0)	1	1 (100)	0 (0)	0 (0)
Klebsiella pneumoniae Proteus	28	25 (89)	1 (4)	2 (7)	24	19 (79)	0 (0)	5 (21)
mirabilis	10	8 (80)	2 (20)	0 (0)	9	7 (78)	1 (11)	1 (11)
Pseudomonas aeruginosa	7	6 (86)	1 (14)	0 (0)	6	4 (67)	0 (0)	2 (33)
Staphylococcus saprophyticus	1	1 (100)	0 (0)	0 (0)	0	0 (-)	0 (-)	0 (-)
Streptococcus agalactiae	2	2 (100)	0 (0)	0 (0)	3	2 (67)	0 (0)	1 (33)
Enterococcus faecalis	6	3 (50)	1 (17)	2 (33)	7	7 (100)	0 (0)	0 (0)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that pathogen alone or in combination with other pathogens.

Table 10c. Clinical Response for Subjects with Pathogens of Primary Interest: FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Pathogen	Levofloxacin N[a]	Cure	Improve	Fail	Lomefloxacin N[a]	Cure	Improve	Fail
Escherichia coli	22	22 (100)	0 (0)	0 (0)	31	25 (81)	5 (16)	1 (3)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that pathogen alone or in combination with other pathogens.

The clinical response rates by diagnosis are presented in Table 11a for sponsor microbiologically evaluable subjects and in Table 11b for FDA microbiologically evaluable subjects. Among the sponsor microbiologically evaluable subjects in the levofloxacin treatment group, clinical success (cured plus improved) was achieved by 93.0% of subjects with complicated UTI, 94.7% of subjects with acute pyelonephritis, and 95.7% of subjects with uncomplicated UTI. In lomefloxacin-treated subjects, the corresponding proportions of subjects with clinical success were 88.5%, 94.9%, and 94.4%, respectively.

Table 11a. Clinical Response Rates by Diagnosis: Sponsor Microbiologically Evaluable Subjects

(Study L91-059)

	Levofloxacin				Lomefloxacin			
Diagnosis	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Complicated UTI	171	145 (84.8)	14 (8.2)	12 (7.0)	165	135 (82.4)	10 (6.1)	19 (11.5)
Acute Pyelonephritis	38	36 (94.7)	0 (0.0)	2 (5.3)	39	31 (79.5)	6 (15.4)	2 (5.1)
Uncomplicated UTI	23	19 (82.6)	3 (13.0)	1 (4.3)	18	15 (83.3)	2 (11.1)	1 (5.6)

Numbers shown in parentheses are percentages for that category.

Table 11b. Clinical Response by Diagnosis: FDA Microbiologically Evaluable Subjects

	Levofloxacin				Lomefloxacin			
Diagnosis	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Complicated UTI	169	143 (85)	14 (8)	12 (7)	158	132 (84)	9 (6)	17 (11)
Acute Pyelonephritis	33	31 (94)	0 (0)	2 (6)	36	28 (78)	6 (17)	2 (6)
Uncomplicated UTI	30	26 (87)	3 (10)	1 (3)	27	21 (78)	3 (11)	3 (11)
Total	232	200 (86)	17 (7)	15 (6)	221	181 (82)	18 (8)	22 (10)

Numbers shown in parentheses are percentages for that category.
[a]N=number of subjects who had that diagnosis.

Table 12 displays the clinical response rates for sponsor microbiologically evaluable subjects by diagnosis and severity. Clinical success rates were similar for mild/moderate versus severe infections. However, the number of subjects with severe infections in both groups was quite small.

Table 12: Clinical Response Rates by Diagnosis and Severity of Infection: Sponsor Microbiologically Evaluable Subjects

(Study L91-059)

	Levofloxacin				Lomefloxacin			
	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Complicated UTI								
Severe	6	5 (83.3)	1 (16.7)	0 (0.0)	4	3 (75.0)	0 (0.0)	1 (25.0)
Mild/Moderate	165	140 (84.8)	13 (7.9)	12 (7.3)	161	133 (82.6)	10 (6.2)	18 (11.2)
Acute Pyelonephritis								
Severe	4	4 (100.0)	0 (0.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	0 (0.0)
Mild/Moderate	34	32 (94.1)	0 (0.0)	2 (5.9)	37	29 (78.4)	6 (16.2)	2 (5.4)
Total Complicated UTI/ Acute Pyelonephritis								
Severe	10	9 (90.0)	1 (10.0)	0 (0.0)	6	5 (83.3)	0 (0.0)	1 (16.7)
Mild/Moderate	199	172 (86.4)	13 (6.5)	14 (7.0)	198	162 (81.8)	16 (8.1)	20 (10.1)
Uncomplicated UTI								
Mild/Moderate	23	19 (82.6)	3 (13.0)	1 (4.3)	18	15 (83.3)	2 (11.1)	1 (5.6)

Numbers shown in parentheses are percentages for that category.

Clinical Signs and Symptoms

The proportions of sponsor microbiologically evaluable subjects with resolution or improvement of clinical signs and symptoms of UTI at the posttherapy visit are presented in Table 13. In general, for both the levofloxacin and lomefloxacin treatment groups, individual signs and symptoms resolved or improved in more than 90% of the subjects, except for incontinence (approximately 70% in both treatment groups).

Table 13: Proportion of Subjects with Resolution or Improvement in Clinical Signs and Symptoms Posttherapy Clinical Assessment: Sponsor Microbiologically Evaluable Subjects (Complicated UTI or Acute Pyelonephritis)

(Study L91-059)

	Levofloxacin				Lomefloxacin			
Signs and Symptoms	Resolved[a,c]	(%)	Improved[b,c]	(%)	Resolved[a,c]	(%)	Improved[b,c]	(%)
Dysuria	150/161	(93.2)	6/161	(3.7)	123/137	(89.8)	7/137	(5.1)
Frequency	146/169	(86.4)	13/169	(7.7)	144/168	(85.7)	11/168	(6.5)
Urgency	120/146	(82.2)	16/146	(11.0)	137/153	(89.5)	6/153	(3.9)
CVA/Flank Pain	63/ 66	(95.5)	2/ 66	(3.0)	55/ 65	(84.6)	8/ 65	(12.3)
Chills	37/ 38	(97.4)	1/ 38	(2.6)	42/ 43	(97.7)	0/ 43	(0.0)
Fever	53/ 54	(98.1)	0/ 54	(0.0)	55/ 56	(98.2)	0/ 56	(0.0)
Incontinence	29/ 63	(46.0)	15/ 63	(23.8)	43/ 65	(66.2)	6/ 65	(9.2)
Nausea	16/ 16	(100.0)	0/ 16	(0.0)	19/ 19	(100.0)	0/ 19	(0.0)
Vomiting	4/ 4	(100.0)	0/ 4	(0.0)	4/ 4	(100.0)	0/ 4	(0.0)

UTI = urinary tract infection, CVA = costovertebral angle.
[a] Signs and symptom present at admission and absent at posttherapy evaluation.
[b] Signs and symptoms were graded as none, mild, moderate, or severe. Improvement was defined as a decrease in severity category without complete resolution.
[c] Denominator represents number of subjects with that sign or symptom at admission.

Microbiologic Results

In vitro susceptibility of all pathogens isolated at admission in the sponsor modified intent-to-treat subjects with an admission pathogen is represented in Table 14.

Table 14: In Vitro Susceptibility of All Pathogens Isolated at Admission: Sponsor Modified Intent-to-Treat Subjects With an Admission Pathogen

(Study L91-059)

	No. (%)[a] of Pathogens			
Susceptibility of Pathogens	Levofloxacin		Lomefloxacin	
Susceptible	252	(96.6%)	224	(85.8%)
Moderately Susceptible	4	(1.5%)	20	(7.7%)
Resistant	5	(1.9%)	17	(6.5%)
Unknown	3		2	
Total No. Pathogens	264		263	

[a] Percentages were based on number of pathogens with known susceptibilities. Pathogens were isolated from 255 subjects in the levofloxacin group and 254 subjects in the lomefloxacin group.

Microbiologic Eradication Rates by Subject

The microbiologic eradication rates at the posttherapy visit for subjects with complicated UTI or acute pyelonephritis who were evaluable by the sponsor for microbiologic efficacy are summarized by treatment group and study center in Table 15a. Among sponsor microbiologically evaluable subjects, the eradication rate was 94.7% in the levofloxacin treatment group, compared with 92.6% in the lomefloxacin treatment group. The 95% confidence interval for the difference (lomefloxacin minus levofloxacin) in eradication rates was [-7.0, 2.8]. *Microbiologic eradication rates are summarized by treatment group and study center for FDA microbiologically evaluable patients with either complicated UTI or acute pyelonephritis in Table 15b, for FDA microbiologically evaluable patients with complicated UTI in Table 15c, and for FDA microbiologically evaluable patients with acute pyelonephritis in Table 15d. In all 3 FDA analyses, no statistically significant treatment differences are detected. In patients with either complicated UTI or acute pyelonephritis and in patients with complicated UTI (FDA analyses), levofloxacin is considered therapeutically equivalent to lomefloxacin. In patients with acute pyelonephritis (FDA analysis), the sponsor is not able to show therapeutic equivalence but they are not expected to (recall the DAIDP "Points to Consider" document requires only 30 acute pyelonephritis patients/arm/study for consideration, thus the studies are never powered to show therapeutic equivalence in acute pyelonephritis). For patients with acute pyelonephritis considered microbiologically evaluable by FDA, levofloxacin obtains a 91% eradication rate while lomefloxacin obtains a 94% eradication rate.*

Table 15a. Microbiologic Eradication Rates and Confidence Intervals by Study Center: Sponsor Microbiologically Evaluable Subjects (Complicated UTI or Acute Pyelonephritis)

(Study L91-059)

	Levofloxacin			Lomefloxacin			
Investigator	N	Eradicated[a,b]	Persisted[a]	N	Eradicated[a,b]	Persisted[a]	95% Confidence Interval[c]
Bakula	8	8 (100.0)	0 (0.0)	9	9 (100.0)	0 (0.0)	(. , .)
Coburn	1	1 (100.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	(. , .)
Cox	37	37 (100.0)	0 (0.0)	37	37 (100.0)	0 (0.0)	(-1.4, 1.4)
Deabate	13	13 (100.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	(-5.0, 5.0)
Faris	13	13 (100.0)	0 (0.0)	6	6 (100.0)	0 (0.0)	(. , .)
Fuselier	0	0 (.)	0 (.)	1	1 (100.0)	0 (0.0)	(. , .)
Green	1	1 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Griffin	3	3 (100.0)	0 (0.0)	3	2 (66.7)	1 (33.3)	(. , .)
Jemsek	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Kane	3	3 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Keeler	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
King	25	23 (92.0)	2 (8.0)	23	22 (95.7)	1 (4.3)	(-12.0, 19.3)
Klimberg	50	49 (98.0)	1 (2.0)	50	47 (94.0)	3 (6.0)	(-12.5, 4.5)
Koper	1	1 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	(. , .)
Leatherman	0	0 (.)	0 (.)	1	1 (100.0)	0 (0.0)	(. , .)
Malek	13	11 (84.6)	2 (15.4)	11	10 (90.9)	1 (9.1)	(-24.2, 35.8)
May	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)	(. , .)
McCrone	1	1 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	(. , .)
Rajfer	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Reid	4	3 (75.0)	1 (25.0)	5	4 (80.0)	1 (20.0)	(. , .)
Sarshik	9	9 (100.0)	0 (0.0)	9	9 (100.0)	0 (0.0)	(. , .)
Serfer	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Tuttle	6	5 (83.3)	1 (16.7)	6	5 (83.3)	1 (16.7)	(. , .)
Urich	0	0 (.)	0 (.)	1	1 (100.0)	0 (0.0)	(. , .)
Valenzuela	4	4 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Wit	0	0 (.)	0 (.)	1	0 (0.0)	1 (100.0)	(. , .)
Witten	3	2 (66.7)	1 (33.3)	3	1 (33.3)	2 (66.7)	(. , .)
Zinner	6	4 (66.7)	2 (33.3)	6	6 (100.0)	0 (0.0)	(. , .)
Combined[d]	71	65 (91.5)	6 (8.5)	73	69 (94.5)	4 (5.5)	(-1.4, 12.3)
Total	283	268 (94.7)	15 (5.3)	284	263 (92.6)	21 (7.4)	(-7.0, 2.8)

[a] Eradication of all pathogens isolated for a subject at admission.

[b] Numbers shown in parentheses are percentages for that category.

[c] Two-sided 95% confidence interval around the difference (lomefloxacin minus levofloxacin) in microbiologic eradication rates were calculated for study centers enrolling 10 or more microbiologically evaluable subjects in each treatment group.

[d] Combined = centers that enrolled fewer than 10 evaluable subjects in either treatment group: Bakula, Coburn, Faris, Fuselier, Green, Griffen, Jemsek, Kane, Keeler, Koper, Leatherman, May, McCrone, Rajfer, Reid, Sarshik, Serfer, Tuttle, Urich, Valenzuela, Wit, Witten, and Zinner.

Table 15b. Microbiologic Eradication Rates and Confidence Intervals By Study Center: FDA Microbiologically Evaluable Subjects (Complicated UTI and Acute Pyelonephritis Only)

Investigator	Levofloxacin		Lomefloxacin		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Cox	37	37 (100)	37	37 (100)	N/A
King	25	23 (92)	22	21 (95)	(-14.6, 21.5)
Klimberg	50	49 (98)	49	47 (96)	(-10.9, 6.7)
Malek	13	11 (85)	11	10 (91)	(-28.0, 40.6)
Other	77	71 (92)	75	66 (88)	(-15.0, 6.6)
Total	202	191 (95)	194	181 (93)	(-6.5, 4.0)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (lomefloxacin minus levofloxacin) in microbiologic eradication rate.

Table 15c. Microbiologic Eradication Rates and Confidence Intervals By Study Center: FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Investigator	Levofloxacin		Lomefloxacin		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Cox	37	37 (100)	37	37 (100)	N/A
King	24	22 (92)	22	21 (95)	(-14.6, 22.2)
Klimberg	42	42 (100)	38	36 (95)	(-14.9, 4.3)
Other	66	60 (91)	61	53 (87)	(-16.5, 8.5)
Total	169	161 (95)	158	147 (93)	(-7.9, 3.5)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (lomefloxacin minus levofloxacin) in microbiologic eradication rate.

Table 15d. Microbiologic Eradication Rates and Confidence Intervals By Study Center: FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Investigator	Levofloxacin		Lomefloxacin		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Other	33	30 (91)	36	34 (94)	(-11.7, 18.8)
Total	33	30 (91)	36	34 (94)	(-11.7, 18.8)

[a]No investigators enrolled 10 or more patients per treatment group with acute pyelonephritis who were considered evaluable by FDA. All investigators are combined under "other".
[b]Numbers shown in parentheses are percentages for that category.
[c]Two-sided confidence interval for the difference (lomefloxacin minus levofloxacin) in microbiologic eradication rate.

Microbiologic Eradication Rates by Pathogen

The microbiologic eradication rates at the posttherapy visit for the sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis in each treatment group are summarized by pathogen category and pathogen (N≥ 5 for either treatment group) in Table 16a (only includes pathogens isolated from urine). The overall microbiologic eradication rates by pathogen in subjects with complicated UTI or acute pyelonephritis in the levofloxacin and lomefloxacin treatment groups were 94.9% and 92.3%, with a 95% confidence interval of [-7.5, 2.3] for the difference between treatments (lomefloxacin minus levofloxacin), assuming independence of multiple pathogens and multiple strains within a subject.

Table 16b summarizes microbiologic eradication rates by pathogen and pathogen category for FDA microbiologically evaluable subjects with complicated UTI. Table 16c summarizes the same information for FDA microbiologically evaluable subjects with acute pyelonephritis. Note: Eradication rates for individual pathogens (in FDA analyses) are shown only for those pathogens requested by the sponsor in their label.

Table 16a. Microbiologic Eradication Rates Summarized by Pathogen Category and Pathogen: Sponsor Microbiologically Evaluable Subjects (Complicated UTI or Acute Pyelonephritis)

(Study L91-059)

Urine Cultures: Pathogen Category/Pathogen	Levofloxacin N	Levofloxacin Eradicated[1]	Lomefloxacin N	Lomefloxacin Eradicated[1]	95% Confidence Interval[2]
Pathogen Category					
Gram-Positive Aerobic Pathogens	19	15 (78.9)	18	13 (72.2)	(-37.1, 23.7)
Gram-Negative Aerobic Pathogens	198	191 (96.5)	190	179 (94.2)	(-6.7, 2.2)
Total by Pathogen	217	206 (94.9)	208	192 (92.3)	(-7.5, 2.3)
Total by Subject	209	198 (94.7)	204	189 (92.6)	(-7.0, 2.8)
Pathogen[4]					
Escherichia coli	119	118 (99.2)	118	116 (98.3)	(-4.1, 2.4)
Klebsiella pneumoniae	31	29 (93.5)	25	23 (92.0)	(-17.3, 14.2)
Proteus mirabilis	11	11 (100.0)	9	9 (100.0)	- -
Staphylococcus faecalis	8	4 (50.0)	8	6 (75.0)	- -
Pseudomonas aeruginosa	9	8 (88.9)	6	4 (66.7)	- -
Enterobacter cloacae	7	6 (85.7)	6	4 (66.7)	- -
Citrobacter freundii	6	4 (66.7)	4	4 (100.0)	- -
Enterobacter sanguinis	2	2 (100.0)	6	6 (100.0)	- -

[1] Numbers shown in parentheses are percentages for that category.
[2] Two-sided 95% confidence interval around the difference (lomefloxacin minus levofloxacin) in microbiologic eradication rates were calculated for pathogens with 10 or more admission isolates in each treatment group.
[3] Eradication of all pathogens isolated for a subject at admission.
[4] N≥5 for either treatment group.

Table 16b. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Complicated UTI Only)

Pathogen Category/Pathogen	Levofloxacin		Lomefloxacin		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	13	11 (85)	13	10 (77)	(-45.5, 30.2)
Gram-negative aerobic pathogens	161	155 (96)	146	139 (95)	(-6.3, 4.1)
Total by pathogen	174	166 (95)	159	149 (94)	(-7.2, 3.8)
Total by subject	169	161 (95)	158	147 (93)	(-7.9, 3.5)
Pathogen					
Citrobacter freundii	5	3 (60)	4	4 (100)	-
Enterobacter cloacae	5	5 (100)	5	4 (80)	-
Escherichia coli	92	91 (99)	78	78 (100)	(-2.2, 4.4)
Klebsiella oxytoca	2	2 (100)	1	1 (100)	-
Klebsiella pneumoniae	28	26 (93)	23	22 (96)	(-13.8, 19.4)
Proteus mirabilis	10	10 (100)	9	9 (100)	-
Pseudomonas aeruginosa	7	6 (86)	6	4 (67)	-
Staphylococcus saprophyticus	1	1 (100)	0	0 (-)	-
Streptococcus agalactiae	2	2 (100)	3	2 (67)	-
Enterococcus faecalis	6	4 (67)	7	6 (86)	-

[a]Numbers shown in parentheses are percentages for that category.

[b]A two-sided confidence interval for the difference (lomefloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Table 16c. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only)

Pathogen Category/Pathogen	Levofloxacin		Lomefloxacin		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	5	3 (60)	4	2 (50)	-
Gram-negative aerobic pathogens	31	30 (97)	33	33 (100)	(-6.1, 12.6)
Total by pathogen	36	33 (92)	37	35 (95)	(-11.4, 17.3)
Total by subject	33	30 (91)	36	34 (94)	(-11.7, 18.8)
Pathogen					
Escherichia coli	22	22 (100)	31	31 (100)	N/A

[a]Numbers shown in parentheses are percentages for that category.

[b]A two-sided confidence interval for the difference (lomefloxacin minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

The one pathogen that was isolated from blood (E. coli in lomefloxacin-treated subject [redacted] was eradicated.

Microbiologic Eradication Rates by Diagnosis and Severity of Infection

The posttherapy microbiologic eradication rates for sponsor microbiologically evaluable subjects in each treatment group are summarized by diagnosis and severity of infection in Table 17. Subjects with complicated UTI had infection eradication rates of 95.3% and 92.1% after treatment with levofloxacin and lomefloxacin, respectively, whereas subjects with acute pyelonephritis had infection eradication rates of 92.1% and 94.9%, respectively. For subjects with complicated UTI or acute pyelonephritis, microbiologic eradication rates were consistently >90% for mild/moderate infections.

Table 17: Microbiologic Eradication Rates Summarized by Diagnosis and Severity of Infection: Sponsor Microbiologically Evaluable Subjects

(Study L91-059)

	Levofloxacin				Lomefloxacin			
	N	Eradicated[a]		Persisted[b]	N	Eradicated[a]		Persisted[b]
Complicated UTI								
Total Severe By Pathogen	6	6	(100.0)	0 (0.0)	5	3	(60.0)	2[c] (40.0)
Total Severe By Subject	6	6	(100.0)	0 (0.0)	4	3	(75.0)	1 (25.0)
Total Mild/Moderate By Pathogen	170	162	(95.3)	8 (4.7)	163	151	(92.6)	12[d] (7.4)
Total Mild/Moderate By Subject	165	157	(95.2)	8 (4.8)	161	149	(92.5)	12 (7.5)
Total Complicated UTI By Pathogen	176	168	(95.5)	8 (4.5)	168	154	(91.7)	14[e] (8.3)
Total Complicated UTI By Subject	171	163	(95.3)	8 (4.7)	165	152	(92.1)	13 (7.9)
Acute Pyelonephritis								
Total Severe By Pathogen	4	4	(100.0)	0 (0.0)	2	2	(100.0)	0 (0.0)
Total Severe By Subject	4	4	(100.0)	0 (0.0)	2	2	(100.0)	0 (0.0)
Total Mild/Moderate By Pathogen	37	34	(91.9)	3 (8.1)	38	36	(94.7)	2 (5.3)
Total Mild/Moderate By Subject	34	31	(91.2)	3 (8.8)	37	35	(94.6)	2 (5.4)
Total Acute Pyelonephritis By Pathogen	41	38	(92.7)	3 (7.3)	40	38	(95.0)	2 (5.0)
Total Acute Pyelonephritis By Subject	38	35	(92.1)	3 (7.9)	39	37	(94.9)	2 (5.1)
Complicated UTI/Acute Pyelonephritis Combined								
Total Severe By Pathogen	10	10	(100.0)	0 (0.0)	7	5	(71.4)	2[c] (28.6)
Total Severe By Subject	10	10	(100.0)	0 (0.0)	6	5	(83.3)	1 (16.7)
Total Mild/Moderate By Pathogen	207	196	(94.7)	11 (5.3)	201	187	(93.0)	14[d] (7.0)
Total Mild/Moderate By Subject	199	188	(94.5)	11 (5.5)	198	184	(92.9)	14 (7.1)
Total Complicated UTI/Pyelonephritis By Pathogen	217	206	(94.9)	11 (5.1)	208	192	(92.3)	16[e] (7.7)
Total Complicated UTI/Pyelonephritis By Subject	209	198	(94.7)	11 (5.3)	204	189	(92.6)	15 (7.4)
Uncomplicated UTI								
Total Mild/Moderate By Pathogen	23	22	(95.7)	1 (4.3)	19	17	(89.5)	2[c] (10.5)
Total Mild/Moderate By Subject	23	22	(95.7)	1 (4.3)	18	16	(88.9)	2 (11.1)
Total Uncomplicated UTI By Pathogen	23	22	(95.7)	1 (4.3)	19	17	(89.5)	2[c] (10.5)
Total Uncomplicated UTI By Subject	23	22	(95.7)	1 (4.3)	18	16	(88.9)	2 (11.1)

Numbers shown in parentheses are percentages for that category.
UTI = urinary tract infection.
[a] Eradication rates by subject reflect eradication of all pathogens isolated for a subject at admission.
[b] Categories of "persisted" and "unknown" combined to create persisted column.
[c] Subject [redacted] was microbiologically evaluable due to clinical failure; the microbiologic eradication rate is unknown because the posttherapy culture was done 1 day posttherapy.
[d] Subject [redacted] had an unknown microbiologic response for the admission pathogen, however, this subject was microbiologically evaluable due to clinical failure.
[e] Subject [redacted] had an unknown microbiologic response for the admission pathogen, however, this subject was microbiologically evaluable due to clinical failure.

Superinfection

In the sponsor microbiologically evaluable group, six subjects in the levofloxacin treatment group and 12 subjects in the lomefloxacin treatment group developed superinfections and had the superinfecting organisms isolated at the posttherapy visit (See Table 18). For these subjects, eight of the isolates with known susceptibility information were susceptible or moderately susceptible to both levofloxacin and lomefloxacin, and four were resistant to both study drugs. In addition, four pathogens were susceptible or moderately susceptible to levofloxacin and resistant to lomefloxacin; the susceptibility to both study drugs was unknown for two isolates.

Table 18. Lists of Subjects with Superinfections: Sponsor's Microbiologically Evaluable Subjects

(Study L91-059)

Subject Number	Period	Pathogen	Type of Specimen	Susceptibility	
				Levofloxacin	Lomefloxacin
Levofloxacin					
	Posttherapy	*Streptococcus sanguis*	Urine	Susceptible	Resistant
	Posttherapy	*Enterococcus*	Urine	Resistant	Resistant
	Posttherapy	*Acinetobacter calcoaceticus*	Urine	Susceptible	Susceptible
	Posttherapy	*Klebsiella pneumoniae*	Urine	Susceptible	Susceptible
	Posttherapy	*Streptococcus faecalis*	Urine	Susceptible	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Susceptible	Susceptible
Lomefloxacin					
	Posttherapy	*Citrobacter*	Urine	Susceptible	Susceptible
	Posttherapy	*Klebsiella pneumoniae*	Urine	Susceptible	Susceptible
	Posttherapy	*Streptococcus faecalis*	Urine	Resistant	Resistant
	Posttherapy	*Staphylococcus aureus*	Urine	Resistant	Resistant
	Posttherapy	*Klebsiella pneumoniae*	Urine	Susceptible	Moderate
	Posttherapy	*Staphylococcus*	Urine	Unknown	Unknown
	Posttherapy	*Enterococcus*	Urine	Unknown	Unknown
	Posttherapy	*Klebsiella*	Urine	Susceptible	Resistant
	Posttherapy	*Klebsiella pneumoniae*	Urine	Susceptible	Susceptible
	Posttherapy	*Serratia marcescens*	Urine	Moderate	Resistant
	Posttherapy	*Enterococcus*	Urine	Resistant	Resistant
	Posttherapy	*Streptococcus faecalis*	Urine	Susceptible	Susceptible

Microbiologic Response at Long-Term Follow-Up

Of the 336 sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis for whom data were available at the long-term follow-up and for whom their long-term response was neither "unknown" or "not applicable", 12 (6.7%) of 178 levofloxacin-treated subjects and 14 (8.9%) of 158 lomefloxacin-treated subjects had a microbiologic relapse. In most cases the pathogens isolated from relapsed subjects were still susceptible to both levofloxacin and lomefloxacin. Among microbiologically evaluable subjects, reinfections (i.e., an infection in which an organism other than the original admission pathogen was isolated) were seen in 15 levofloxacin-treated subjects, and 18 lomefloxacin-treated subjects. In most cases, the isolates were found to be susceptible to both study drugs.

Summary of Key Efficacy Results

The clinical success rates and microbiologic eradication rates are summarized by diagnosis for the levofloxacin and lomefloxacin groups in Table 19 for various sponsor analysis groups. There was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response (See Table 20).

Table 19: Summary of Sponsor Key Efficacy Results: Clinical and Microbiologic Response Rates at Posttherapy for Subjects With Complicated UTI or Acute Pyelonephritis

(Study L91-059)

Response/Group	Levofloxacin Clinical Success or Microbiologic Eradication Rates[a]	Lomefloxacin Clinical Success or Microbiologic Eradication Rates[a]	95% Confidence Interval[b]
Clinical Response			
Microbiologically Evaluable			
Complicated UTI	159/171 (93.0)	146/165 (88.5)	
Acute Pyelonephritis	36/ 38 (94.7)	37/ 39 (94.9)	
Complicated UTI/Acute Pyelonephritis	195/209 (93.3)	183/204 (89.7)	(-8.2, 2.0)
Modified Intent-to-Treat			
Complicated UTI	216/232 (93.1)	193/230 (83.9)	
Acute Pyelonephritis	49/ 55 (89.1)	50/ 56 (89.3)	
Complicated UTI/Acute Pyelonephritis	265/287 (92.3)	243/286 (85.0)	(-12.7, -2.0)
Microbiologic Response			
Microbiologically Evaluable			
Complicated UTI	163/171 (95.3)	152/165 (92.1)	
Acute Pyelonephritis	35/ 38 (92.1)	37/ 39 (94.9)	
Complicated UTI/Acute Pyelonephritis	198/209 (94.7)	189/204 (92.6)	(-7.0, 2.8)
Modified Intent-to-Treat With an Admission Pathogen			
Complicated UTI	170/187 (90.9)	162/183 (88.5)	
Acute Pyelonephritis	35/ 42 (83.3)	40/ 47 (85.1)	
Complicated UTI/Acute Pyelonephritis	205/229 (89.5)	202/230 (87.8)	(-7.7, 4.3)

[a] Denominator for clinical success rate = cured + improved + failed + unable to evaluate. Denominator for microbiologic eradication = eradication + persistence + unknown.

[b] Two-sided 95% confidence interval around the difference (lomefloxacin minus levofloxacin) in clinical success or microbiologic eradication rates.

NOTE: Microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a subject at admission.

UTI = urinary tract infection

Table 20: Summary of Sponsor Key Efficacy Results: Cross-Tabulation of Microbiologic Response Versus Clinical Response at Posttherapy for Microbiologically Evaluable Subjects With Complicated UTI or Acute Pyelonephritis

(Study L91-059)

	Clinical Response											
	Levofloxacin						Lomefloxacin					
Microbiologic Response	N	Cured		Improved		Failed	N	Cured		Improved		Failed
Complicated UTI												
Eradicated	163	144	(88.3)	13	(8.0)	6 (3.7)	152	134	(88.2)	10	(6.6)	8 (5.3)
Persisted	8	1	(12.5)	1	(12.5)	6 (75.0)	13	2	(15.4)	0	(0.0)	11 (84.6)
Acute Pyelonephritis												
Eradicated	36	36	(100.0)	0	(0.0)	0 (0.0)	37	31	(83.8)	5	(13.5)	1 (2.7)
Persisted	3	1	(33.3)	0	(0.0)	2 (66.7)	2	0	(0.0)	1	(50.0)	1 (50.0)
Complicated UTI/Acute Pyelonephritis												
Eradicated	199	179	(90.4)	13	(6.6)	6 (3.0)	189	165	(87.3)	15	(7.9)	9 (4.8)
Persisted	11	2	(18.2)	1	(9.1)	8 (72.7)	15	2	(13.3)	1	(6.7)	12 (80.0)

NOTE: Microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a subject at admission.

UTI = urinary tract infection

SAFETY RESULTS

Table 21 summarizes the incidence of adverse events by body system. The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal (approximately 11% incidence in both treatment groups) and nervous systems (approximately 7% incidence in both treatment groups) and consisted primarily of headache, nausea, constipation, diarrhea, and dizziness. The frequency of adverse events within the different body systems was generally similar in the two treatment groups, except for skin and appendages disorders such as pruritus and photosensitivity reaction (1.8% for levofloxacin and 7.5% for lomefloxacin). The majority of adverse events were mild or moderate in severity; 21 subjects had adverse events considered marked in severity (10 in the levofloxacin-treated group and 11 in the lomefloxacin-treated group). Eight (2.5%) levofloxacin-treated subjects and 16 (5.0%) lomefloxacin-treated subjects had adverse events considered by the investigator to be probably or definitely related to study drug (drug- related). Two subjects had marked drug-related adverse events (one in the levofloxacin-treated group with rash and one in the lomefloxacin group with herpes simplex and photosensitivity reaction). Of the 647 subjects evaluable for safety, 27 (4.2%) subjects discontinued study drug due to adverse events, nine (2.8%) of the 325 subjects evaluable for safety in the levofloxacin group and 18 (5.6%) of the 322 subjects evaluable for safety in the lomefloxacin group. These adverse events included primarily gastrointestinal complaints or skin disorders in the levofloxacin group (nausea and pruritus) and gastrointestinal complaints, skin disorders, psychiatric disorders, or central and peripheral nervous system-related symptoms in the lomefloxacin group (mainly nausea, dizziness, insomnia, and pruritus).

Four (1.2%) subjects in the levofloxacin treatment group and seven (2.2%) subjects in the lomefloxacin treatment group reported serious or potentially serious adverse events, only one of which (dyspnea in a subject who took levofloxacin) was potentially drug-related. The remaining serious adverse events were most likely related to the subjects' underlying conditions. One subject in each treatment group died shortly after participating in the study, but neither death was attributed to study drug. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs occurred infrequently and were generally comparable between the two treatment group.

Table 21: Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety

(Study L91-059)

Body System	Levofloxacin (N=325) No.	(%)	Lomefloxacin (N=322) No.	(%)	95% Confidence Interval*
Gastrointestinal System Disorders	36	(11.1)	36	(11.2)	(-4.9, 5.1)
Central & Peripheral Nervous System Disorders	21	(6.5)	23	(7.1)	(-3.4, 4.7)
Body as a Whole - General Disorders	10	(3.1)	15	(4.7)	(-1.5, 4.7)
Psychiatric Disorders	7	(2.2)	14	(4.3)	(-0.7, 5.1)
Skin and Appendages Disorders	6	(1.8)	24	(7.5)	(2.2, 9.0)
Musculoskeletal System Disorders	6	(1.8)	6	(1.9)	(-2.2, 2.3)
Respiratory System Disorders	5	(1.5)	8	(2.5)	(-1.4, 3.3)
Vision Disorders	2	(0.6)	0	(0.0)	(-1.6, 0.4)
Metabolic and Nutritional Disorders	2	(0.6)	1	(0.3)	(-1.5, 0.8)
Heart Rate and Rhythm Disorders	2	(0.6)	1	(0.3)	(-1.5, 0.9)
Platelet, Bleeding & Clotting Disorders	2	(0.6)	2	(0.6)	(-1.4, 1.4)
Reproductive Disorders, Female[b]	2	(1.0)	4	(1.8)	(-1.7, 3.4)
Hearing and Vestibular Disorders	1	(0.3)	1	(0.3)	(-1.0, 1.0)
Special Senses Other, Disorders	1	(0.3)	2	(0.6)	(-0.9, 1.5)
Cardiovascular Disorders, General	1	(0.3)	1	(0.3)	(-1.0, 1.0)
Vascular (Extracardiac) Disorders	1	(0.3)	3	(0.9)	(-0.7, 2.0)
Urinary System Disorders	1	(0.3)	4	(1.2)	(-0.6, 2.4)
Reproductive Disorders, Male[b]	1	(0.8)	1	(1.0)	(-2.8, 3.1)
Neoplasms	1	(0.3)	0	(0.0)	(-1.1, 0.4)
Resistance Mechanism Disorders	1	(0.3)	4	(1.2)	(-0.6, 2.4)
Total with Adverse Events (%)	74	(22.8)	100	(31.1)	(1.3, 15.2)

*Two-sided 95% confidence interval around the difference (lomefloxacin minus levofloxacin) in incidence of adverse events.

[b]Percentages calculated from the total number of women or men in each group, as appropriate. One hundred twenty-four men and 201 women who were evaluable for safety received levofloxacin; 105 men and 217 women received lomefloxacin.

Adverse events (primary terms) reported for at least 2.0% of subjects in either treatment group are presented in Table 22. The most frequently reported adverse event was nausea, which occurred at a comparable rate in the levofloxacin- and lomefloxacin-treated subjects (4.3% versus 4.7%). Of the remaining adverse events, headache was more common with levofloxacin, while dizziness, pruritus, and photosensitivity reaction were more common with lomefloxacin.

Table 22: Incidence of Frequently Reported (≥2.0%) Adverse Events Summarized by Body System and Primary Term: Subjects Evaluable for Safety

(Study L91-059)

Body System/Primary Term	Levofloxacin (N=325) No. Subjects	%	Lomefloxacin (N=322) No. Subjects	%
All Body Systems	74	22.8	100	31.1
Skin and Appendages Disorders	6	1.8	24	7.5
Pruritus	4	1.2	9	2.8
Photosensitivity Reaction	0	0.0	7	2.2
Central & Peripheral Nervous System Disorders	21	6.5	23	7.1
Headache	15	4.6	9	2.8
Dizziness	3	0.9	14	4.3
Gastrointestinal System Disorders	36	11.1	36	11.2
Nausea	14	4.3	15	4.7
Constipation	8	2.5	6	1.9
Diarrhea	6	1.8	8	2.5
Abdominal Pain	5	1.5	8	2.5

*Primary term reported by ≥2.0% of subjects in either treatment group.

The majority of adverse events were mild or moderate in severity. Ten subjects in the levofloxacin treatment group reported one or more adverse events of marked severity of various types; with the exception of two reports of diarrhea in levofloxacin-treated subject 2702, no single event was reported more than once (see Table 23). Eleven subjects in the lomefloxacin treatment group also reported one or more marked adverse events, including photosensitivity reaction in three subjects and gastrointestinal hemorrhage in two subjects. Most of the marked adverse events were considered by the investigator as unrelated or remotely related to the study drug. One subject in each treatment group had marked drug-related adverse events (rash in one levofloxacin-treated subject and herpes simplex and photosensitivity reaction in one lomefloxacin-treated subject). Four of the 21 subjects with marked adverse events discontinued study drug treatment (two in each group).

Table 23: Subjects With Adverse Events of Marked Severity

(Study L91-059)

Subject Number	Age	Sex	Adverse Event	Relationship To Drug[a]
Levofloxacin				
	80	F	Back Pain	Remote
	72	F	Rash	Probable
	83	M	Urinary Retention	None
	38	F	Depression[‡]	None
	71	M	Carcinoma (prostate cancer)[‡]	None
	67	M	Insomnia	Possible
	84	F	Asthenia	Remote
			Nausea	Remote
	67	F	Constipation	Possible
	63	F	Diarrhea	Possible
			Diarrhea	Remote
	62	F	Hypertension Aggravated	Possible
Lomefloxacin				
	63	F	Cerebrovascular Disorder[‡,b]	None
	75	F	GI Hemorrhage[‡]	None
	60	F	Abdominal Pain[‡]	Remote
			Asthenia[‡]	Remote
			Disseminated Intravascular Coagulation	None
			GI Hemorrhage[‡]	None
			Renal Failure Acute	None
			Sepsis	None
	32	F	Photosensitivity Reaction	Possible
	27	F	Photosensitivity Toxic Reaction	Possible
			Somnolence	Possible
	39	F	Headache	None
	25	F	Ectopic Pregnancy[‡]	None
	63	F	Ketosis[‡]	None
	49	F	Herpes Simplex	Probable
			Photosensitivity Reaction	Probable
	74	F	Mouth Dry	None
	54	F	Back Pain	None

[a] Based on investigator's assessment.
[b] Stroke. * Subject also had a markedly abnormal laboratory value.
** Subject discontinued due to adverse event.
‡ Serious or potentially serious adverse event.

Adverse Events By Gender

The overall incidence of adverse events was higher in women than in men for both the levofloxacin group (28.4% vs. 13.7%) and the lomefloxacin group (35.9% vs. 21.0%). This difference was primarily attributed to adverse events of the GI system and the central and peripheral nervous system. When comparing the incidence of drug-related adverse events, it was noted that all eight drug-related events (mainly GI system) reported in the levofloxacin treatment group

occurred in women. When comparing the incidence of marked adverse events, all 11 marked adverse events in the lomefloxacin treatment group occurred in women.

Discontinuations Due to Adverse Events

Of the 647 subjects evaluable for safety, 27 (4.2%) subjects discontinued the study drug due to adverse events, including nine (2.8%) of the 325 subjects evaluable for safety in the levofloxacin treatment group and 18 (5.6%) of the 322 subjects evaluable for safety in the lomefloxacin treatment group. A summary of discontinuations due to adverse events appears in Table 24.

Table 24: Subjects Who Discontinued Therapy Due to Adverse Events

(Study L91-059)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	72	F	Dyspnea[f]	1	Moderate	Probable	1
			Rash	1	Marked	Probable	
	83	F	Constipation	8	Mild	Remote	8
	77	F	Headache	1	Moderate	Possible	2
			Nausea	1	Mild	Possible	
	67	F	Diarrhea	2	Moderate	Probable	2
			Headache	2	Moderate	Probable	
			Nausea	2	Moderate	Probable	
	54	F	Pruritus	3	Moderate	Possible	5
	41	M	Pruritus	7	Mild	Remote	7
	79	F	Nausea	1	Moderate	Possible	1
			Rigors	1	Moderate	Possible	
			Vomiting	1	Moderate	Possible	
	84	F	Asthenia	5	Marked	Remote	6
			Myalgia	6	Moderate	Remote	
			Nausea	6	Marked	Remote	
	79	M	Pruritus	2	Moderate	Possible	2
Lomefloxacin							
	62	F	Diarrhea	2	Moderate	Possible	2
	73	F	Concentration Impaired	3	Moderate	Possible	5
	32	F	Insomnia	1	Moderate	Probable	2
			Nervousness	2	Moderate	Probable	
	73	F	Dizziness	2	Moderate	Remote	3
	75	F	Insomnia	1	Moderate	Remote	1
			Nervousness	1	Moderate	Remote	
	79	M	Rash erythematous	6	Moderate	Probable	10
	54	F	Stomatitis	4	Mild	Possible	4
			Stomatitis	4	Mild	Possible	
			Back Pain	5	Mild	None	
	78	F	Dizziness	1	Moderate	Possible	3
			Nausea	1	Moderate	Possible	
	70	F	Dysphagia	1	Mild	Probable	1
			Insomnia	1	Mild	Probable	
			Nausea	1	Mild	Probable	
	70	F	Dizziness	1	Moderate	Possible	3
			Ear Disorder[c]	1	Moderate	Possible	
			Headache	1	Mild	Possible	
			Nausea	1	Moderate	Possible	
	53	F	Nausea	1	Mild	Remote	8
			Pruritus	1	Mild	Remote	
	61	F	Vaginal Hemorrhage	4	Mild	None	2
	74	F	Nausea	2	Mild	Possible	3
	68	M	Dizziness	8	Moderate	Probable	7
	59	F	Pruritus	3	Moderate	Probable	3
			Rash	3	Moderate	Probable	
	70	M	Rash	9	Moderate	Definite	9
			Urticaria	9	Moderate	Definite	
	63	F	Ketosis[d,e]	3	Marked	None	3
	49	F	Herpes Simplex	6	Marked	Probable	8
			Photosensitivity Reaction	8	Marked	Probable	

[a]Relative to start of therapy (Day 1). [b]Based on investigator's assessment. [c]Subject stated "ear feels plugged". [d]Diabetic ketoacidosis. [e]Serious or potentially serious adverse event. [f]* Subject also had a markedly abnormal laboratory value.

Serious or Potentially Serious Adverse Events, Including Deaths

Four (1.2%) subjects in the levofloxacin treatment group and seven (2.2%) subjects in the lomefloxacin treatment group reported a serious or potentially serious adverse event during or up to approximately one month after completing study therapy, including one levofloxacin-treated subject ([redacted]) and one lomefloxacin-treated subject ([redacted] who died approximately one month after completing study therapy due to progression of their underlying disease (See Table 25).

In one case ([redacted] dyspnea), the serious adverse event was judged by the investigator to be probably related to study drug. In all other cases, the events were considered by the investigators to be unrelated or remotely related to the study drug (or of unknown relation); most were attributed to the subjects' underlying conditions. Of the 11 subjects with serious or potentially serious adverse events, two subjects withdrew from the study because of the adverse events.

Table 25: Subjects Who Had Serious or Potentially Serious Adverse Events

(Study L91-059)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	72	F	Dyspnea	1	Moderate	Probable	1
	92	F	Dehydration	15 (5 PT)	Unknown	Unknown	10
			Atrial Fibrillation	15 (5 PT)	Unknown	Unknown	
			Hypokalemia	15 (5 PT)	Unknown	Unknown	
			Cardiac Failure[c]	-	Unknown	Remote	
			Cerebral Hemorrhage[d]	42 (32 PT)	Unknown	Remote	
	38	F	Depression	10	Marked	None	10
	71	M	Carcinoma (prostate cancer)	10	Marked	None	10
Lomefloxacin							
	63	F	Cerebrovascular Disorder[e]	18 (4 PT)	Marked	None	14
	76	F	GI Hemorrhage	26 (12 PT)	Marked	None	14
	60	F	Abdominal Pain	23 (9 PT)	Marked	Remote	14
			Asthenia	23 (9 PT)	Marked	Remote	
			GI Hemorrhage	24 (10 PT)	Marked	None	
			Disseminated Intravascular Coagulation[c]	24 (10 PT)	Unknown	None	
			Sepsis[c]	24 (10 PT)	Unknown	None	
			Acute Renal Failure[c]	24 (10 PT)	Unknown	None	
	86	F	Atrial Fibrillation	8	Moderate	None	14
	25	F	Ectopic Pregnancy	6	Marked	None	14
	63	F	Ketosis[f]	3	Marked	None	3
	76	M	Deep Thrombophlebitis	6	Moderate	None	14

[a] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy, relative to the last day of study drug administration.

[b] Based on investigator's assessment.

[c] This adverse event does not appear in the individual study report data base but was captured as serious in the RWJPRI serious adverse event reporting data base. It is therefore reflected as serious in the data base for the NDA Integrated Safety Summary.

[d] This serious adverse event occurred after the scheduled posttherapy visit and therefore does not appear on the case report form or in the data base for this individual study report. However, this event was collected as part of the RWJPRI serious adverse event reporting data base and therefore is reflected in the data base for the NDA Integrated Safety Summary.

[e] Stroke.

[f] Diabetic ketoacidosis.

* Subject discontinued due to this adverse events.

† Subject subsequently died due to progression of these serious adverse events.

Clinical Laboratory Tests

There were no clinically significant mean changes from admission for any laboratory analyte in the levofloxacin-treated or lomefloxacin-treated group, with comparable results in both groups. A summary of markedly abnormal laboratory values after therapy start in subjects with admission data available is shown in Table 26. A list of subjects experiencing treatment-emergent marked abnormalities is presented in Table 27.

Table 26: Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

(Study L91-059)

	Levofloxacin		Lomefloxacin	
Laboratory Test	Proportion[a]	%	Proportion[a]	%
Blood Chemistry				
Elevated Glucose	4/304	1.3	7/301	2.3
Decreased Glucose	3/304	1.0	3/301	1.0
Elevated Potassium	0/306	0.0	1/296	0.3
Elevated Alkaline Phosphate	0/306	0.0	1/297	0.3
Hematology				
Decreased Neutrophils	2/297	0.7	0/293	0.0
Decreased Lymphocytes	6/297	2.0	0/293	0.0

[a] Numerator = number of subjects with a treatment-emergent markedly abnormal test value, and denominator = number of subjects evaluable (i.e., admission and posttherapy data available) for that analyte.

Table 27: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

(Study L91-059)

Subject Number	Age	Sex	Laboratory Test (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[b]	Follow-up Value (Therapy Day)	Duration of Therapy (Days)
Levofloxacin								
	80	F	Glucose (<70 or >200 mg/dL)	123.00	56.00	15 (5 PT)	–	10
	88	M	Neutrophils (<1 x 10³/μL)	3.57	0.86	16 (6 PT)	–	10
	88	F	Glucose (<70 or >200 mg/dL)	156.00	287.00	3 (1 PT)	–	2
	81	F	Lymphocytes (<1 x 10³/μL)	1.71	0.81	15 (5 PT)	–	10
	33	M	Glucose (<70 or >200 mg/dL)	78.00	47.00	21 (11 PT)	–	10
	37	M	Neutrophils (<1 x 10³/μL)	1.49	0.91	18 (8 PT)	–	10
	64	F	Lymphocytes (<1 x 10³/μL)	1.48	0.97	19 (9 PT)	–	10
	81	M	Lymphocytes (<1 x 10³/μL)	1.68	0.96	7	2.02 19 (8 PT)	9
	64	F	Glucose (<70 or >200 mg/dL)	140.00	289.00	16 (6 PT)	–	10
	76	F	Lymphocytes (<1 x 10³/μL)	1.25	0.82	17 (7 PT)	–	10
	67	M	Lymphocytes (<1 x 10³/μL)	2.16	0.94	4	–	4
	40	F	Glucose (<70 or >200 mg/dL)	90.00	51.00	15 (5 PT)	–	10
	85	F	Lymphocytes (<1 x 10³/μL)	1.98	0.97	18 (8 PT)	–	10
	52	M	Glucose (<70 or >200 mg/dL)	114.00	223.00	18 (8 PT)	–	10
	56	F	Glucose (<70 or >200 mg/dL)	106.00	208.00	15 (5 PT)	–	10
Lomefloxacin								
	47	M	Alkaline Phosphatase (>250 IU/L)	152.00	544.00	20 (8 PT)	–	14
	56	F	Potassium (<3.0 or >6.0 mEq/L)	3.80	7.30	4	–	4
	56	F	Glucose (<70 or >200 mg/dL)	224.00	62.00	23 (9 PT)	–	14
	64	F	Glucose (<70 or >200 mg/dL)	122.00	378.00	19 (5 PT)	–	14
	58	M	Glucose (<70 or >200 mg/dL)	67.00	245.00	22 (8 PT)	–	14
	70	F	Glucose (<70 or >200 mg/dL)	154.00	286.00	7 (4 PT)	–	3
	63	M	Glucose (<70 or >200 mg/dL)	106.00	66.00	20 (6 PT)	–	14
	68	F	Glucose (<70 or >200 mg/dL)	136.00	266.00	22 (8 PT)	–	14
	27	F	Glucose (<70 or >200 mg/dL)	261.00	463.00	22 (8 PT)	–	14
	70	F	Glucose (<70 or >200 mg/dL)	77.00	212.00	19 (5 PT)	–	14
	64	M	Glucose (<70 or >200 mg/dL)	136.00	325.00	22 (7 PT)	–	15
	40	F	Glucose (<70 or >200 mg/dL)	332.00	61.00	5	–	5

a Only range given in table. b Relative to start of therapy (Day 1). NOTE: PT refers to number of days posttherapy, relative to last day of study drug administration. * Subject discontinued due to adverse event

SUMMARY AND DISCUSSION

Sponsor microbiologically evaluable subjects with complicated UTI had infection eradication rates of 95.3% and 92.1% after treatment with levofloxacin and lomefloxacin, respectively, whereas subjects with acute pyelonephritis had infection eradication rates of 92.1% and 94.9%, respectively. In subjects with complicated UTI or acute pyelonephritis, levofloxacin treatment resulted in 99.2% eradication of the most common pathogen (E. coli), 93.5% eradication of the second most common pathogen (K. pneumoniae), and 100% eradication of the third most common pathogen (P. mirabilis). The corresponding rates for lomefloxacin were 98.3%, 92.0%, and 100%. Levofloxacin treatment also provided clinical responses comparable to those observed with lomefloxacin. When the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success," the clinical success rates among the sponsor microbiologically evaluable subjects with complicated UTI or acute pyelonephritis were 93.3% with levofloxacin and 89.7% with lomefloxacin, with a 95% confidence interval for the difference of [-9.2, 2.0]. Only 12 pathogens among all pathogens isolated at admission were ultimately identified as resistant to levofloxacin versus 31 for lomefloxacin. In addition, 15 of the 31 lomefloxacin-resistant pathogens were fully susceptible to levofloxacin.

The overall incidence of adverse events was lower in the levofloxacin treatment group (22.8%) than in the lomefloxacin treatment group (31.1%). Gastrointestinal and central and peripheral nervous system symptoms were the most common adverse events, and occurred at a frequency of approximately 11% and 7%, respectively. In addition, skin and appendages adverse events (primarily pruritus and photosensitivity reaction) were reported by a statistically significantly higher proportion of lomefloxacin-treated subjects than levofloxacin-treated subjects. Dizziness, pruritus, and photosensitivity reaction occurred more often in the lomefloxacin group (4.3%, 2.8%, and 2.2%, respectively) than in the levofloxacin group (0.9%, 1.2%, and 0.0%, respectively), whereas headache occurred more often in the levofloxacin group (4.6%) than in the lomefloxacin group (2.8%).

The majority of adverse events were assessed as mild or moderate in severity. Eight (2.5%) subjects in the levofloxacin treatment group and 16 (5.0%) subjects in the lomefloxacin treatment group had adverse events considered by the investigator to be drug-related. The only drug- related adverse events reported by ≥ 1.0% of the subjects were vaginitis (1.0%) in the levofloxacin group and photosensitivity reaction (1.2%) in the lomefloxacin group. Of the two subjects with marked drug-related adverse events, one was in the levofloxacin group (rash) and one was in the lomefloxacin group (photosensitivity reaction and herpes simplex). Nine (2.8%) of the 325 subjects evaluable for safety in the levofloxacin group and 18 (5.6%) of the 322 subjects evaluable for safety in the lomefloxacin group discontinued the study drug due to adverse events. Four subjects in the levofloxacin group and seven subjects in the lomefloxacin group reported serous or potentially serious adverse events, only one of which was probably related to study drug (dyspnea in a subject who received levofloxacin).

One subject in each group died approximately one month after completing study therapy. Neither death was considered by the investigators to be related to study drug.

CONCLUSIONS

Levofloxacin was safe, well tolerated, and effective in the treatment of subjects with complicated urinary tract infections. Clinical cure rates, clinical success rates, and microbiologic eradication rates in the levofloxacin treatment group were considered therapeutically equivalent to those observed in the lomefloxacin group for FDA microbiologically evaluable patients with either complicated UTI or acute pyelonephritis.

Complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* were supported by this study. Complicated urinary tract infections due to other organisms (sought in the proposed label) were not supported by this study alone because the numbers of patients who had complicated UTI due to these organisms were too low (< 10 patients in the levofloxacin arm).

This study alone supports the indication of acute pyelonephritis due to *E. coli*.

REVIEWERS' CONCLUSIONS OF EFFICACY FOR COMPLICATED URINARY TRACT INFECTIONS AND ACUTE PYELONEPHRITIS

Because low numbers of organisms were identified as the etiology for complicated urinary tract infections, a combination analysis was performed to assess the microbiologic eradication rates by pathogen category and pathogen in FDA microbiologically evaluable subjects. This combined analysis is shown in Table 1. These results indicate that the combination of the two pivotal complicated UTI studies support the treatment of complicated UTI for infections due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterococcus faecalis, and Enterobacter cloacae. Klebsiella oxytoca, Staphylococcus saprophyticus, Citrobacter frundii, and Streptococcus agalactiae* were also sought by the sponsor in the proposed label. However, the combined analysis did not support this claim because there were too few patients that had complicated UTI due to these organisms (< 10 organism in the combined levofloxacin treatment arms for the two studies).

Table 1. Combined Analysis of Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Complicated UTI Only) - Studies K91-058 and L91-059

	Levofloxacin		Ciprofloxacin or Lomefloxacin	
Pathogen Category/Pathogen	N	Eradicated[a]	N	Eradicated[a]
Pathogen Category				
Gram-positive aerobic pathogens	23	20 (87)	25	17 (68)
Gram-negative aerobic pathogens	279	266 (95)	247	235 (95)
Total by pathogen	302	286 (95)	272	252 (93)
Total by subject	282	265 (93)	262	243 (93)
Pathogen				
Citrobacter freundii	7	5 (71)	7	6 (86)
Enterobacter cloacae	13	13 (100)	9	8 (89)
Escherichia coli	140	136 (97)	130	129 (99)
Klebsiella oxytoca	6	6 (100)	5	5 (100)
Klebsiella pneumoniae	54	52 (96)	37	35 (95)
Proteus mirabilis	19	18 (94)	11	11 (100)
Pseudomonas aeruginosa	17	13 (76)	13	11 (84)
Staphylococcus saprophyticus	1	1 (100)	0	0 (-)
Streptococcus agalactiae	2	2 (100)	4	4 (100)
Enterococcus faecalis	12	10 (83)	17	12 (70)

[a]Numbers shown in parentheses are percentages for that category.

The only organism for acute pyelonephritis that the sponsor indicated in the proposed labeling was *Escherichia coli.* When combining the two FDA analyses for the microbiologic eradication rates among microbiologically evaluable subjects (Table 2), it can be seen that levofloxacin clearly was efficacious in the treatment of acute pyelonephritis due to *Escherichia coli.*

Table 2. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Acute Pyelonephritis Only) - Studies K91-058 and L91-031

	Levofloxacin		Ciprofloxacin or Lomefloxacin	
Pathogen Category/Pathogen	N	Eradicated[a]	N	Eradicated[a]
Pathogen Category				
Gram-positive aerobic pathogens	13	10 (77)	13	9 (69)
Gram-negative aerobic pathogens	72	70 (97)	84	82 (98)
Total by pathogen	85	80 (94)	97	91 (94)
Total by subject	78	73 (94)	92	86 (93)
Pathogen				
Escherichia coli	53	53 (100)	71	69 (97)

[a]Numbers shown in parentheses are percentages for that category.

68 Pages
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MEDICAL AND STATISTICAL OFFICER'S MAIN SAFETY CONCLUSIONS

The data submitted from NDAs 20-624 and 20-625 support the safety of levofloxacin when given for those indications proposed. The safety and tolerability profiles were comparable to approved comparator antimicrobial agents and other quinolone agents given for similar indications.

Detailed analyses of syndromes and disorders associated with the administration of some or all quinolone agents--hypoglycemia, seizures, tendon rupture, phototoxicity, pancreatitis, cardiac toxicity, crystalluria, ocular toxicities, rhabdomyolysis, and the multiple organ-system events that characterize the "temafloxacin syndrome"--indicate that the expected risk of these events among levofloxacin-treated subjects appears to be quite low. Of note is the markedly lower incidence of phototoxicity as compared with lomefloxacin when given for complicated urinary tract infections. The data indicate that levofloxacin is not likely to have the safety problems associated with temafloxacin.

MAIN MEDICAL AND STATISTICAL OFFICER'S CONCLUSIONS

1) Levofloxacin (tablets and i.v. solution) is safe for the proposed indications of uncomplicated skin and skin structure infections, complicated urinary tract infections, acute pyelonephritis, community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis.

2) Levofloxacin (tablets and i.v. solution) is efficacious for the proposed indications (reviewed by this Medical Officer) of uncomplicated skin and skin structure infections, complicated urinary tract infections and acute pyelonephritis. For main efficacy conclusions for acute bacterial sinusitis, community acquired pneumonia, and acute bacterial exacerbation of chronic bronchis.

Robert Hopkins MD

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Medical Reviewer

Nancy Silliman

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Statistical Reviewer

cc: Archival: NDA 20-634
Archival: NDA 20-635
HFD-520
HFD-520/Dr. Hopkins
HFD-520/Dr. Silliman
HFD-520/Dr. Frank
HFD-520/Dr. Albuerne MDA 11/12/01
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HFD-520/Dr. Shetty
HFD-520/Dr. Ajayi
HFD-520/Ms. Lesane
HFD-725/Dr. Harkins

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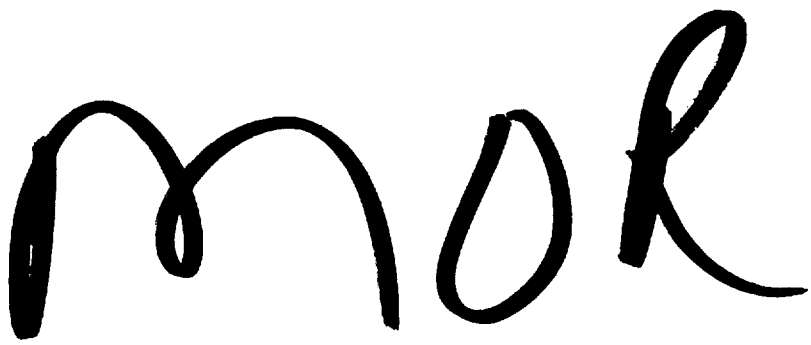

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

Tablets & Injections 250mg 500mg

NDA/PLA/PMA # 20-634 20-635 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Levaquin (levofloxacin) Action: AP AE NA

Applicant R.W. Johnsons Therapeutic Class IS

Indication(s) previously approved —
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Not approval letter (For supplement answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[illegible], Project Manager 12-9-96
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-634, 20-635
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

** Safety and effectiveness in children and adolescents below the age of 18 years of age have not been established. Quinolones, including levofloxacin, causes arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS.**) **

DEBARMENT CERTIFICATION

The R.W. Johnson Pharmaceutical Research Institute certifies that we did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or 306 (b) of the Federal Food Drug and Cosmetic Act in connection with this Four-Month Safety Update to our pending New Drug Application.

NDA 20-634
ELEQUIN™(levofloxacin tablets) Tablets
Item 13
Patent Information

Levofloxacin is protected by the following:

U.S. Patent No.	Patent Type	Expiration Date	Owner	U.S. Agent
4,382,892	Drug Substance (Broad patent covers compound regardless of steriochemistry)	Sept. 2, 2001	Daiichi Seiyaku, Co., Ltd. Tokyo, Japan	Daiichi Pharmaceutical 1 Parker Plaza Fort Lee, NJ 07024
5,053,407	Drug Substance	Oct. 1, 2008	Daiichi Pharmaceutical Co., Ltd Tokyo, Japan	

MEDICAL OFFICER'S REVIEW
OF FINAL SAFETY UPDATE
Levofloxacin NDAs 20-634 and 20-635

On December 3, RPI submitted the final safety update for NDAs 20-634 and 20-635. It was agreed that this information would be submitted in a summary format at the November 19, 1996 meeting. This summary contains information received since the October 31, 1995 data cut-off date for the Four-Month Safety Update.

It is estimated that approximately million prescriptions for levofloxacin have been filled in Japan. In addition, levofloxacin has been given to approximately 10,000 subjects who participated in clinical studies conducted in the United States, Japan, and other countries.

This safety update mainly comprised serious adverse event reports from ongoing studies that were not considered as primary or supportive studies, or from marketed product information from Japan.

A study was considered "primary" for the purpose of safety analyses if it was a pivotal efficacy study or a primary PK study or it was sponsored by PRI.

Primary Studies
In the primary studies, there were four new subjects who reported serious adverse events from one study (HR355/1/USA/103/GP) sponsored by PRI (Sponsor Table 1).

Other Sources
Safety information was also gathered from other studies, spontaneous safety information from Japan, and a literature review.

Other Studies
A total of 13 studies were conducted: four by seven by one by NIH, and one by Eight of the 13 studies had new or updated safety information (serious adverse events, SAEs) as shown in Sponsor Table 2. As of July 31, 1996, SAEs had been reported for 382 subjects in these eight studies, including 113 subjects who died.

As seen in Sponsor Table 2, the percent of patients with serious adverse events among studies ranged between 2% and 17% for levofloxacin and between 4% and 17% for controls. The percent of deaths among studies ranged between 0% and 8% for levofloxacin and between 1% and 9% for controls. The highest number of serious adverse events and deaths occurred in a study of suspected bacteremia/sepsis (HR355/2/MN/304-SP) where 8% and 9% of patients died in the levofloxacin and imipenam control arm, respectively. There is no evidence to suggest that levofloxacin is associated with more serious adverse events or deaths as compared with control agents when used to treat similar indications.

Review of Sponsor Table 3 which details the incidence by body system and primary term of new serious adverse events reported from other studies, suggests that there is no significant difference in SAE frequency when comparing levofloxacin with comparison agents.

Thirty-three deaths were reported in an NIH-sponsored trial evaluating the treatment of pulmonary mycobacterium tuberculosis in HIV infected subjects filed to NIH IND conducted with levofloxacin (Sponsor Table 4). For patients whom causes of death was identified, they primarily died of their underlying diseases.

Marketed Product Information from Japan
Sixty new SAEs were submitted to PRI from November 1, 1995 to July 31, 1996. It is estimated that approximately [redacted] million additional prescriptions have been filled during the period between January and

MAIN MEDICAL AND STATISTICAL OFFICER'S CONCLUSIONS

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Nancy Silliman

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cc: Archival: NDA 20-634
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HFD-520/Ms. Lesane
HFD-725/Dr. Harkins

Table 1: Listing of Subjects with Newly Reported Serious Adverse Events in Primary Study HR355/1/USA/103/GP
(November 1, 1995 through July 31, 1996)

Subject	Sex	Age	Adverse Event	Primary Term	Adverse Event Start	Adverse Event Stop	Serious	Assoc.	Outcome
Study Number: 1GB-103GP									
Drug Code: Study Drug									
Investigator Number: 0001									
21	M	68	Fatal metastatic carcinoma of bronchus	Condition Aggravated	Unknown	96Mar27	Y	N	Death
			Fatal metastatic carcinoma of bronchus	Pulmonary Carcinoma	Unknown	96Mar27	Y	N	Death
			Flu	Influenza-Like Symptoms	96Mar14	Unknown	N	N	Unknown
			Hospitalization for ERCP	Gastrointestinal Disorder NOS	96Mar07	96Mar07	Y	N	Recovered
			Jaundice due to liver metastases	Jaundice	96Feb23	Unknown	Y	N	Unknown
			Liver metastases from lung cancer	Hepatic Neoplasm	96Feb23	96Mar27	Y	N	Death
33	F	69	Metastatic small cell carcinoma of lung	Pulmonary Carcinoma	96Apr17	96May14	Y	N	Death
			Widespread liver metastases	Hepatic Neoplasm	96Apr17	96May14	Y	N	Death
35	M	75	"Desaturation" during bronchoscopy	Hypoxia	96May01	96May17	Y	N	Recovered
39	M	67	Pain (assc. with susp. cancer of lung)	Pain	96May22	96Jun07	Y	N	Disability

NOS=Not otherwise specified.

Table 2: Incidence of Serious Adverse Events Reported in Other Studies Through July 31, 1996

Protocol No	Indication	Study Design	Subjects Enrolled Through 10/31/95	Subjects Enrolled Through 7/31/96	Subjects Who Had Serious Adverse Events (SAEs) SAEs Through 10/31/95	SAEs Through 7/31/96	Deaths Through 10/31/95	Deaths Through 7/31/96
[redacted] OTHER STUDIES								
Completed Studies								
HR355/2/MN/301-CB	Acute exacerbation of chronic bronchitis	Multicenter, double-blind, randomized, active-controlled (2 arms on LFLX 1 arm on CEFU)	836[a]	561 LFLX 271 CEFU 7 NONE	106	82 LFLX 31 CEFU 1 NONE	17	14 LFLX 4 CEFU
FF/93/355/02	Community-acquired pneumonia	Multicenter, double-blind, randomized, active-controlled (2 arms on LFLX 1 arm on AMOX)	472	348 LFLX 168 AMOX 2 NONE	22	17 LFLX 7 AMOX	2	0 LFLX 2 AMOX
HR355/2/MN/301-LR	Pneumonia in hospitalized patients	Multicenter, open, randomized, active-controlled	577	319 LFLX[b] 306 CEFT[b]	43 LFLX 39 CEFT	55 LFLX 54 CEFT 1 NONE	18 LFLX 16 CEFT	22 LFLX 24 CEFT 1 NONE
HR355/2/MN/305-AH	Intraabdominal infections	Multicenter, open, randomized, active-controlled	80	165 LFLX[b] 158 CFLX[b]	3 LFLX 3 CFLX 1 NONE	24 LFLX 25 CFLX 1 NONE	0 LFLX 1 CFLX 1 NONE	1 LFLX 4 CFLX 1 NONE
FF94/355/05	Pleural fluid penetration	Phase I, single-dose, non-comparative		12 LFLX		1 LEVO		1 LEVO
Ongoing Studies								
HR355/2/MN/304-SP	Suspected bacteremia/sepsis	Multicenter, open, randomized active-controlled	28	178 LFLX[b] 177 IMIP[b]	3 LFLX 4 IMIP	28 LFLX 29 IMIP 1 NONE	3 LFLX 2 IMIP	14 LFLX 16 IMIP 1 NONE
HR355/2/MN/303-NE	Infection/fever in neutropenic patients	Multicenter, open, randomized, active-controlled	56	59 LFLX[b] 58 IMIP[b]	1 LFLX 4 IMIP	2 LFLX 5 IMIP	1 LFLX 3 IMIP	1 LFLX 4 IMIP
		HAG Total through July 31, 1995:	2049	1642 LFLX[b] 1138 COMP[b] 9 NONE	50 LFLX 50 Comparator 1 None 128 Unknown	209 LFLX 151 Comparator 4 None	22 LFLX 22 Comparator 1 None 19 Unknown	53 LFLX 54 Comparator 3 None
[redacted] UK STUDY								
HR355/DPL-E18	Uncomplicated SSTI	Multi-center, double-blind, randomized, active control (2 arms on LFLX 1 arm on AMOX)	701	469 LFLX 232 AMOX 2 NONE	18	9 LFLX 9 AMOX	3	0 LFLX 3 AMOX

[a] It is known that two of these subjects did not receive study drug

[b] Only total enrollment figures are provided. A small number of each assigned treatment group may not have received drug

NOTE: LFLX = levofloxacin, CEFU = cefuroxime axetil, AMOX = amoxicillin/clavulanic acid, CEFT = ceftriaxone, IMIP = imipenem/cilastatin, CFLX = ciprofloxacin, NONE = no study drug given, COMP = comparator. "Unknown" refers to subjects in two HAG double-blind studies for which the blind had not been broken as of the 4/30/95 date.

TABLE 3: INCIDENCE BY BODY SYSTEM AND PRIMARY TERM OF NEW SERIOUS ADVERSE EVENTS REPORTED FROM OTHER [redacted] STUDIES (NOVEMBER 1, 1995 THROUGH JULY 31, 1996)

BODY SYSTEM	DRUGCODE	PRIMARY	N
BODY AS A WHOLE - GENERAL DISORDERS	LEVO	ADE, NOS	2
	COMPARATOR	ADE, NOS	1
	LEVO	ASTHENIA	2
	COMPARATOR	CHEST PAIN SUBSTERNAL	1
	LEVO	CONDITION AGGRAVATED	10
	COMPARATOR	CONDITION AGGRAVATED	14
	LEVO	FEVER	1
	COMPARATOR	FEVER	2
	LEVO	HYPERPYREXIA MALIGNANT	1
	LEVO	INFECTION TBC	2
	COMPARATOR	INFECTION TBC	1
	LEVO	MALAISE	1
	COMPARATOR	MALAISE	2
	LEVO	MULTISYSTEM ORGAN FAILURE	1
	COMPARATOR	MULTISYSTEM ORGAN FAILURE	6
	COMPARATOR	SUDDEN DEATH	2
	LEVO	THERAPEUTIC RESPONSE DECREASED	6
	COMPARATOR	THERAPEUTIC RESPONSE DECREASED	7
	LEVO	THERAPEUTIC RESPONSE INCREASED	1
CARDIOVASCULAR DISORDERS, GENERAL	LEVO	CARDIAC FAILURE	6
	COMPARATOR	CARDIAC FAILURE	5
	LEVO	CIRCULATORY FAILURE	3
	COMPARATOR	CIRCULATORY FAILURE	4
	COMPARATOR	HYPERTENSION PULMONARY	1
	LEVO	HYPOTENSION	2
CENTR & PERIPH NERV SYST DISORDERS	LEVO	BRAIN STEM DISORDER	1
	LEVO	COMA	2
	COMPARATOR	CONVULSIONS	1
	LEVO	CONVULSIONS GRAND MAL	1
	LEVO	ENCEPHALOPATHY	2
	COMPARATOR	ENCEPHALOPATHY	1
	LEVO	HEMIPLEGIA	2
	COMPARATOR	HEMIPLEGIA	1
	LEVO	MENINGITIS	1
	LEVO	PARALYSIS	2
COLLAGEN DISORDERS	LEVO	WEGENER'S GRANULOMATOSIS	1
FETAL DISORDERS	COMPARATOR	ATRIAL SEPTAL DEFECT	1
GASTROINTESTINAL SYSTEM DISORDERS	COMPARATOR	ABDOMINAL PAIN	1
	LEVO	DIARRHEA	1
	COMPARATOR	DIARRHEA, CLOSTRIDIUM DIFFICILE	1
	LEVO	DIVERTICULITIS	1
	COMPARATOR	DIVERTICULITIS	1
	COMPARATOR	DUODENAL ULCER HEMORRHAGIC	1
	COMPARATOR	GASTRIC ULCER	1
	LEVO	GASTROINTESTINAL DISORDER NOS	1
	COMPARATOR	GASTROINTESTINAL DISORDER NOS	3
	COMPARATOR	GI HEMORRHAGE	2
	COMPARATOR	HEMATEMESIS	1
	COMPARATOR	ILEUS	1
	LEVO	INTESTINAL OBSTRUCTION	1
	COMPARATOR	INTESTINAL OBSTRUCTION	1
	COMPARATOR	INTESTINAL PERFORATION	1
	COMPARATOR	NAUSEA	1
	LEVO	PANCREATITIS	2

TABLE 3: INCIDENCE BY BODY SYSTEM AND PRIMARY TERM OF NEW SERIOUS ADVERSE EVENTS REPORTED FROM OTHER [redacted] STUDIES (NOVEMBER 1, 1995 THROUGH JULY 31, 1996)

BODY SYSTEM	DRUGCODE	PRIMARY	N
GASTROINTESTINAL SYSTEM DISORDERS (Continued)	LEVO	PERITONITIS	1
	LEVO	VOMITING	1
	COMPARATOR	VOMITING	1
HEART RATE AND RHYTHM DISORDERS	LEVO	ARRHYTHMIA ATRIAL	1
	LEVO	BRADYCARDIA	2
	COMPARATOR	BRADYCARDIA	2
	LEVO	CARDIAC ARREST	2
	COMPARATOR	CARDIAC ARREST	3
	LEVO	FIBRILLATION ATRIAL	3
	COMPARATOR	FIBRILLATION VENTRICULAR	2
	COMPARATOR	TACHYCARDIA SUPRAVENTRICULAR	1
LIVER AND BILIARY SYSTEM DISORDERS	LEVO	CHOLECYSTITIS	1
	COMPARATOR	CHOLELITHIASIS	1
	COMPARATOR	GAMMA-GT INCREASED	1
	COMPARATOR	SGPT INCREASED	1
METABOLIC AND NUTRITIONAL DISORDERS	LEVO	DIABETES MELLITUS	2
	LEVO	HYPERKALEMIA	1
MUSCULOSKELETAL SYSTEM DISORDERS	LEVO	FRACTURE PATHOLOGICAL	1
	LEVO	OSTEOMYELITIS	1
MYO ENDO PERICARDIAL & VALVE DISORDERS	LEVO	CORONARY ARTERY DISORDER	1
	COMPARATOR	ENDOCARDITIS	1
	LEVO	HEMOPERICARDIUM	1
	LEVO	MYOCARDIAL INFARCTION	6
	LEVO	PERICARDIAL EFFUSION	1
	LEVO	PERICARDITIS	1
NEOPLASMS	COMPARATOR	BLADDER CARCINOMA	1
	LEVO	GI NEOPLASM MALIGNANT	2
	COMPARATOR	GI NEOPLASM MALIGNANT	3
	COMPARATOR	LYMPHOMA MALIGNANT	1
	LEVO	PULMONARY CARCINOMA	1
	COMPARATOR	PULMONARY CARCINOMA	4
	COMPARATOR	RENAL CARCINOMA	1
PLATELET,BLEEDING & CLOTTING DISORDERS	COMPARATOR	DISSEM. INTRAVASC. COAGULATION	2
	LEVO	EMBOLISM PULMONARY	1
	LEVO	HEMORRHAGE NOS	2
	COMPARATOR	PURPURA THROMBOCYTOPENIC	1
	COMPARATOR	THROMBOSIS CEREBRAL	2
PSYCHIATRIC DISORDERS	LEVO	CONFUSION	2
	LEVO	DELIRIUM	1
RED BLOOD CELL DISORDERS	LEVO	ANEMIA	1
	COMPARATOR	ANEMIA	2
	COMPARATOR	SPLEEN DISORDER	1
REPRODUCTIVE DISORDERS, MALE	COMPARATOR	PROSTATIC DISORDER	1
RESISTANCE MECHANISM DISORDERS	LEVO	ABSCESS	1
	COMPARATOR	ABSCESS	5
	LEVO	HEALING IMPAIRED	2
	COMPARATOR	HEALING IMPAIRED	1
	LEVO	INFECTION	3
	COMPARATOR	INFECTION	1
	LEVO	SEPSIS	1
	COMPARATOR	SEPSIS	5

TABLE 3: INCIDENCE BY BODY SYSTEM AND PRIMARY TERM OF NEW SERIOUS ADVERSE EVENTS REPORTED FROM OTHER [redacted] STUDIES (NOVEMBER 1, 1995 THROUGH JULY 31, 1996)

BODY SYSTEM	DRUGCODE	PRIMARY	N
RESPIRATORY SYSTEM DISORDERS	LEVO	APNEA	2
	LEVO	BRONCHITIS	1
	COMPARATOR	BRONCHITIS	1
	COMPARATOR	BRONCHOSPASM	2
	COMPARATOR	COUGHING	1
	LEVO	DYSPNEA	1
	LEVO	HEMOTHORAX	1
	COMPARATOR	HYPOVENTILATION	1
	COMPARATOR	HYPOXIA	1
	COMPARATOR	PLEURAL EFFUSION	2
	LEVO	PNEUMONIA	5
	COMPARATOR	PNEUMONIA	4
	LEVO	PNEUMOTHORAX	1
	LEVO	PULMONARY EDEMA	1
	COMPARATOR	PULMONARY EDEMA	4
	LEVO	RESPIRATORY DISORDER	2
	COMPARATOR	RESPIRATORY DISORDER	3
	LEVO	RESPIRATORY INSUFFICIENCY	5
	COMPARATOR	RESPIRATORY INSUFFICIENCY	7
	LEVO	UPPER RESP TRACT INFECTION	1
SKIN AND APPENDAGES DISORDERS	LEVO	CELLULITIS	1
	LEVO	RASH	1
	LEVO	SKIN DISORDER	1
URINARY SYSTEM DISORDERS	LEVO	HEMATURIA	1
	COMPARATOR	MICTURITION DISORDER	1
	LEVO	OLIGURIA	2
	COMPARATOR	PYELONEPHRITIS	2
	LEVO	RENAL FAILURE ACUTE	1
	COMPARATOR	RENAL FAILURE ACUTE	3
	LEVO	RENAL FUNCTION ABNORMAL	1
VASCULAR (EXTRACARDIAC) DISORDERS	LEVO	CEREBROVASCULAR DISORDER	2
	COMPARATOR	CEREBROVASCULAR DISORDER	3
	COMPARATOR	FLUSHING	1
	COMPARATOR	HEPATIC INFARCTION	1
	LEVO	PERIPHERAL ISCHAEMIA	1
	COMPARATOR	VEIN DISORDER	1
VISION DISORDERS	COMPARATOR	BLINDNESS	1
WHITE CELL AND RES DISORDERS	COMPARATOR	LEUCOPENIA	1
	COMPARATOR	LEUKOCYTOSIS	1
OVERALL	LEVO		68
	COMPARATOR		66

Table 4

Summary of Death Notification
through 11/30/95
Protocol: TB Treatment (CPCRA 019/ACTG 222)
Induction Phase

Patient ID	Date of Death	Primary Causes
	02/03/95	1: 0A0449 HIV DISEASE PROGRESSION UNSPEC
	05/16/93	1: 0P4151 EMBOLI PULMONARY 2: 0PS128 PNEUMOTHORAX NEC 3: 0P0119 MYCOBACTERIUM PULMONARY TB NEC
	07/23/93	1: 1C9049 ANEURYSM BLEEDING NEC 2: 0B4109 HEART ATTACK MYOCARDIAL INFARCT 3: 0P4151 EMBOLI PULMONARY
	06/26/95	1: 0A0318 MAC NEC 2: 0Z7832 WASTING NEC
	12/14/93	1: 0A9993 CATHETER RELATED SEPSIS NEC 2: 1A11289 CANDIDA FUNGEMIA 3: 0J5781 BLOOD IN STOOL MELENA
	12/10/93	1: 0PS070 ASPIRATION PNEUMONIA DUE TO INH 2: 3N0785 CMV ENCEPHALITIS + 3: 0A4275 ARREST CARDIORESPIRATORY
	01/30/94	1: 1A7989 DEATH EVENT NOS
	09/17/93	1: 2A0318 DISSEMINATED MAI NEC
	02/01/94	1: 0B4275 ARREST CARDIAC 2: 3N1300 BRAIN TOXOPLASMOSIS PROVEN +
	07/05/95	1: 0P7991 ARREST RESPIRATORY 2: 0A0318 MAC NEC
	08/21/95	1: 1A7989 DEATH EVENT NOS

Table 4

Summary of Death Notification
through 11/30/95
Protocol: TB Treatment (CPCRA 019/ACTG 222)
Continuation Phase

Patient ID	Date of Death	Primary Causes
	12/24/94	1: 0A0389 SEPSIS NEC 2: 2J5589 COLITIS NEC
	05/26/95	1: 0A0389 SEPSIS NEC 2: 0P4829 BACTERIAL PNEUMONIA 3: 3P0119 MYCOBACTER TUBERCULOSIS PULMONA
	07/20/95	1: 0A0179 EXTRA-PULMONARY TB NEC
	09/03/95	1: 2N1300 BRAIN TOXOPLASMOSIS CLINICAL Dx
	04/10/95	1: 5Z7832 AIDS DEFINING HIV WASTING -
	02/01/95	1: 0A1369 PARASITIC INFECTION NEC 2: 0B4280 CHF
	08/15/95	1: 0A0429 ACQUIRED IMMUNODEFICIENCY DISEA 2: 0Z7832 WASTING NEC 3: 0A0785 CMV CYTOMEGALOVIRUS NEC -
	09/25/94	1: 0A4275 ARREST CARDIORESPIRATORY 2: 0A0429 ACQUIRED IMMUNODEFICIENCY DISEA 3: 0N0463 LEUKOENCEPHALOPATHY MULTIFOCAL
	06/22/95	1: 0AE9509 DRUG OVERDOSE
	04/28/94	1: 0A1175 CRYPTOCOCCOSIS INFECTION NEC - 2: 0P51881 FAILURE RESPIRATORY ACUTE CHRON
	09/22/94	1: 0P0119 MYCOBACTERIUM PULMONARY TB NEC 2: 1A1739 KAPOSI'S SARCOMA
	11/30/94	1: 0A0449 HIV DISEASE PROGRESSION UNSPECI
	07/28/94	1: 0H20280 LYMPHOMA NEC -
	07/15/94	1: 0P1363 PCP NEC -
	09/28/94	1: 3P1363 PNEUMOCYSTIS CARINII PNEUMONIA
	07/15/95	1: 1A7989 DEATH EVENT NOS
	12/25/94	1: 0A0449 HIV DISEASE PROGRESSION UNSPECI

Table 4

Summary of Death Notification
through 11/30/95
Protocol: TB Treatment (CPCRA 019/ACTG 222)
Continuation Phase

Patient ID	Date of Death	Primary Causes
	10/23/95	1: 0Z7832 WASTING NEC
		2: 0N0463 LEUKOENCEPHALOPATHY MULTIFOCAL
		3: 2N2989 AIDS DEMENTIA +
	04/30/95	1: 0N1175 CNS DISORDER CRYPTOCOCCOSIS NEC
		2: 1A1739 KAPOSI'S SARCOMA
	05/16/95	1: 0A4275 ARREST CARDIORESPIRATORY
		2: 0A0429 ACQUIRED IMMUNODEFICIENCY DISEA
		3: 0A0389 SEPSIS NEC
	04/19/95	1: 0A0429 ACQUIRED IMMUNODEFICIENCY DISEA
	05/23/95	1: 0A0429 ACQUIRED IMMUNODEFICIENCY DISEA
		2: 0L5728 FAILURE HEPATIC

Addendum to Medical Officer's Review of NDA 20-634
Levaquin® (levofloxacin) Tablets
Addendum to Medical Officer's Review of NDA 20-635
Levaquin® (levofloxacin) Intravenous Injection

Date: December 19, 1996

Indication: Community-acquired Pneumonia

Purpose: Re-evaluation of *Legionella pneumophilia* and *Klebsiella pneumoniae* cases from the following Clinical Studies

1. Pivotal and supportive studies from which cases of community-acquired pneumonia due to *Klebsiella pneumonia* and *Legionella pneumophilia* were obtained:

1.1. Pivotal studies conducted primarily in the United States:

1.1.1. Study K90-071: A multicenter, randomized, open-label study to compare the safety and efficacy of levofloxacin (488 mg PO or 500 mg IV QD for 7-14 days) with ceftriaxone sodium (1 GM IV q12h or 2 GM IV q24h for 7-14 days) OR cefuroxime axetil (500 mg PO BID for 7-14 days) in the treatment of community acquired pneumonia in adults

1.1.2. Study M92-075: A multicenter, noncomparative, open-label study to evaluate the safety and efficacy of levofloxacin (500 mg PO or IV QD for 7-14 days) in the treatment of community acquired pneumonia in adults

1.2. Supportive foreign study:

1.2.1. 3355E-CLN025 (Daiichi): Multicenter, double-blind, randomized, active-controlled study comparing levofloxacin (300 mg PO QD for 7 days) with levofloxacin (300 mg PO BID for 7 days) with amoxicillin (1 GM PO TID for 7-14 days) in the treatment of community acquired pneumonia in adults

1.3. Supportive study conducted in the United States:

1.3.1 LOFBIV Multi 001: Multicenter, open-label, non-comparative study to assess the safety of levofloxacin(250 mg or 500 mg levofloxacin IV/PO once daily for 5 to 14 days, depending on the diagnosis) in the treatment of bacterial infections of the respiratory tract, skin, and urinary tract. A minimum of three full doses of intravenous levofloxacin was to be administered, after which the subject could be switched to oral levofloxacin for the duration of therapy.

2. Regulatory History

After completion of the Medical Officer's Review of the two pivotal studies for community-acquired pneumonia, there were too few microbiologically evaluable cases of *Klebsiella pneumoniae* and *Legionella pneumophilia* to support a claim for the use of levofloxacin for the treatment of community-acquired pneumonia due to these organisms. The sponsor requested review of additional cases of pneumonia due to these organisms enrolled in (1) the supportive foreign study 3355E-CLN025 and (2) the supportive U.S. study LOFBIV Multi 001.

2. Summary of FDA nonevaluable cases of community acquired pneumonia from Protocol 90-071 and 92-075.

The total number of FDA microbiologically nonevaluable isolates of *Klebsiella pneumoniae* from levofloxacin-treated patients was 5: 2 in K90-071 and 3 in M92-075. The total number of FDA microbiologically nonevaluable cases of *Legionella pneumoniae* from levofloxacin-treated patients was 3: 2 in K90-071 and 1 in M92-075. Tables 4.1 and 4.2, below, contain a summary of the FDA microbiologically nonevaluable cases of community-acquired pneumonia due to *Klebsiella pneumoniae* and *Legionella pneumophilia*.

Table 2.1
Community-acquired pneumonia (Protocols K90-071 and M92-075)
FDA nonevaluable cases of *Klebsiella pneumoniae* and *Legionella pneumoniae*

Microorganism	Protocol K90-071	Protocol M92-075
Klebsiella pneumoniae	2	3
Legionella pneumophilia	2	1

Table 2.2
Community-acquired pneumonia (Protocols K90-071 and M92-075)
Reasons for Microbiologic nonevaluability
FDA nonevaluable cases of *Klebsiella pneumoniae* and *Legionella pneumoniae*

Microorganism	Protocol	Patient Number	Reason for Microbiologic Nonevaluability
Klebsiella pneumoniae	K90-071		EOT clinical evaluation posttherapy day 3 with no EOS evaluation
			Residual sputum production at EOT never cultured
	M92-075		Concurrent antimicrobial (Ofloxacin study day 14-15 for Prostate Bx)
			CrCl 48.7 mL/min with no dosage adjustment
			RWJPRI nonevaluable: EOT posttherapy day 14 with no EOS evaluation
Legionella pneumophilia	K90-071		Missed three doses (clinical failure)
			Insufficient course of therapy (4 days)
	M92-075		RWJPRI unevaluable: LTFU

On reevaluation with the team leader medical officer, it was felt that four of the patients originally categorized as microbiologically nonevaluable could be added back to the evaluable patient pool without compromising the integrity of the analysis. Three of these patients were in study M92-075, and one was in Study K90-071. These patients are summarized in Table 4.3, below.

Table 2.3
Community-acquired pneumonia (Protocols K90-071 and M92-075)
FDA microbiologically nonevaluable cases of *Klebsiella pneumoniae* and *Legionella pneumoniae* made microbiologically evaluable on reevaluation

Pathogen	Protocol	Patient Number	FDA Clinical Outcome	FDA Microbiologic Outcome	Reason for Microbiologic Nonevaluability
Klebsiella pneumoniae	M92-075		CURE	ERADICATED	Concurrent antimicrobial (Ofloxacin study day 14-15 for Prostate Bx)
			CURE	ERADICATED	CrCl 48.7 mL/min with no dosage adjustment
			CURE	ERADICATED	RWJPRI nonevaluable: EOT posttherapy day 14 with no EOS evaluation
Legionella pneumophilia	K90-071		FAILURE	PERSISTENCE	Missed three doses (clinical failure)

3. Additional data on cases of community-acquired pneumonia causes by *Klebsiella pneumoniae* and *Legionella pneumophilia* submitted by the Sponsor on November 20, 1996:

Table 3
Community-acquired pneumonia
Additional cases of *Klebsiella pneumoniae* and *Legionella* pneumoniae
(Protocol LOFBIV Multi 001)

Pathogen	Protocol	Patient Number	FDA Clinical Assessment	FDA microbiologic Assessment	Brief description of case
Legionella pneumophilia	LOFBIV Multi 001		CURE	ERADICATED (PRESUMED)	44 WM presented with fever, chills, cough productive of purulent sputum, SOB and pleuritic chest pain. Admission physical examination remarkable for temperature of 103.6 °F, tachypnea of 24, tachycardia and rales. Admission CXR remarkable for lingular infiltrate consistent with pneumonia. Diagnostic serologies revealed a titer if 1:1024 for *Chlamydia pneumoniae* IgG and a fourfold fall in *Legionella* specific antibody from admission to poststudy. The patient received levofloxacin 500 mg IV/PO QD for 14 days with complete resolution of clinical symptoms and CXR findings by the posttherapy visit.
	LOFBIV Multi 001		CURE	ERADICATED (PRESUMED)	37 BF smoker presented with fever, chills, cough productive of purulent sputum, SOB and pleuritic chest pain. Admission physical examination remarkable for temperature of 101 °F, tachypnea of 26, tachycardia, egophony, diminished breath sounds and rales. Admission CXR remarkable for left lower lobe infiltrate consistent with pneumonia. Sputum culture grew *Streptococcus pneumoniae*. Diagnostic serologies revealed a fourfold rise in *Legionella* specific antibody from admission to poststudy. The patient received levofloxacin 500 mg IV/PO QD for 13 days with complete resolution of clinical symptoms and CXR findings by the posttherapy visit.
Klebsiella pneumoniae	LOFBIV Multi 001		CURE	ERADICATED (PRESUMED)	75 Bm smoker presented with fever, cough productive of purulent sputum, SOB and pleuritic chest pain. Admission physical examination remarkable for temperature of 97.7 °F, tachypnea of 26, tachycardia, egophony, diminished breath sounds and rales. Admission CXR remarkable for right lower lobe infiltrate consistent with pneumonia. Sputum culture grew *Klebsiella pneumoniae*. The patient received levofloxacin 500 mg IV/PO QD for 14 days with complete resolution of clinical symptoms and CXR findings by the posttherapy visit.

On evaluation with the team leader medical officer, it was felt that all three of these patients could be added back to the microbiologically evaluable patient pool without compromising the integrity of the analysis.

4.2. Summary tables for efficacy variables including patients added after reevaluation data on community-acquired pneumonia:

On reevaluation with the team leader medical officer, it was felt that a total of seven patients could be added to the microgiologicall evaluable cohort without compromising the integrity, as discussed above. The repeat analysis of the efficacy data for the treatment of community-acquired pneumonia caused by *Klebsiella pneumoniae* and *Legionella pneumophilia* is summarized in Section 6.1 and Section 6.2, below.

4.1. Klebsiella pneumoniae

The total number of microbiologically evaluable isolates of *Klebsiella pneumoniae* from levofloxacin-treated patients was 10: 1 in K90-071, 8 in M92-075, and 1 in LOFBIV Mult 001. The total number of isolates of *Klebsiella pneumoniae* was 7 in ceftriaxone/cefuroxime-treated patients in protocol K90-071. Table 6.1 summarizes the efficacy data on cases of community-acquired pneumonia due to *Klebsiella pneumoniae*.

Table 4.1
Overall analysis for *Klebsiella pneumoniae*
FDA Clinically and Microbiologically Evaluable Patients
Community-acquired Pneumonia (Protocols K90-071 and M92-075)

Efficacy parameter	Treatment arm	Protocol	N* (%)	95% CI**
Clinical cure rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	1/1 (100) 7/8 (88) 1/1 (100) 9/10 (90)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	2/7 (29)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	1/1 (100) 8/8 (100) 1/1 (100) 10/10 (100)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	2/7 (29)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	1/1 (100) 81 (100) 1/1 (100) 10/10 (100)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	3/7 (43)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	1/1 (100) 8/8 (100) 1/1 (100) 10/10 (100)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	2/7 (29)	---

*N=number of subjects who had that pathogen alone or in combination with other pathogens. Numbers shown in parentheses are percentages for that category.

**Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in clinical response rates was calculated for subsets with 10 or more clinically evaluable patients with admission isolates of *Klebsiella pneumoniae* in each treatment group

***Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in microbiologic eradication rate was calculated for subsets with 10 or more microbiologically evaluable isolates in each treatment group

Note that there are insufficient numbers of isolates to calculate 95% confidence interval s for any of the parameters of efficacy. Thus, the total number of isolates is adequate to support the inclusion of *Klebsiella pneumoniae* in the labeling, and the absolute clinical response rates and microbiologic eradication rate would support the use of levofloxacin for the treatment of community-acquired pneumoniae due to *Klebsiella pneumoniae*.

4.2. Legionella pneumophilia

The total number of FDA microbiologically evaluable cases of *Legionella pneumoniae* from levofloxacin-treated patients was 10: 4 in K90-071 and 4 in M92-075 and 2 in LOFBIV Multi 001. The total number of cases of *Legionella pneumophilia* was 1 in ceftriaxone/cefuroxime-treated patients in protocol K90-071. Although the Medical Officer's Evaluability Criteria, Section 11.2.2 of the Medical Officer's Review of Studies K90-071 and M92-075, allowed for both culture and serologic methods in the diagnosis of *Legionella pneumophilia* infection, the microbiologically evaluable patient cohort was composed entirely of cases diagnosed by serologic methods.

Table 4.2
Overall analysis for *Legionella pneumophilia*
FDA Clinically and Microbiologically Evaluable Patients
Community-acquired Pneumonia (Protocols K90-071 and M92-075)

Efficacy parameter	Treatment arm	Protocol	N* (%)	95% CI**
Clinical cure rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	3/4 (75) 1/4 (25) 2/2 (100) 6/10 (60)	N/A --- N/A N/A
	Ceftriaxone/cefuroxime	K90-071	0/2 (0)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	3/4 (75) 2/4 (50) 2/2 (100) 7/10 (70)	N/A --- N/A N/A
	Ceftriaxone/cefuroxime	K90-071	0/2 (0)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	3/4 (75) 2/4 (50) 2/2 (100) 7/10 (70)	N/A --- N/A N/A
	Ceftriaxone/cefuroxime	K90-071	1/1 (100)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Multi 001 Overall	3/4 (75) 2/4 (50) 2/2 (100) 7/10 (70)	N/A --- N/A N/A
	Ceftriaxone/cefuroxime	K90-071	0/2 (0)	---

*N=number of subjects who had that pathogen alone or in combination with other pathogens. Numbers shown in parentheses are percentages for that category.

**Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in clinical response rates was calculated for subsets with 10 or more clinically evaluable patients with admission isolates of *Legionella pneumophilia* in each treatment group

***Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in microbiologic eradication rate was calculated for subsets with 10 or more microbiologically evaluable isolates in each treatment group

Note that there are insufficient numbers of cases to calculate 95% confidence intervals for any of the parameters of efficacy. Thus, the total number of cases is adequate to support the inclusion of *Legionella pneumophilia* in the labeling, and the absolute clinical response rates and microbiologic eradication rate would support the use of levofloxacin for the treatment of community-acquired pneumoniae due to *Legionella pneumophilia*.

5. Recommendations:

The Medical Officer considers the above data to be sufficient to support a claim for the use of levofloxacin in the treatment of community-acquired pneumonia caused by *Klebsiella pneumoniae* and *Legionella pneumophilia*.

20-Dec-96

Karen A, Frank, M.D., FACP
Medical Officer, HFD-520

cc: Archival: NDA 20-634
Archival: NDA 20-635
HFD-520/MO/RHopkins
HFD-520/MO/KFrank
HFD-520/Stat/NSilliman
HFD-520/TLMO/MAlbuerne 12/20/96
HFD-520/DepDivDir/RAlbrecht
HFD-520/DepDivDir/LGavrolovich
HFD-520/ActgDivDir/DFeigal 12/20/96
HFD-520/Stat/DLin
HFD-520/Pharm/SJoshi
HFD-520/Micro/DKing
HFD-520/Biopharm/FAjayi
HFD-520/CSO/FLesane