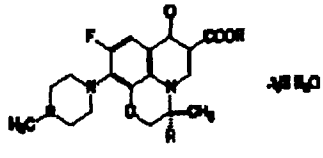
Medical Officer's Review
NDA 20-634 Levaquin® (levofloxacin) Tablets
NDA 20-635 Levaquin® (levofloxacin) Intravenous Injection

Sponsor: R.W. Johnson Pharmaceutical Research Institute
Route 202, P.O. Box 300
Raritan, New Jersey 08869-0602
(908) 704-4600

Medical Officer: Karen A. Frank, M.D.
(Respiratory tract indications only)

Date of Submission: December 21, 1995
Date of CDER Stamp: December 22, 1995
Date received by Medical Officer: December 22, 1995
Date review initiated: March 25, 1996
Date review completed: December 18, 1996

Generic name: levofloxacin
Trade name: Levaquin®
Drug Class: chiral fluorinated carboxyquinolone
Levofloxacin is the L-isomer of the racemic drug substance ofloxacin.
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 (tablet form is hemihydrate)
Chemical formula:



Molecular formula: $C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$
Molecular Weight: 370.38
Dosage Forms: Tablet (NDA 20-364)
Solution (NDA 20-635)
Route of administration: Oral (NDA 20-634)
Solution (NDA 20-635)

Proposed Respiratory Tract Indications:

1. Acute Bacterial Sinusitis.
2. Acute Exacerbation of Chronic Bronchitis
3. Community-acquired Pneumonia

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Medical Officer's Review of NDA 20-634
Levaquin® (levofloxacin tablets) Tablets

Indication: Acute Bacterial Sinusitis due to *Streptococcus pneumoniae, Moraxella catarralis, Haemophilus influenzae,* or *Staphylococcus aureus*

Overview of Clinical Studies in Acute Bacterial Sinusitis:

1. Pivotal studies conducted primarily in the United States:
   - 1.1. Study MR92-040: A multicenter, randomized study to compare the safety and efficacy of oral levofloxacin with amoxicillin/clavulanate potassium in the treatment of acute sinusitis in adults
   - 1.2. Study N93-006: A multicenter, noncomparative study to evaluate the safety and efficacy of oral levofloxacin in the treatment of acute sinusitis in adults
2. Supportive foreign study:
   - 2.1. Study F93-5501: A multicenter, noncomparative study to evaluate the safety and efficacy of oral levofloxacin in the treatment of acute sinusitis in adults (Not reviewed in this document)

Protocol: MR92-040

Study Title: A multicenter, randomized study to compare the safety and efficacy of oral levofloxacin with amoxicillin/clavulanate potassium in the treatment of acute sinusitis (due to *Streptococcus pneumoniae, Moraxella catarralis, Haemophilus influenzae,* or *Staphylococcus aureus*) in adults

Study dates: Date Study initiated: August 26, 1993
Date Study Completed: July 11, 1994

1. Study Objective:

The objective of the study was to compare the safety and efficacy of levofloxacin 500 mg PO once a day for 10 to 14 days to amoxicillin 500 mg/clavulanate 125 mg PO three times per day for the treatment of acute bacterial sinusitis caused by susceptible organisms, specifically *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*[1].

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[1] Study MR92-040 Full Clinical and Statistical Report, Document Number 335915.1, Vol 154. *Staphylococcus aureus* was not listed as a pathogen in the original study objective, although the company is requesting it as a pathogen in the label.

Medical officer's comment: *Staphylococcus aureus* was not listed as a pathogen in the original study objective, although the sponsor is requesting to list this organism as a pathogen in the label. Also, this was not a microbiologically controlled study, so that no information regarding specific pathogens can be extracted from this study.

2. Protocol design:

The protocol was an unblinded, open-label, randomized, active-control, multicenter study.

3. Diagnostic criteria:

The primary diagnosis of acute bacterial sinusitis was defined by clinical and radiographic signs and symptoms of acute sinusitis:

3.1. **Clinical:** Subjects with a diagnosis of acute sinusitis as evidenced by the following signs and symptoms: including fever, headache, purulent nasal discharge, facial pain,or malar tenderness

3.2. **Radiographic:** Radiographic evidence supporting the diagnosis of acute sinusitis including, but not limited to, maxillary haziness, mucosal thickening, air-fluid levels.

3.3. **Microbiologic:** A microbiologic evaluation was not included in the diagnostic criteria for this protocol.

4. Inclusion and exclusion criteria:

The inclusion/exclusion criteria for this protocol were as elaborated below. There was no microbiologic evaluation incorporated into the study, thus only clinical and radiologic criteria were incorporated into the inclusion/exclusion criteria.

4.1. Inclusion criteria:

4.2.1. Inclusion Criteria as per Original Protocol dated February 12, 1993:

Subjects could be included in the study if they satisfied the following:

1. Age: 18 or older
2. Sex: male or female
3. All subjects must be appropriate candidates for oral therapy. Patients in nursing homes could be enrolled if they were ambulatory and were able to carry out the activities of daily life.
4. Subjects with a diagnosis of acute sinusitis as evidenced by the following:
   - (i) signs and symptoms of acute sinusitis, including fever, headache, purulent nasal discharge, facial pain, or malar tenderness
   - (ii) radiographic evidence supporting this diagnosis
5. If female, the subject must
   - (I) have been post-menopausal for at least one year, or
   - (ii) have had a hysterectomy, or
   - (iii) have had a tubal ligation, or
   - (iv) have taken oral contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods during the study, or
   - (v) use another acceptable method of contraception and agree to continue with the same method during the study.
6. If female and of childbearing potential, the subject must have had

(I) a normal menstrual flow within one month prior to study entry
(ii) a negative pregnancy test (serum β-subunit hCG) immediately prior to entry. If obtaining the serum pregnancy test result would cause a delay in treatment, a subject may be entered on the basis of a negative urine pregnancy test sensitive to at least 50 mIU/mL, pending results of the serum pregnancy test. Subsequently, if the result of the serum test was positive, the subject must have been discontinued from the study and followed as indicated.
7. Completion of the confidential follow-up form.
8. Reading and signing of the informed consent (and California Bill of Rights, if applicable) after the nature of the study had been fully explained.

4.1.2. Inclusion Criteria as per Protocol Amendment #1 dated February 24, 1994:

The inclusion criteria were unchanged from the original protocol except for the clarification of the definition of acute sinusitis to acute **bacterial** sinusitis.

4.2. Exclusion criteria:

4.2.1. Exclusion Criteria as per Original protocol dated February 12, 1993:

Subjects with any of the following criteria were not eligible for admission into the study:

1. Subjects with known HIV infection
2. Subjects with chronic sinusitis
3. Previous allergic or serious adverse reaction to levofloxacin, amoxicillin/ clavulanate potassium, or any other members of the quinolone or beta-lactam classes of antimicrobials
4. Calculated creatinine clearance less than or equal to 20 mL/min
5. Requirement of a second systemic antimicrobial agent
6. Effective systemic antimicrobial therapy within 48 hours prior to admission
7. Use of an investigational agent within 30 days prior to admission
8. Pregnancy or a nursing mother
9. Previous treatment under this protocol
10. Any disorder or disease that might interfere with the evaluation of the study drugs
11. Presence of any seizure disorder or condition requiring the administration of major tranquilizers.

4.2.2. Exclusion Criteria as per Protocol Amendment #1 dated February 24, 1994:

The exclusion criteria were unchanged from the original protocol except for the following clarification of the definition of chronic sinusitis:

2. Subjects with chronic sinusitis **(defined as duration of current symptoms for more than four weeks or more than two other episodes of acute sinusitis within the previous twelve months)**

5. Concomitant use of medications and other antimicrobial agents:

The appropriate use of antihistamines and decongestants during this study to facilitate sinus drainage was to be encouraged. Use of these medications was to

be noted on the CRF. The use of other medications during the study was to be minimized. Administration of nonstudy systemic antimicrobials was to be prohibited, and aluminum-magnesium based antacids (e.g., Maalox ®) as well as mineral supplements or vitamins with iron or minerals were to be strongly discouraged because of their potential to decrease the bioavailability of study drug. However, if administration of an antacid was necessary, it was to be administered at least two hours before or after levofloxacin or amoxicillin/clavulanate potassium administration. If the administration of any other medication was required, it was to be reported on the subject's CRF.

6. Efficacy Criteria per Sponsor:

Clinical Response Rating was to be assessed at posttherapy evaluation and at poststudy (28 to 32 days after the end of therapy). The **primary efficacy variable** was clinical response, assessed by the investigator as cured, improved, failed, or unable to evaluate at each of these time points. The **clinical cure rate** was to be evaluated by determining the percentage of clinically evaluable subjects who were cured, and the **clinical success rate** was to be based on the percentage of clinically evaluable subjects who were cured or improved.

6.1. Posttherapy evaluation:

At the posttherapy visit (2 to 5 days after completion of therapy), the investigator was to assess the clinical response as cured, improved, failed, or unable to evaluate. The definitions for these assessments are as follows:

Cured - Disappearance of signs and symptoms with radiographic evidence of stabilization/improvement at the posttherapy visit with no further therapy required.
Improved - Incomplete resolution of signs and symptoms or incomplete resolution of radiographic signs of acute sinusitis and no further therapy required.
Failed - No clinical response to therapy or worsening of the radiographic evidence of infection.
Unable to Evaluate - Subject did not return for follow-up evaluation.

6.2. Post-study evaluation

At the poststudy visit (28 to 32 days after the end of therapy), the investigator was to again assess the clinical response for those subjects with a successful outcome (i.e., cured or improved) at posttherapy. The clinical response at poststudy was to be assessed as cured, improved, relapse, or unable to evaluate. The definitions for these assessments are as follows:

Cured - Complete resolution of signs and symptoms.
Improved - Continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period and no further therapy required.
Relapse - Resolution or improvement of signs and symptoms at posttherapy visit but reappearance or deterioration of signs and symptoms of the infection at Poststudy visit.
Unable to Evaluate - No Poststudy evaluations.

7. Schedule and procedures for evaluation of efficacy criteria:

The presence or absence of five **clinical signs and symptoms** of acute bacterial sinusitis (facial pain, headache, fever, purulent nasal discharge, and malar tenderness) was to be assessed at admission, at posttherapy (or early

withdrawal), and at poststudy (28 to 32 days after completion of therapy). The results of radiographic examinations (e.g., sinus X-ray, CT, US, MRI) were to be reported as normal or abnormal at admission and posttherapy, and changes from admission to posttherapy were to be categorized by the investigator as resolved, improved, worsened, or no change. Radiographic examinations were to be repeated at the poststudy evaluation for subjects with suspected relapse.

7.1. Clinical Evaluation at Baseline/Prestudy Evaluation:

The presence or absence of five clinical signs and symptoms of acute bacterial sinusitis (facial pain, headache, fever, purulent nasal discharge, and malar tenderness) and radiographic evidence of acute sinusitis (mucosal thickening, air fluid levels)) were to be evaluated at the time of enrollment (Day 1).

7.2. Clinical Response Rating at Post-therapy Evaluation (Two to Five Days After Completion of Therapy)

At the post-therapy visit, two to five days after the end of therapy, the investigator was to assess the clinical response as cured, improved, failed, or unable to evaluate. The definitions for these assessments are as follows:

Cured - Disappearance of signs and symptoms with radiographic evidence of stabilization/improvement at the posttherapy visit with no further therapy required.
Improved - Incomplete resolution of signs and symptoms or incomplete resolution of radiographic signs of acute sinusitis and no further therapy required.
Failed - No clinical response to therapy or worsening of the radiographic evidence of infection.
Unable to Evaluate - Subject did not return for follow-up evaluation.

7.3. Clinical Response Rating at Post-study Evaluation (28 to 32 Days After Completion of Therapy)

At the poststudy visit, 28 to 32 days after the end of therapy, the investigator was to again assess the clinical response for those subjects with a successful outcome (i.e., cured or improved) at posttherapy.

7.3.1. The clinical response at poststudy was assessed as cured, improved, relapse, or unable to evaluate. The definitions for these assessments are as follows:

Cured - Complete resolution of signs and symptoms.
Improved - Continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period and no further therapy required.
Relapse - Resolution or improvement of signs and symptoms at posttherapy visit but reappearance or deterioration of signs and symptoms of the infection at Poststudy visit.
Unable to Evaluate - No Poststudy evaluations.

7.3.2. Radiographic examinations were to be repeated at the poststudy evaluation for subjects with suspected relapse. The main findings from the radiographic tests were also to be described.

7.3.3. Microbiologic evaluations were to be performed on patients with suspected failure or relapse only as felt to be indicated by the

investigator.

8. Discontinuation from study:

Subjects could 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 including evaluation of signs and symptoms, physical examination and vital signs, culture and gram stain of sinus aspirate if indicated, and clinical laboratory tests were to be performed. The investigator was to record the reason for premature discontinuation on the subject's CRF.

9. Evaluability Criteria:

9.1. Evaluability criteria as per Sponsor:

9.1.1. Evaluability criteria as outlined in Original Protocol dated February 12, 1993:

To be evaluable for clinical efficacy, subjects were not to be classified in any of the following categories:

1. Unevaluable for safety (no data available)
2. Unconfirmed clinical diagnosis (no recorded clinical signs/symptoms at admission or negative admission sinus X-ray)
3. Insufficient course of therapy

-Subject did not take the study drug for at least seven days

-Subjects who took the study drug greater than 48 hours but less than 7 days because they were judged a clinical failure by the investigator were evaluable

4. Effective concomitant therapy

-Subject took an effective systemic antimicrobial agent within 48 hours prior to start of therapy, or following therapy prior to post-therapy

-If the subject took an effective systemic antimicrobial because they had been judged by the investigator, they were evaluable.

5. Lost to follow-up but relayed safety information
6. Other protocol violation, e.g.,

-post-therapy (End-of-therapy or EOT) visit was **not** 2-10 days after completion of therapy. The exception to this was when the patient was discontinued as a clinical failure at the EOT visit and this visit was on the last day of therapy--this patient was evaluable

-subject failed specific entrance criteria

-subject re-entered the study after discontinuation

-subject did not take at least 70% of the assigned study drug

-subject took study drug for more than 14 days (unless due to a persistent pathogen)

declared clinical failures at the posttherapy visit, but did not have a poststudy follow-up, here the failure declared at post-therapy was carried forward.

4. A symptomatic response could be evaluated at both the **posttherapy** and **poststudy** time points.

5. In terms of **defining the time point for test-of cure**, the amended protocol specified that clinical evaluation at the **posttherapy/EOT** (2-10 days posttherapy) visit was to be the primary clinical endpoint. The medical officer chose to use the **poststudy/EOS** (28-32 days posttherapy) evaluation as the primary clinical endpoint: the rationale for this decision are delineated in the following paragraphs.

5.1. With regard to establishing time point for follow-up after treatment of acute bacterial sinusitis, both (1) the **natural history of the disease** and (2) the **half-life of the antimicrobial agent** under investigation need to be taken into account.

5.1.1. In regard to the **natural history of acute bacterial sinusitis**, there are multiple sources in both the medical and otolaryngology literature that suggest that acute sinusitis should resolve within 3 weeks:

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[3] Frazier LM, Corey GR. Acute Bacterial Sinusitis. NCMJ 47(3):115-7, 1986.

[4] Richtsmeier WJ, Medical and Surgical Management of Sinusitis in Adults. Ann Otol Rhinol Laryngol 101:46-50, 1992.

[5] Godley FA. Chronic Sinusitis: An Update. Am Fam Phys 45(5):2190-8, 1992.

[6] Melen I. Chronic Sinusitis: Clinical and Pathophysiological Aspects. Acta Otolaryngol Suppl 151:45-8, 1994.

[7] Gwaltney JM. Therapeutic approach to sinusitis: Antiinfectious therapy as the baseline of management. Otolaryngol Head Neck Surg 103:876, 1990.

5.1.2. The windows for follow-up after an episode of acute bacterial sinusitis will be the same for patients treated with any **antimicrobial agent with a relatively short half-life**. It is only in the case of a prolonged half-life that the window for follow-up needs to be extended because blood levels and tissue levels persist far beyond the last dose of the antimicrobial drug. For levofloxacin, whose serum half-life is 6.34-6.39 hours in the clinical tablet, the window of follow-up can be the same as for other antibiotics with relatively short half-lives.

5.1.2.1. The **IDSA Guidelines** recommend standard follow-up after an episode of acute bacterial sinusitis as follows:

5.1.2.2. Recent **regulatory precedent** for the appropriate time point for test of cure has been established in other reviews of antimicrobial agents with short half-lives for the indication of acute bacterial sinusitis :

[8] Chow AW, et.al. General Guidelines for the evaluation of New Anti-Infective Drugs for the Treatment of Respiratory Tract Infections: Sinusitis. Clin Infect Dis 15(Suppl 1): 77, 1992.

[9] Leissa B. Medical Officer's Review of NDA 50-621, Suppl.004, 014, 015, 016, p.B4-B5, p. C14, final draft 05-Dec-91.

[10] Rakowsky A. Medical Officer's Review of NDAs 50-664 and 50-665, Supplement 003, p.08, final draft 21 May-95.

Thus, the basis for the decision to use **the EOS evaluation (28-32 days posttherapy) as the primary clinical endpoint** was based on the fact that: (1) the original (2-5 days posttherapy) and the extended (2-10 days post-therapy) windows for the EOT visit were to early in the course of the disease to be definitive time points for test-of-cure, since the accepted duration of (treated) bacterial sinusitis is three weeks, and (2) while the EOS evaluation (28-32 days posttherapy) may not be the optimal time point for test of cure (because relapses at this late a time point may not be definitively attributed to the study drug), this later time point was superior to the earlier time point for the test-of-cure evaluation, since it beyond the time point at which acute sinusitis should have fully resolved and thus is a more stable point estimate.

6. In regards to **categorization of the clinical response**, the sponsor defined the clinical response at both the EOT and the EOS visits according to the "cured-improved-failed-relapsed" scale delineated in sections 7.2 and 7.3.1 above. The medical officer considered that, since both the medical and otolaryngology literature would suggest that acute sinusitis should completely resolve within 3 weeks, the category of "improved" was not applicable to the evaluation at the EOS visit. Thus, **the clinical evaluation at the EOS visit was changed to a dichotomous variable "cure\failed"**, predominantly on the presence or absence of the ANY of the **major/cardinal signs/symptoms of acute bacterial sinusitis** as defined in the inclusion criteria of the study protocol:

The basis for this decision are documented in the following paragraphs taken from the ENT and medical literature:

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[11] Frazier LM, Corey GR. Acute Bacterial Sinusitis. NCMJ 47(3):115-7, 1986.

[12] Richtsmeier WJ, Medical and Surgical Management of Sinusitis in Adults. Ann Otol Rhinol Laryngol 101:46-50, 1992.

[13] Godley FA. Chronic Sinusitis: An Update. Am Fam Phys 45(5):2190-8, 1992.

Furthermore, symptoms indicative of treatment failure in acute sinusitis may be subtle: the only symptom present in a case of treatment failure may be the persistence of purulent nasal discharge. Gwaltney summarizes the issue in the following:

7. In regards to **categorization of minor symptoms/signs** (such as isolated congestion and post nasal drip (PND), that were not cardinal signs and symptoms of acute bacterial sinusitis (as defined by the inclusion criteria of the protocol) the medical officer attempted to determine if these were attributable to (1) pre-existing allergic rhinitis or chronic sinusitis or (2) represented a cohort of patient who were treatment failures progressing into subacute/chronic sinusitis.

There exists debate in the literature regarding the pathophysiology of chronic sinusitis. There are authors who argue that chronic sinusitis arises primarily from chronic obstruction of the sinus ostia secondary to anatomic abnormalities of the osteomeatal complex through which the sinuses drain into the nose[17]. Others argue that it generally arises from untreated, partially treated or treatment failure of acute sinusitis[18]. Patients with chronic sinusitis rarely present with spiking fevers, purulent discharge and peripheral leukocytosis. Instead, they present with a constellation of symptoms which usually includes not only the "triad" of chronic sinusitis (sinus congestion, postnasal drip, and fatigue), but also retrobulbar pressure/headaches, daily facial pain,

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[14] Melen I. Chronic Sinusitis: Clinical and Pathophysiological Aspects. Acta Otolaryngol Suppl 151:45-8, 1994.

[15] Gwaltney JM. Therapeutic approach to sinusitis: Antiinfectious therapy as the baseline of management. Otolaryngol Head Neck Surg 103:876, 1990.

[16] Gwaltney JM. The microbial etiology and antimicrobial therapy of adults with acute community acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 90:457-62, 1992.

[17] Messerklinger W. On the drainage of the normal frontal sinus of man. Acta Otolaryngol 63:176-81, 1967; Stammberger H. Endoscopic endonasal surgery-concepts in the treatment of recurrent sinusitis. Otolaryngol Head Neck Surg 94:143-56, 1986; Stammberger H. Nasal and paranasal sinus endoscopy. Endoscopy 18:213-8, 1986.

[18] Kern EB. Suppurative (bacterial) sinusitis. Postgrad Med 81(4):194-210, 1987.

daily headaches for several weeks, ear pain, and ear blockage[19]. Of particular note, "Nasal airway obstruction and post-nasal drip may be the only complaints"[20]. Because of the subtly of symptoms comprising the syndrome of chronic sinusitis, the medical officer applied the following criteria to the analysis of the "minor symptoms" of nasal congestion and postnasal drip remaining at the EOS visit:

(i) if the subject has a history of allergic rhinitis AND had resolution of all major symptoms of sinusitis, these symptoms were attributed to the allergic rhinitis;
(ii) if the subject had ANY other symptoms of acute sinusitis, these symptoms were considered indicative of clinical failure;
(iii) patients with congestion and/or PND **WITHOUT** other signs and symptoms of sinusitis or a history of allergic rhinitis were evaluated as a separate subset to determine whether, if this cohort was treated as clinical failures that were progressing into a subacute/chronic sinusitis, this would affect the relative cure rates of the two treatment arms.

8. In regards to the use of concomitant antibiotic therapy **from the time of enrollment through the end-of study visit**, the following criteria were applied:

(i) A patient was **fully clinically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

- Within 48 hours prior to enrollment in the protocol
- During the treatment period
- From the end of the treatment period to the poststudy evaluation
- At the evaluation for clinical relapse

(ii) if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **clinically unevaluable**;
(iii) if the patient received an alternative antimicrobial **AND** there was **no documentation of an alternative diagnosis** for which the alternative antimicrobial may have been prescribed, the patient was designated a **clinical failure** and **clinically evaluable (only) as a treatment failure.**

9. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

(i) for patients designated as a clinical cure at EOS, a minimum of 7 days or 70% of the minimum dose specified by the protocol;

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[19] Godley FA. Chronic Sinusitis: An Update. Am Fam Phys 45(5):2190-2199, 1992;

[20] Kern AB. Postgrad Med. 81(4): 198.

(ii) for patients designated a clinical failure at EOS, a minimum of 72 hours of study drug was to have been taken;
(iii) for the levofloxacin arm, no more than 2 missed doses within the dosing interval requiring extension of the dosing interval to complete the full 10-14 doses of therapy.

10. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

10. Investigators and study sites:

Protocol MR92-040 was conducted by 28 investigators at a total of 33 separate sites, all within the United States. These are summarized in Table 10.1, below.

Table 10.1: Investigators and Study Sites (Protocol MR92-040)

Investigator	Study Site(s)
Jeffrey Adelglass, M.D.	Dallas Clinical Research, Inc., Dallas, TX; USA Trinity Professional Plaza, Carrollton, TX; USA
James Applegate, M.D.	FamilyCare, Wyoming, MI; USA FamilyCare, Grand Rapids, MI; USA
Lee Bruner, M.D.	Ochsner Clinic of Baton Rouge, Baton Rouge, LA; USA
Allah R. Cass, M.D.	The Univ. of Texas Medical Branch at Galveston, Galveston, TX; USA
Ricco Caisson, M.D.	Carolina Ear, Nose and Throat, PA, Orangeburg, SC; USA
C. Andrew DeAbate, M.D.	Metairie, LA; USA; New Orleans, LA; USA Walden Health Care, Kenner, LA; USA
David L. Dworzack, M.D.	Boys Town National Research Institute, Omaha, NE; USA
Thomas B. Edwards, M.D.	Albany Medical College, Albany, NY; USA
James V. Felicetta, M.D.	Carl T. Hayden VAMC, Phoenix, AZ; USA
Robert A. Fiddes, M.D., J.D., F.C.L.M.	Southern California Research Institute, Whittier, CA; USA
Claude B. Goswick, Jr., M.D.	G & S Studies, Inc., Bryan, TX; USA
Jay Grossman, M.D.	Allergy Care Consultants, Ltd., Tucson, AZ; USA
Guy H. Handley, M.D.	Birmingham, AL; USA
William M. Hunter, M.D.	Lovelace Scientific Resources, Albuquerque, NM; USA
Boris Kerzner, M.D.	Pikesville, MD; USA
Craig F. LaForce, M.D.	Carolina Allergy & Asthma Consultants, P.A., Raleigh, NC; USA Carolina Allergy & Asthma Consultants, Chapel Hill, NC; USA
David Levine, D.O.	Broward Family Health Center, Ft. Lauderdale, FL; USA
Benjamin Levy, M.D.	Hartford Center For Clinical Research, Hartford, CT; USA
J. Tyler Martin, M.D.	Norfolk, NE; USA
Phillip McElvaine, M.D.	El Paso, TX; USA
Carl M. Nechtman, M.D.	Norwood Clinic, Birmingham, AL; USA
David S. Pearlman, M.D.	Colorado Allergy & Asthma Clinic, P.C., Aurora, CO; USA
Anthony D. Puopolo, M.D.	Milford Emergency Assoc., Milford, MA; USA High St. Medical Center, Clinton, MA; USA
Lance A. Rudolph, M.D.	New Mexico Medical Group, P.C., Albuquerque, NM; USA
Joel P. Smith, Jr., M.D., P.C.	Atlanta Medical Associates, Atlanta, GA; USA
Alan A. Wanderer, M.D.	Allergy & Asthma Consultants and Research Center, P.C., Englewood, CO; USA
William J. Stein, M.D.	Rochester, NY; USA
Welby Winstead, M.D.	Louisville, KY; USA

11. Study Population:

Six hundred fifteen (615) subjects were enrolled in this study. The intent-to-treat groups include 307 subjects who were randomized to the levofloxacin treatment group and 308 subjects who were randomized to the amoxicillin/clavulanate treatment group. One subject [redacted] randomized to the levofloxacin group actually received amoxicillin/clavulanate; hence, the numbers of subjects who received levofloxacin and amoxicillin/clavulanate were 306 and 309, respectively. This one misdosed subject who received amoxicillin/clavulanate instead of levofloxacin was clinically evaluable and, therefore, is included in the analyses based on clinically evaluable subjects. The clinical response for this subject was "improved" at the posttherapy evaluation and "cured" at the poststudy evaluation.

Table 11.1

Number of Subjects by Analysis Group and Study Center (Study MR92-040)

	Levofloxacin			Amoxicillin/Clavulanate		
Investigator	Modified Intent-to-Treat	Clinically Evaluable		Modified Intent-to-Treat	Clinically Evaluable	
Adelglass	18	16	(88.9)	18	18	(100.0)
Applegate	3	3	(100.0)	3	2	(66.7)
Bruner	5	5	(100.0)	6	5	(83.3)
Cass	5	4	(80.0)	4	4	(100.0)
Caisson	17	15	(88.2)	15	13	(86.7)
Deabate	35	34	(97.1)	36	32	(88.9)
Dworzack	0	0	–	1	1	(100.0)
Edwards	14	14	(100.0)	16	16	(100.0)
Felicetta	1	1	(100.0)	1	0	(0.0)
Fiddes	12	4	(33.3)	12	9	(75.0)
Goswick	16	16	(100.0)	18	18	(100.0)
Grossman	9	9	(100.0)	8	8	(100.0)
Handley	14	13	(92.9)	13	12	(92.3)
Hunter	9	9	(100.0)	10	7	(70.0)
Kerzner	3	3	(100.0)	3	2	(66.7)
LaForce	15	12	(80.0)	16	14	(87.5)
Levine	1	1	(100.0)	1	1	(100.0)
Levy	4	3	(75.0)	4	3	(75.0)
Martin	1	1	(100.0)	1	1	(100.0)
McElvaine	28	20	(71.4)	29	20	(69.0)
Nechtman	20	16	(80.0)	18	16	(88.9)
Pearlman	7	7	(100.0)	7	6	(85.7)
Puopolo	16	14	(87.5)	16	14	(87.5)
Rudolph	5	5	(100.0)	4	4	(100.0)
Smith	12	10	(83.3)	13	12	(92.3)
Stein	16	15	(93.8)	15	12	(80.0)
Wanderer	19	17	(89.5)	19	16	(84.2)
Winstead	1	0	(0.0)	2	2	(100.0)
TOTAL	**306**	**267**	**(87.3)**	**309**	**268**	**(86.7)**

12. Efficacy as per sponsor:

12.1. Study Population

The sponsor emphasized efficacy data from the clinically evaluable group, with a less detailed description of supportive results from the modified intent-to-treat groups.

Table 12.1
Numbers of Subjects and Summaries for Each Analysis Center

	Clinically Evaluable	Modified Intent-to-Treat	Intent-to-Treat	Evaluable for Safety
Levofloxacin Treatment Group	267	306	307	297
Amoxicillin/Clavulanate Treatment Group	268	309	308	302
Analyses or Summaries Performed:				
Demographics	X	X	X	X
Extent of Therapy	X	X		
Clinical Response	X	X	X	
Signs/Symptoms	X	X		
Radiographic Findings	X			
Adverse Events				X
Laboratory Results				X
Vital Signs				X

12.1.1. Demographic Characteristics of Intent-to Treat Cohort:

Six hundred fifteen subjects were enrolled in this study at 28 centers. The intent-to-treat groups include 307 subjects who were randomized to the levofloxacin treatment group and 308 subjects who were randomized to the amoxicillin/clavulanate treatment group. One subject ([redacted]) randomized to the levofloxacin group actually received amoxicillin/clavulanate; hence, the numbers of subjects who received levofloxacin and amoxicillin/clavulanate were 306 and 309, respectively. This one misdosed subject who received amoxicillin/clavulanate instead of levofloxacin was clinically evaluable and, therefore, is included in the analyses based on clinically evaluable subjects. The clinical response for this subject was "improved" at the posttherapy evaluation and "cured" at the poststudy evaluation. The demographic and baseline (admission) characteristics for the modified intent-to-treat groups are summarized in below and were comparable between the levofloxacin and amoxicillin/clavulanate treatment groups. The mean age for all subjects was 38.9±13.4 years with a range of 18 to 85 years. Women accounted for 63.4% of all subjects enrolled, and Caucasians for 73.0%. There were no statistically significant differences ($p^3 0.27$) between the two treatment groups for any of the demographic features tested (i.e., age, sex, race) for any of the analysis groups.

Table 12.1.1.A
Demographic and Baseline Characteristics:
Modified Intent-to-treat Subjects (Protocol M92-040)

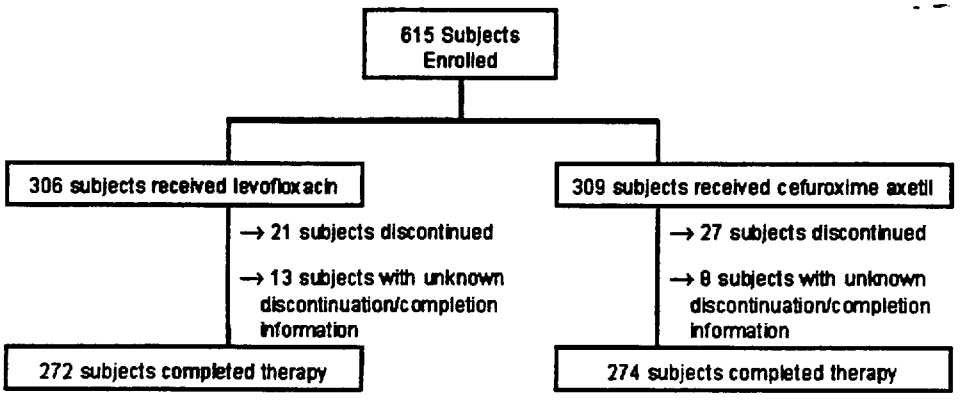
	Levofloxacin (N=306)		Amoxicillin/Clavulanate (N=309)		Total (N=615)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	115	(37.6)	110	(35.6)	225	(36.6)
Women	191	(62.4)	199	(64.4)	390	(63.4)
Race						
Caucasian	220	(71.9)	229	(74.1)	449	(73.0)
Black	44	(14.4)	44	(14.2)	88	(14.3)
Oriental	3	(1.0)	1	(0.3)	4	(0.7)
Hispanic	37	(12.1)	34	(11.0)	71	(11.5)
Other	2	(0.7)	1	(0.3)	3	(0.5)
Age (Years)						
≤45	216	(70.6)	224	(72.5)	440	(71.5)
46-64	73	(23.9)	74	(23.9)	147	(23.9)
≥65	17	(5.6)	11	(3.6)	28	(4.6
N	306		309		615	
Mean±SD	39.2±13.9		38.6±12.8		38.9±13.4	
Range	[redacted]		[redacted]		[redacted]	
Weight (lb)						
N	302		304		606	
Mean±SD	174.0±43.4		166.8±40.6		170.4±42.1	
Range	[redacted]		[redacted]		[redacted]	
Missing	4		5		9	
Height (in)						
N	301		307		608	
Mean±SD	66.5±4.0		66.6±4.0		66.5±4.0	
Range	[redacted]		[redacted]		[redacted]	
Missing	5		2		7	

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.1.2. Discontinuation/Completion Information

Of the 615 subjects enrolled in the study, 306 received levofloxacin and 309 received amoxicillin/clavulanate (modified intent-to-treat group). As shown in Figure 1, of the 293 subjects in the levofloxacin group with known discontinuation/completion information, 21 (7.2%) discontinued therapy prematurely and 272 (92.8%) completed therapy according to the regimen prescribed by the investigator. Discontinuation/completion information is unknown for an additional 13 subjects who did not return for the final visit. Of the 301 subjects in the amoxicillin/clavulanate treatment group with known discontinuation/completion information, 27 (9.0%) discontinued therapy prematurely and 274 (91.0%) completed therapy. There were an additional eight subjects in this group with unknown discontinuation/completion information. The most common reason for discontinuation in both treatment groups was an adverse event.

Figure 12.2.A
Discontinuation/Completion Information:
Modified Intent-to Treat Cohort (Protocol M92-040)***



***Note that the control arm was mistakenly labelled by the sponsor as cefuroxime axetil, when it should heve been amoxicillin/clavulanate

Table 12.2
Reasons for Discontinuation of Therapy:
Modified Intent-to Treat Cohort (Protocol M92-040)

	Levofloxacin		Amoxicillin/ Clavulanate	
Reason	No.	(%)[a]	No.	(%)[a]
Adverse Event	11	(3.8)	16	(5.3)
Clinical Failure	6	(2.0)	6	(2.0)
Personal Reason	2	(0.7)	1	(0.3)
Other	2[b]	(0.7)	4[c]	(1.3)
Total Discontinued	21	(7.2)	27	(9.0)
Total with Discontinuation/Completion Information	293	(100.0)	301	(100.0)
Total With Unknown Discontinuation/Completion Information	13		8	

[a] Percentages based on total number with discontinuation/completion information.
[b] Subject [redacted] was discontinued because of a possible history of seizure disorder (protocol violation). Subject [redacted] was discontinued because the subject felt treatment was ineffective.
[c] Subjects [redacted] and [redacted] were discontinued because of a positive pregnancy test. Subject [redacted] was discontinued because of noncompliance in adhering to the dosing schedule, and Subject [redacted] was discontinued because of radiologic failure.

12.1.3. Demographics of Clinically Evaluable Cohort:

Two hundred sixty-seven (87.3%) subjects in the levofloxacin treatment group and 268 (86.7%) subjects in the amoxicillin/clavulanate treatment group were clinically evaluable. The main reasons that subjects were not clinically evaluable were inappropriate posttherapy evaluation date (levofloxacin and amoxicillin/clavulanate groups) and insufficient course of therapy (amoxicillin/clavulanate group). Modified Intent-to-treat analysis categorizes patients according to the treatment actually received, which takes into account the small percentage of dispensing errors in the study. For this protocol, analysis for evaluability was done on the cohort defined by Modified-Intent-to-Treat, which reassigned one patient who inadvertently received amoxicillin/clavulanate instead of levofloxacin. The demographic and baseline characteristics of the subjects included in the clinically evaluable group were comparable to the previously described modified intent-to-treat analysis group with respect to age, sex, racial composition, and other baseline characteristics. There were no statistically significant differences ($p^3 0.27$) found between the treatment groups for the variables tested (i.e., age, sex, race).

Table 12.1.3A
Primary Reasons for Clinical Nonevaluability:
Modified Intent-to-Treat Subjects (Study MR92-040)[21]

Reasons	Levofloxacin (N=306)	Amoxicillin/Clavulanate (N=309)
Inappropriate Posttherapy Evaluation Date	17	14
Unevaluable for Safety	9	7
Insufficient Course of Therapy	8	15
No Posttherapy Evaluation	4	1
Clinical Diagnosis Unconfirmed	1	2
Effective Concomitant Therapy	0	1
Other Protocol Violation	0	1 b
Total Unevaluable For Efficacy	**39 (12.7%)**	**41 (13.3%)**

Subjects counted only once. b Subject [redacted] noncompliance with dosing instructions.

[21] Adopted from Table 8, page 35, Vol.1.154.

Table 12.1.3B

Demographic and Baseline Characteristics: Clinically Evaluable Subjects (Study MR92-040)

		Levofloxacin (N=267)		Amoxicillin/Clavulanate (N=268)	
		No.	(%)	No.	(%)
Sex	Men	99	(37.1)	96	(35.8)
	Women	168	(62.9)	172	(64.2)
Race	Caucasian	199	(74.5)	208	(77.6)
	Black	37	(13.9)	35	(13.1)
	Oriental	3	(1.1)	1	(0.4)
	Hispanic	26	(9.7)	23	(8.6)
	Other	2	(0.7)	1	(0.4)
Age (Years)	<45	187	(70.0)	196	(73.1)
	46-64	63	(23.6)	64	(23.9)
	>65	17	(6.4)	8	(3.0)
	N	267		268	
	Mean±SD	39.5±14.1		38.3±12.4	
	Range	18-85		18-84	
Weight (lb)	N	263		263	
	Mean±SD	174.0±43.0		166.5±40.4	
	Range	100-350		96-350	
	Missing	4		5	
Height (in)	N	263		266	
	Mean±SD	66.5±4		66.6±3.9	
	Range	57-76		56-76	
	Missing	4		2	

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.1.4. Extent of Exposure.

The mean duration of therapy was 13 days for levofloxacin-treated subjects and 12 days for amoxicillin/ clavulanate-treated subjects; the medians were 14 and 12, respectively. At the time of admission there were no subjects who were believed to have renal impairment, and no adjustment in dosage was made for this reason. Three subjects required dosage adjustments due to subject dosing errors. Two levofloxacin-treated subjects took levofloxacin b.i.d. before the dosage was adjusted to once a day. One amoxicillin/clavulanate-treated subject [redacted] mistakenly took study drug q12h on two separate occasions before the dosage was adjusted to q8h.

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Table 12.4
Extent of Exposure:
Modified Intent-to-treat Cohort (Protocol M92-040)

Extent of Exposure	Levofloxacin (N=306)	Amoxicillin/Clavulanate (N=309)
Days on Therapy*		
Unknown	12	7
1	2	2
2	4	1
3	0	6
4	2	4
5	1	3
6	1	1
7	4	0
8	0	1
9	1	1
10	66	66
11	7	58
12	9	9
13	6	8
14	164	57
15	16	68
16	1	12
17	0	1
18	1	1
19	1	1
21	6	0
22	2	1
23	0	1
Mean±SD	13.0±3.0	12.0±3.1
Median	14	12
Number of Doses		
Total with Dosing Information	294	301
Total Unknown Dosing Information	12	8
Mean±SD	12.7±3.0	34.6±8.9
Median	14	36
Range	1-21	1-63

NOTE: Levofloxacin had a q24h dosing schedule and amoxicillin/clavulanate had a q8h dosing schedule. The total planned duration of therapy was 10 to 14 days for both treatment groups.

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

945 **12.1.5. Compliance:**

Subjects were to receive either one 500-mg levofloxacin tablet once daily or one amoxicillin/clavulanate tablet containing 500 mg amoxicillin and 125 mg clavulanate every eight hours. The total planned duration of therapy for both treatment groups was 10 to 14 days, but therapy could be 950 extended at the discretion of the investigator if indicated. A minimum of seven days of therapy was required for subjects to be considered clinically evaluable; subjects who had failed clinically (in the judgment of the investigator) and had taken more than 48 hours of study drug were not classified as unevaluable due to insufficient course of therapy. One 955 amoxicillin/clavulanate-treated subject [redacted] did not comply with the dosing regimen (i.e., took only 12 tablets over an eight-day period) and was, therefore, discontinued from the study. Most subjects took the study medication according to the regimen assigned.

12.1.6. Concomitant Therapies:

Comparable percentages of subjects in the modified intent-to-treat groups for levofloxacin and amoxicillin/clavulanate treatment took concomitant therapies.

12.1.7. Protocol Variations

There were no significant protocol variations reported during the study except for the drug dispensing and dosing errors previously described including one subject [redacted] in the amoxicillin/clavulanate group who was discontinued for failure to comply with the dosing schedule. One subject (415) in the levofloxacin group was discontinued from the study because it was determined after the subject was admitted that she might possibly have had a history of seizure disorders.

12.2. Efficacy Results as per Sponsor:

This section of the report focuses primarily on results of the primary efficacy analyses of clinical response, based on the group of subjects evaluable for clinical efficacy. The results from the modified intent-to-treat and intent-to-treat groups were generally consistent with those from the clinically evaluable group and are provided as attachments in the Supporting Data section at the end of the text, with a brief description in this section for selected variables.

12.2.1. Clinical Response to Treatment

12.2.1.2. Clinical Response Rating at Posttherapy Evaluation (Two to Five Days After Completion of Therapy)

The clinical response to therapy for subjects who were clinically evaluable is summarized by treatment group and study center in Table 12.2.1. below. Among clinically evaluable subjects in the levofloxacin treatment group, 58.4% were cured and 30.0% were improved, compared with 58.6% and 28.7% in the amoxicillin/clavulanate treatment group. Thirty-one (11.6%) subjects in the levofloxacin treatment group and 34 (12.7%) subjects in the amoxicillin/clavulanate treatment group failed treatment. In the modified intent-to-treat group, levofloxacin treatment resulted in 54.2% cure, 30.4% improvement, and 11.1% failure; 4.2% of subjects could not be evaluated; amoxicillin/clavulanate treatment resulted in 53.7% cure, 30.1% improvement, and 13.6% failure; 2.6% of subjects could not be evaluated. Similar results were found in the intent-to-treat group.

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Table 12.2.1
Clinical Response Rates By Investigator:
Sponsor's Clinically Evaluable Subjects (Protocol M92-040)

	Levofloxacin						Amoxicillin/Clavulanate					
Investigator	N	Cured		Improved		Failed	N	Cured		Improved		Failed
Adelglass	16	11	(68.8)	3	(18.8)	2 (12.5)	18	9	(50.0)	7	(38.9)	2 (11.1)
Applegate	3	1	(33.3)	1	(33.3)	1 (33.3)	2	2	(100.0)	0	(0.0)	0 (0.0)
Bruner	5	2	(40.0)	3	(60.0)	0 (0.0)	5	2	(40.0)	2	(40.0)	1 (20.0)
Cass	4	2	(50.0)	2	(50.0)	0 (0.0)	4	3	(75.0)	0	(0.0)	1 (25.0)
Cassone	15	3	(20.0)	10	(66.7)	2 (13.3)	13	5	(38.5)	6	(46.2)	2 (15.4)
Deabate	34	26	(76.5)	7	(20.6)	1 (2.9)	32	27	(84.4)	4	(12.5)	1 (3.1)
Dworzack	0	0	–	0	–	0 –	1	1	(100.0)	0	(0.0)	0 (0.0)
Edwards	14	3	(21.4)	6	(42.9)	5 (35.7)	16	6	(37.5)	6	(37.5)	4 (25.0)
Felicetta	1	0	(0.0)	1	(100.0)	0 (0.0)	0	0	–	0	–	0 –
Fiddes	4	3	(75.0)	1	(25.0)	0 (0.0)	9	7	(77.8)	1	(11.1)	1 (11.1)
Goswick	16	16	(100.0)	0	(0.0)	0 (0.0)	18	17	(94.4)	1	(5.6)	0 (0.0)
Grossman	9	4	(44.4)	4	(44.4)	1 (11.1)	8	0	(0.0)	7	(87.5)	1 (12.5)
Handley	13	11	(84.6)	1	(7.7)	1 (7.7)	12	10	(83.3)	2	(16.7)	0 (0.0)
Hunter	9	6	(66.7)	3	(33.3)	0 (0.0)	7	6	(85.7)	1	(14.3)	0 (0.0)
Kerzner	3	1	(33.3)	2	(66.7)	0 (0.0)	2	1	(50.0)	0	(0.0)	1 (50.0)
LaForce	12	2	(16.7)	7	(58.3)	3 (25.0)	14	3	(21.4)	7	(50.0)	4 (28.6)
Levine	1	1	(100.0)	0	(0.0)	0 (0.0)	1	1	(100.0)	0	(0.0)	0 (0.0)
Levy	3	0	(0.0)	3	(100.0)	0 (0.0)	3	0	(0.0)	3	(100.0)	0 (0.0)
Martin	1	1	(100.0)	0	(0.0)	0 (0.0)	1	1	(100.0)	0	(0.0)	0 (0.0)
McElvaine	20	17	(85.0)	2	(10.0)	1 (5.0)	20	17	(85.0)	1	(5.0)	2 (10.0)
Nechtman	16	12	(75.0)	3	(18.8)	1 (6.3)	16	8	(50.0)	6	(37.5)	2 (12.5)
Pearlman	7	3	(42.9)	2	(28.6)	2 (28.6)	6	2	(33.3)	1	(16.7)	3 (50.0)
Pucpolo	14	11	(78.6)	0	(0.0)	3 (21.4)	14	11	(78.6)	0	(0.0)	3 (21.4)
Rudolph	5	2	(40.0)	2	(40.0)	1 (20.0)	4	3	(75.0)	0	(0.0)	1 (25.0)
Smith	10	4	(40.0)	2	(20.0)	4 (40.0)	12	5	(41.7)	6	(50.0)	1 (8.3)
Stein	15	12	(80.0)	3	(20.0)	0 (0.0)	12	6	(50.0)	4	(33.3)	2 (16.7)
Wanderer	17	2	(11.8)	12	(70.6)	3 (17.6)	16	2	(12.5)	12	(75.0)	2 (12.5)
Winstead	0	0	–	0	–	0 –	2	2	(100.0)	0	(0.0)	0 (0.0)
Combined*	55	26	(47.3)	24	(43.6)	5 (9.1)	55	31	(56.4)	15	(27.3)	9 (16.4)
TOTAL	267	156	(58.4)	80	(30.0)	31 (11.6)	268	157	(58.6)	77	(28.7)	34 (12.7)

Numbers shown in parentheses are percentages for that category.

* Combined = those study centers that enrolled fewer than 10 clinically evaluable subjects in each treatment group: Applgate, Bruner, Cass, Dworzack, Felicetta, Fiddes, Grossman, Hunter, Kerzner, Levine, Levy, Martin, Pearlman, Rudolph, and Winstead.

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". Two-sided 95% confidence intervals around the difference in clinical success rates were calculated to evaluate therapeutic equivalence between treatments. Among clinically evaluable subjects, levofloxacin treatment resulted in 88.4% clinical success while amoxicillin/clavulanate treatment resulted in 87.3% clinical success, with a 95% confidence interval of [-6.8, 4.6] for the difference (amoxicillin/clavulanate minus levofloxacin) in success rates. All of the treatment differences in this confidence interval lie below the upper bound of 15% suggested by the FDA's Anti-Infective "Points to Consider" guideline for establishing clinical equivalence of treatments with success rates between 80% and 89%.

Table 12.2.2.
Clinical Success Rates and Confidence Intervals at Posttherapy Evaluation by Investigator: Sponsor's Clinically Evaluable Subjects (Protocol M92-040)

	Levofloxacin			Amoxicillin/Clavulanate			
Investigator	N	Success[a]	Failure[a]	N	Success[a]	Failure[a]	95% Confidence Interval[b]
Adelglass	16	14 (87.5)	2 (12.5)	18	16 (88.9)	2 (11.1)	(-23.5, 26.3)
Applegate	3	2 (66.7)	1 (33.3)	2	2 (100.0)	0 (0.0)	–
Bruner	5	5 (100.0)	0 (0.0)	5	4 (80.0)	1 (20.0)	–
Cass	4	4 (100.0)	0 (0.0)	4	3 (75.0)	1 (25.0)	–
Cassone	15	13 (86.7)	2 (13.3)	13	11 (84.6)	2 (15.4)	(-32.0, 27.9)
Deabate	34	33 (97.1)	1 (2.9)	32	31 (96.9)	1 (3.1)	(-10.0, 9.7)
Dworzack	0	0 –	0 –	1	1 (100.0)	0 (0.0)	–
Edwards	14	9 (64.3)	5 (35.7)	16	12 (75.0)	4 (25.0)	(-25.7, 47.2)
Feliceta	1	1 (100.0)	0 (0.0)	0	0 –	0 –	–
Fiddes	4	4 (100.0)	0 (0.0)	9	8 (88.9)	1 (11.1)	–
Goswick	16	16 (100.0)	0 (0.0)	18	18 (100.0)	0 (0.0)	(-3.1, 3.1)
Grossman	9	8 (88.9)	1 (11.1)	8	7 (87.5)	1 (12.5)	–
Handley	13	12 (92.3)	1 (7.7)	12	12 (100.0)	0 (0.0)	(-11.0, 26.3)
Hunter	9	9 (100.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	–
Kerzner	3	3 (100.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	–
LaForce	12	9 (75.0)	3 (25.0)	14	10 (71.4)	4 (28.6)	(-41.8, 34.7)
Levine	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
Levy	3	3 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	–
Martin	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
McElvaine	20	19 (95.0)	1 (5.0)	20	18 (90.0)	2 (10.0)	(-23.6, 13.6)
Nechtman	16	15 (93.8)	1 (6.3)	16	14 (87.5)	2 (12.5)	(-29.5, 17.0)
Pearlman	7	5 (71.4)	2 (28.6)	6	3 (50.0)	3 (50.0)	–
Pucpolo	14	11 (78.6)	3 (21.4)	14	11 (78.6)	3 (21.4)	(-34.0, 34.0)
Rudolph	5	4 (80.0)	1 (20.0)	4	3 (75.0)	1 (25.0)	–
Smith	10	6 (60.0)	4 (40.0)	12	11 (91.7)	1 (8.3)	(-7.5, 70.8)
Stein	15	15 (100.0)	0 (0.0)	12	10 (83.3)	2 (16.7)	(-41.9, 8.6)
Wanderer	17	14 (82.4)	3 (17.6)	16	14 (87.5)	2 (12.5)	(-22.3, 32.6)
Winstead	0	0 –	0 –	2	2 (100.0)	0 (0.0)	–
Combined[c]	55	50 (90.9)	5 (9.1)	55	46 (83.6)	9 (16.4)	(-20.6, 6.0)
TOTAL	267	236 (88.4)	31 (11.6)	268	234 (87.3)	34 (12.7)	(-6.8, 4.6)

[a] Numbers shown in parentheses are percentages for that category.
[b] Two-sided 95% confidence interval around the difference (amoxicillin/clavulanate minus levofloxacin) between treatments in clinical success rates (cured and improved) were calculated for study centers enrolling 10 or more clinically evaluable subjects in each treatment group.
[c] Combined = those study centers that enrolled fewer than 10 clinically evaluable subjects in each treatment group: Applegate, Bruner, Cass, Dworzack, Feliceta, Fiddes, Grossman, Hunter, Kerzner, Levine, Levy, Martin, Pearlman, Rudolph, and Winstead.

Confidence intervals computed for each study center with 10 or more clinically evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers. The cure rates for the two treatment groups for all centers combined were similar (58.4% for levofloxacin, 58.6% for amoxicillin/clavulanate), with a 95% confidence interval on the difference in cure rates of [-8.4, 8.7]. Differences between treatment groups in cure rates with associated 95% confidence intervals are plotted by study center and analysis group. Similar results were generally observed in the two treatment groups across study centers and analysis groups. The results observed for the evaluable subject group that indicate equivalence between treatment groups were also observed across various sex, age, and race subgroups. In the modified intent-to-treat group, the clinical success rates for levofloxacin and amoxicillin/clavulanate were 84.6% and 83.8%, respectively. To evaluate consistency across all analysis groups in clinical success rates, 95% confidence intervals for the difference in success rates are provided and presented graphically. The individual confidence intervals for all of the analysis groups are centered below zero and are consistent with therapeutic equivalence of the two treatments regarding clinical success rates.

12.2.1.3. Clinical Response Rating at Poststudy Evaluation (28 to 32 Days After Completion of Therapy)

Clinical response rates at the poststudy evaluation are summarized and cross-tabulated against clinical response rates at the posttherapy visit in Table 12.2.3 for clinically evaluable subjects who had a poststudy evaluation performed. (*Thirty-one subjects in the levofloxacin group and 34 subjects in the amoxicillin/clavulanate group had failed at the posttherapy evaluation and were not included in this analysis; an additional three subjects in each group did not have poststudy evaluations performed).* Of 233 levofloxacin-treated subjects who were cured or improved at the posttherapy evaluation and had poststudy evaluations done approximately four weeks later, only five had relapsed by the time of the poststudy evaluation, including two (1.3%) of the 154 who had been cured and three (3.8%) of the 79 who had improved. Among amoxicillin/clavulanate-treated subjects, the relapse rates were 1.9% and 7.9%, respectively, for subjects who were cured or improved at posttherapy.

Table 12.2.3
Clinical Response Rate at Poststudy Evaluation:
Sponsor's Clinically Evaluable Subjects (Protocol M92-040)

Change from Admission to Posttherapy	Levofloxacin (N=262)[b]		Amoxicillin/Clavulanate (N=262)[b]	
	No.	(%)	No.	(%)
Resolved	94	(35.9%)	93	(35.5%)
Improved	121	(46.2%)	122	(46.6%)
Worsened	31	(11.8%)	28	(10.7%)
No Change	16	(6.1%)	19	(7.3%)

[a] All subjects had abnormal radiographic findings at admission.
[b] Five subjects in the levofloxacin group and six subjects in the amoxicillin/clavulanate group did not have a posttherapy radiographic examination.

12.1.4. Clinical Signs and Symptoms

The proportions of clinically evaluable subjects with resolution of each clinical sign and symptom of sinusitis based on the posttherapy examination are presented in Table 12.2.4. For both the levofloxacin and amoxicillin/clavulanate treatment groups, there was clearing of one or more individual symptoms from admission to posttherapy in approximately 80% or more of the subjects.

Table 12.2.4.
Resolution of Clinical signs and Symptoms at Posttherapy Evaluation: Sponsor's Clinically Evaluable Patients (Protocol M92-040)

	Levofloxacin		Amoxicillin/ Clavulanate	
Signs & Symptoms	Resolved[a]	%	Resolved[b]	%
Facial Pain	208/243	(85.6)	202/243	(83.1)
Headache	195/234	(83.3)	192/236	(81.4)
Fever	70/ 76	(92.1)	74/ 74	(100.0)
Purulent Nasal Discharge	203/249	(81.5)	199/249	(79.9)
Malar Tenderness	167/179	(93.3)	163/183	(89.1)

[a] Sign/symptom present at admission and absent at posttherapy evaluation.
[b] Denominator represents number of subjects with that sign or symptom at admission.

12.2.1.5. Radiographic Findings

The proportions of clinically evaluable subjects with resolution, improvement, worsening of, or no change in abnormal admission radiographic findings at the posttherapy evaluation are presented in Table 12.2.5. Of 262 clinically evaluable levofloxacin-treated subjects with abnormal admission radiographic findings who underwent posttherapy radiographic examination, 215 (82.1%) showed either resolution (35.9%) or improvement (46.2%); similarly, of 262 clinically evaluable amoxicillin/clavulanate-treated subjects, 215 (82.1%) showed either resolution (35.5%) or improvement (46.6%).

Table 12.2.5
Summary of Radiographic Findings at Posttherapy Evaluation: Sponsor's Clinically Evaluable Subjects (Protocol M92-040)

Change from Admission to Posttherapy	Levofloxacin (N=262)[b]		Amoxicillin/Clavulanate (N=262)[b]	
	No.	(%)	No.	(%)
Resolved	94	(35.9%)	93	(35.5%)
Improved	121	(46.2%)	122	(46.6%)
Worsened	31	(11.8%)	28	(10.7%)
No Change	16	(6.1%)	19	(7.3%)

[a] All subjects had abnormal radiographic findings at admission.
[b] Five subjects in the levofloxacin group and six subjects in the amoxicillin/clavulanate group did not have a posttherapy radiographic examination.

12.2.6. Microbiologic Results for Subjects Who Failed Therapy

Cultures were obtained from four of the 65 clinically evaluable subjects who failed therapy (two levofloxacin-treated and two amoxicillin/clavulanate-treated subjects). Cultures from three subjects did not produce any pathogen growth; culture from the fourth (amoxicillin/clavulanate-treated) subject yielded *Haemophilus aphrophilus*, *Eikenella corrodens*, and *Streptococcus milleri*, all of which were susceptible to both levofloxacin and amoxicillin/clavulanate.

12.3. Sponsor's Summary of Efficacy Results

The objective of this study was to compare the safety and therapeutic efficacy of 500 mg levofloxacin administered orally once daily for 10 to 14 days with that of 500 mg amoxicillin/125 mg clavulanate administered orally thrice daily for 10 to 14 days in the treatment of acute bacterial sinusitis. Clinical response to treatment (evaluated by the investigator two to five days posttherapy as cured, improved, failed, or unable to evaluate based on clinical signs and symptoms and radiographic findings) was the primary efficacy variable and was based primarily on the group of subjectsevaluable for clinical efficacy. In all analysis groups examined, levofloxacin was found to be both effective and safe in the treatment of acute bacterial sinusitis.

The results obtained in this study for the levofloxacin and amoxicillin/clavulanate groups are valid for comparison for several reasons. The two treatment groups were determined by randomization and were comparable with respect to demographics and other admission characteristics, premature discontinuation rates, extent of exposure, concomitant medications, enrollment at study centers, reasons for exclusion, and clinical signs and symptoms. Given the similar composition of the two groups, any differences or similarities in clinical response or adverse event profiles can be attributed to the individual drugs. Levofloxacin treatment provided comparable clinical responses to those observed with amoxicillin/clavulanate. When the clinical response categories of "cured" and "improved" were combined into a single category of "Clinical Success", levofloxacin treatment resulted in 88.4% clinical success for clinically evaluable subjects, while amoxicillin/clavulanate treatment resulted in 87.3% clinical success. The 95% confidence interval of [-6.8, 4.6] for the difference (amoxiciliin/clavulanate minus levofloxacin) in clinical success rates supports therapeutic equivalence between the two treatments. Both treatment groups also had similar percentages (approximately 80% or more) of subjects experiencing resolution of one or more of the clinical signs and symptoms of sinusitis: facial pain, headache, fever, purulent nasal discharge, and malar tenderness. Similar low percentages of the subjects rated "cured" or "improved" at posttherapy had relapsed within 28 to 32 days after the termination of therapy; 2.1% and 3.9% of the total "cured" and "improved" subjects underwent relapse in the levofloxacin and amoxicillin/clavuanate treatment groups, respectively.

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with acute bacterial sinusitis. The clinical responses in the levofloxacin treatment group were therapeutically equivalent to those observed in the amoxicillin/clavulanate treatment group. These data support the efficacy of levofloxacin for acute bacterial sinusitis.

13. Efficacy as per Medical Officer:

13.1. FDA Evaluable Patient Population

Of the intent-to-treat cohort of 615 patients , the medical officer deemed 529 patients (86% or 529/615) clinically evaluable: 263 in the levofloxacin arm and 266 in the amoxicillin arm. Of the 14% (86/615) that were clinically unevaluable, the medical officer concurred with the sponsor's assessment of unevaluable in 57% (49/86) of cases. In 43% (37/86) of the cases the medical officer felt that patients deemed clinically evaluable by the sponsor were not evaluable according the the FDA evalaubility criteria: these are summarized in Table 13.1.A and Table 13.1.B, below. The reasons for nonevaluability for the entire cohort of FDA Nonevalauble Patients is summarized in Table 13.2.A and Table 13.2.B, located in the in the following Section 13.2.

Table 13.1.A
FDA Clinically Evaluable Patients:
Subgroups of Sponsor's Intent-to-treat Cohort (Protocol M92-040)

Intent-to-treat Cohort N (%) 615 (100%) Levofloxacin 306/615 (49.8%) Amoxicillin/clavulanate 309/615 (50.2%)			
FDA Clinically Evaluable 529 529/615 (86%)		**FDA Clinically Unevaluable** 86 86/615 (14%)	
Levofloxacin	**Amoxicillin/ clavulanate**	**Levofloxacin**	**Amoxicillin/ clavulanate**
263 263/529 (49.7%) 263/615 (42.8%)	266 266/529 (50.3%) 266/615 (43.2%)	43 43/86 (50%) 43/615 (7%)	43 43/86 (50%) 43/615 (7%)

Table 13.1.B
Demographic and Baseline Characteristics:
FDA Clinically Evaluable Cohorts (Protocol M92-040)

	FDA Clinically Evaluable Patients N (%)		
	ALL N (%)	Levofloxacin N (%)	Amoxicillin/clavulanate N (%)
TOTAL	529	263/529 (50%)	266/529 (50%)
Sex			
M	196/529 (37%)	98/263 (37%)	98/266 (37%)
F	333/529 (63%)	165/263 (63%)	168/266 (63%)
Race			
Caucasian	396/529 (75%)	196/263 (75%)	200/266 (75%)
Black	73/529 (15%)	34/263 (13%)	39/266 (15%)
Hispanic	54/529 (10%)	29/263 (11%)	25/266 (9%)
Asian	4/529 (<1%)	3/263 (1%)	1/266 (<1%)
Other	2/529 (<1%)	1/263 (<1%)	1/266 (<1%)
Age (yrs)			
≤45	379/529 (72%)	185/263 (70%)	194/266 (73%)
46-64	124/529 (23%)	61/263 (23%)	63/266 (24%)
≥65	26/529 (5%)	17/263 (6%)	9/266 (3%)

13.2. Reasons For Nonevaluabilty: FDA Evaluable Patient Population

Table 13.2.A
Reasons for Nonevaluability:
Patients Evaluable by Sponsor but Nonevaluable by FDA
(Protocol M92-040)

Reason for Nonevaluability Subgroups of reasons for Nonevaluability	Levo	Amox/clav	Total
Protocol violation	5	11	16
History of Chronic Sinusitis/Acute Exacerbation of Chronic Sinusitis	5	10	15
History of Seizure Disorder	0	1	1
Exceeded 14 days of therapy: unevaluable as clinical cure	4	2	6
Insufficient therapy	1	0	1
Concomitant Antimicrobial	2	2	4
Inadequate Clinical Evaluation: No End-of-study (EOS) visit	4	2	6
TOTAL Reasons***	16	17	33
TOTAL Patients	14	17	31

*** Patient [redacted] was unevaluable because of both a history of chronic sinusitis and concomitant antimicrobials. Patient [redacted] was unevaluable because of an extended course of antimicrobials and no EOS visit.

Table 13.2.B.
Reasons for Nonevaluability: FDA Nonevaluable Patients (ALL)
(Protocol M92-040)

Reason for Nonevaluability Subgroups of reasons for Nonevaluability	Levo	Amox/clav	Total
Insufficient Course of therapy	9	10	19
Clinical Diagnosis Unconfirmed	0	1	1
Protocol violation	6	12	18
History of Chronic Sinusitis/Acute Exacerbation of Chronic Sinusitis*	6	10	16
History of Seizure Disorder	0	1	1
Other	0	1	1
Exceeded 14 days of therapy	4	2	6
Effective Concomitant Antimicrobial	2	3	5
Inappropriate clinical evaluation	7	4	11
Inadequate Clinical Evaluation	17	11	28
No End-of-study evaluation/Lost-to-follow-up	17	10	27
Equivocal clinical data**	0	1	1
TOTAL Reasons***	45	43	88
TOTAL Patients	43	43	86

* Patient [redacted] was considered clinically unevaluable by the sponsor because of an inappropriate EOT evaluation date, but the medical officer felt that his patient, who had a history of sinus surgery, had symptomatology suggestive of chronic, rather than acute, sinusitis

** Patient [redacted] was considered clinically unevaluable by the sponsor because of an inappropriate EOT evaluation date, but the medical officer considered this patient clinically unevaluable at the EOS visit because of contradictory data (symptoms of subacute/chronic sinusitis without confirmatory X-ray evidence)

*** Patient [redacted] was unevaluable because of both a history of chronic sinusitis and the use of concomitant antimicrobials. Patient [redacted] was unevaluable because of an extended course of antimicrobial and absense of EOS visit

13.3. Clinical Efficacy: FDA Evaluable Patient Cohort

The overall efficacy rate and efficacy rates by investigator were calculated for the cohort of FDA evaluable patients, and these are summarized in Table 13.3.A, below. The overall cure rate was 79% (209/263) for levofloxacin and 74% (197/266) for amoxicillin/clavulanate, with 95% confidence interval around the difference being (-13.0 to 2.2). Thus, the efficacy rates for the two treatments were statistically equivalent. The 95% confidence intervals around the difference between treatment arms overlapped zero when calculted for each investigative site, indicating that no one site biased the overall efficacy result.

Table 13.3.A
Poststudy Clinical Cure Rates and Confidence Intervals By Investigator: FDA Clinically Evaluable Subjects (Protocol M92-040)

Investigator	Levofloxacin		Amoxicillin/ Clavulanate		95% Confidence Interval[b]
	N	Cure[a]	N	Cure[a]	
Adelglass	15	12 (80)	18	11 (61)	(-55.3, 17.5)
Applegate	3	1 (33)	2	1 (50)	-
Bruner	4	3 (75)	5	4 (80)	-
Cass	5	5 (100)	4	3 (75)	-
Cassone	13	9 (69)	13	8 (62)	(-51.8, 36.5)
Deabate	33	32 (97)	32	30 (94)	(-16.5, 10.1)
Dworzack	0	0 (-)	1	1 (100)	-
Edwards	14	7 (50)	15	12 (80)	(-10.0, 70.0)
Felicetta	1	1 (100)	1	0 (0)	-
Fiddes	7	7 (100)	11	9 (82)	-
Goswick	16	16 (100)	18	17 (94)	(-22.0, 10.9)
Grossman	7	3 (43)	7	2 (29)	-
Handley	13	10 (77)	12	12 (100)	(-7.8, 54.0)
Hunter	9	9 (100)	8	7 (88)	-
Kerzner	3	1 (33)	2	1 (50)	-
LaForce	10	7 (70)	13	9 (69)	(-47.5, 46.0)
Levine	0	0 (-)	1	1 (100)	-
Levy	3	3 (100)	2	2 (100)	-
Martin	1	0 (0)	1	0 (0)	-
McElvaine	21	20 (95)	20	16 (80)	(-39.9, 9.4)
Nechtman	18	15 (83)	14	9 (64)	(-55.8, 17.7)
Pearlman	3	2 (67)	4	0 (0)	-
Puopolo	15	11(73)	16	10 (63)	(-49.9, 28.2)
Rudolph	5	4 (80)	3	1 (33)	-
Smith	10	5 (50)	10	9 (90)	(-6.1, 86.1)
Stein	16	15 (94)	15	11 (73)	(-52.2, 11.4)
Wanderer	18	11 (61)	16	9 (56)	(-43.9, 34.2)
Winstead	0	0 (-)	2	2 (100)	-
Total[c]	263	209 (79)	266	197 (74)	(-13.0, 2.2)

[a] Poststudy clinical outcome is defined by the reviewing medical officer as either cure or failure (i.e., no improvement category is used). Numbers shown in parentheses are percentages for that category.

[b] Two-sided confidence interval for the difference (amoxicillin/clavulanate minus levofloxacin) in poststudy clinical cure rate. This was calculated for investigators enrolling 10 or more clinically evaluable subjects in each treatment group.

Two patients with equivocal data were removed from the evaluable patient cohort. Patient [redacted] was considered clinically unevaluable by the sponsor because of an inappropriate EOT evaluation date, but the medical officer felt that this patient, who had a history of sinus surgery, had symptomatology suggestive of chronic, rather than acute, sinusitis. Patient [redacted] was considered clinically unevaluable by the sponsor because of an inappropriate EOT evaluation date, but the medical officer considered this patient clinically unevaluable at the EOS visit because of symptoms of subacute/ chronic sinusitis (congestion/purulent discharge) with sinus X-rays without evidence of sinusitis. [redacted] would be added to the levofloxacin are as a cure, and patient [redacted] would be added to the amoxicillin/clavulanate arm as a failure. thus, addition of these two patients to the evaluable patient cohort would have only served to improve the efficacy of levofloxacin compared to amoxicillin/clavulanate. The evaluable patient cohort used by the medical officer afforded a more conservative analysis of efficacy.

It is of note that these overall cure rates do not take into account the proportion of patients who had persistent PND at EOS evaluation, and thus may represent a population of patients that had failed treatment, and, therefore, might influence overall outcome. An analysis was done to (1) calculate a "worst case" scenario, in which all of the cases of PND were counted as clinical failures, and (2) investigate the proportion of patients who had a pre-existing history of allergic rhinitis, and thus in whom the persistent postnasal drip could be reasonably attributed to the underlying disorder of allergic rhinitis and not to progression to subacute/chronic sinusitis and (3) investigate the scenario under which only those patients with PND without a baseline history of allergic rhinitis were counted as clinical failures.

Table 13.3.B
Analysis of the relationship between baseline allergic rhinitis and persistent postnasal drip at post-study evaluation in patients treated for acute bacterial sinusitis: FDA evaluable patients (Protocol M92-040)

	All FDA Evaluable Patients (N=529)			FDA Evaluable Patients Levofloxacin Arm (N=263)			FDA Evaluable Patients Amoxicillin/clavulanate Arm (N=266)		
	No PND	PND	TOTAL	NO PND	PND	TOTAL	NO PND	PND	TOTAL
Allergic Rhinitis	66 66/76 87%	10 10/44 9% 10/76 13%	76	31 31/38 82%	7 7/22 32% 7/38 18%	38	35 35/38 92%	3 3/22 14% 3/38 8%	38
No Allergic Rhinitis	0	34 34/44 77%	34	0	15 15/22 68%	15	0	19 19/22 86%	15
Total	66	44	110	31	22	53	35	22	53

Thus, of all evaluable patients (combined treatment arms) 44/529 (8.3%) had residual PND *without other major symptoms of sinusitis* at the EOS evaluation (patients with PND in the setting of other major symptoms of acute sinusitis were not included in this subgroup, but were counted as clinical failures). When the analysis was done by treatment arm, 22/263 (8.4%) in the levofloxacin arm and

22/266 (8.3%) in the amoxicillin/clavulanate arm had isolated PND at the time of EOS evaluation, and thus may have represented treatment failures.

Using the worse case scenario, in which all of the 44 patients with PND at post-study evaluation are counted as clinical failures, regardless of a history of pre-existing allergic rhinitis at the time of admission, the cure rate for the levofloxacin arm would be 71% (187/263) and for the amoxicillin/clavulanate arm would be 66% (175/266). The 95% confidence interval around the difference between these two cure rates is (-3.0 to 13.6).Thus, even in this theoretical worse case scenario, levofloxacin meets DAIDP standards for therapeutic equivalence to amoxicillin/clavulanate.

Of the 22 patients in the levofloxacin arm with PND, 7/22 (32%) had a history if allergic rhinitis (AR), and, thus, the PND could be attributed to the underlying AR. Of the patients in the amoxicillin/clavulanate arm with PND, 3/22 (14%) had a history if allergic rhinitis, and thus the PND could be attributed to the underlying AR. Thus, 68% (15/22) of patients with PND in the levofloxacin arm and 86% (19/22) of patients with PND in the amoxicillin/clavulanate arm had no underlying disorder to which the PND could be attributed and thus, hypothetically, may have represented treatment failures. Thus, if these hypothetical failures were subtracted from their respective treatment arms, the theoretical overall cure rate for the levofloxacin arm would be 74% (194/263) and that for the amoxicillin/clavulanate arm would be 67% (178/266). Thus, if the patients who had residual PND at EOS evaluation are counted as clinical failures, it only increases the relative cure rate of levofloxacin in comparison to amoxicillin/clavulanate.

14. Safety Evaluation as per Sponsor:

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any postadmission data were available. Subjects were classified according to the drug that was received. Five hundred ninety-nine (97.4%) of 615 subjects enrolled were evaluated for safety. Of the 599 subjects, 297 received levofloxacin and 302 received amoxicillin/clavulanate. Sixteen subjects (nine in the levofloxacin treatment group and seven in the amoxicillin/clavulanate treatment group) were lost to follow-up with no safety information and, therefore, excluded from the safety analysis.

14.2. Overview of Safety Data

The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal (GI) and central and peripheral nervous systems and consisted primarily of nausea, diarrhea, and headache. The incidence of GI-related adverse events was greater in the amoxicillin/clavulanate group (31.8%) than in the levofloxacin group (15.8%), with the difference being statistically significant. The most common adverse event, diarrhea, was reported by 19.9% of amoxicillin/clavulanate-treated subjects, compared with 6.4% of levofloxacin-treated subjects. Adverse events in the other body systems occurred in fewer than 10% of subjects and were comparable between the two treatment groups, except for a statistically significant difference in psychiatric disorders (4.0% in the levofloxacin group versus 1.0% in the amoxicillin/clavulanate group). Psychiatric events in the levofloxacin group consisted primarily of insomnia (2.4% of subjects). The most frequently reported adverse events were nausea, diarrhea, and headache; nausea and headache were reported by similar percentages of subjects in each treatment group (6.7% and 6.1%, for levofloxacin and 6.6% and 6.0%, for amoxicillin/clavulanate). In contrast, diarrhea was reported more frequently in the amoxicillin/clavulanate group (19.9%) compared to the levofloxacin group (6.4%).

Table 14.2.1
Incidence of Frequently Reported (≥2%) Adverse Events:
Subjects Evaluable for Safety (Protocol M92-040)

	Levofloxacin (N=297)		Amoxicillin/Clavulanate (N=302)	
Body System/Primary Term	No.	(%)	No.	(%)
All Body Systems	114	(38.4)	146	(48.3)
Gastrointestinal System Disorders				
Nausea	20	(6.7)	20	(6.6)
Diarrhea	19	(6.4)	60	(19.9)
Abdominal Pain	6	(2.0)	13	(4.3)
Dyspepsia	4	(1.3)	8	(2.6)
Vomiting	3	(1.0)	9	(3.0)
Flatulence	2	(0.7)	9	(3.0)
Central & Peripheral Nervous System Disorders				
Headache	18	(6.1)	18	(6.0)
Dizziness	4	(1.3)	8	(2.6)
Psychiatric Disorders				
Insomnia	7	(2.4)	0	(0.0)
Female Reproductive Disorders				
Vaginitis	2	(1.1)†	11	(5.7)†
Resistance Mechanism Disorders				
Genital Moniliasis	3	(1.0)	12	(4.0)

* Primary term reported by ≥2.0% of subjects in either treatment group.
† Percentages calculated from the total number of women in each treatment group. The total number of women who received levofloxacin was 185 and the total number of women who received amoxicillin/clavulanate was 194.

Twenty-two (7.4%) levofloxacin-treated subjects and 64 (21.2%) amoxicillin/clavulanate-treated subjects had adverse events considered by the investigator to be probably or definitely drug-related. Of the nine subjects with marked drug-related adverse events, three were in the levofloxacin group and six were in the amoxicillin/clavulanate group. Twenty-seven subjects discontinued study drug due to adverse events, 11 (3.7%) of 297 subjects evaluable for safety in the levofloxacin group and 16 (5.3%) of 302 subjects evaluable for safety in the amoxicillin/clavulanate group. In the levofloxacin group, the subjects who discontinued due to adverse events included four subjects with urticaria, rash, or pruritus, four subjects with GI-related adverse events, one subject with both skin- and GI-related adverse events, and one subject each with asthenia/dizziness and influenza-like symptoms. In the amoxicillin/clavulanate group, all adverse event discontinuations were due to GI-related complaints except one case (fatigue). There were two serious or potentially serious adverse events reported, chest pain (two occurrences in one subject) and anemia; both adverse events occurred in levofloxacin-treated subjects within the first week after therapy was completed and neither was considered by the investigator to be related to study drug administration. No deaths occurred during the study. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs occurred infrequently and were comparable across treatment groups.

One hundred fourteen (38.4%) of 297 subjects evaluated for safety in the levofloxacin treatment group and 146 (48.3%) of 302 safety-evaluable subjects in the amoxicillin/clavulanate treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. This difference between treatments in the overall rate of adverse events was statistically significant (i.e., the 95% confidence interval does not include zero). Body systems with the highest reported incidence of adverse events were the gastrointestinal (GI) system and the central and peripheral nervous system. The incidence of GI-related adverse events was greater in the amoxicillin/clavulanate group (31.8%) than in the levofloxacin group (15.8%), with the difference being statistically significant (95% confidence interval is [9.1, 22.8]). Adverse events in the other body systems occurred in fewer than 10% of subjects and were comparable between the two treatment groups, except for a statistically significant difference in psychiatric disorders (4.0% in the levofloxacin group vs. 1.0% in the amoxicillin/clavulanate group). Psychiatric events in the levofloxacin group consisted primarily of insomnia (2.4% of subjects) in addition to isolated reports of agitation, anxiety, nervousness, sleep disorder, and somnolence. Although the differences were not statistically significant, the incidence of female reproductive disorders (primarily vaginitis) and resistance mechanism disorders (primarily genital moniliasis) appeared to be greater in the amoxicillin/clavulanate group than in the levofloxacin group.

Table 14.2.2.
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol M92-040)

Body System	Levofloxacin (N=297) N	(%)	Amoxicillin/ Clavulanate (N=302) N	(%)	95% Confidence Interval[a]
Gastrointestinal System Disorders	47	(15.8)	96	(31.8)	(9.1, 22.8)
Central & Peripheral Nervous System Disorders	22	(7.4)	25	(8.3)	(-3.6, 5.3)
Skin and Appendages Disorders	13	(4.4)	11	(3.6)	(-4.0, 2.6)
Respiratory System Disorders	13	(4.4)	15	(5.0)	(-3.0, 4.1)
Body as a Whole-General Disorders	13	(4.4)	10	(3.3)	(-4.3, 2.2)
Psychiatric Disorders	12	(4.0)	3	(1.0)	(-5.7, -0.4)
Resistance Mechanism Disorders	7	(2.4)	15	(5.0)	(-0.6, 5.8)
Reproductive, Female Disorders	4	(2.2)[b]	12	(6.2)[b]	(-0.2, 8.3)
Hearing and Vestibular Disorders	3	(1.0)	6	(2.0)	(-1.1, 3.1)
Musculoskeletal System Disorders	2	(0.7)	3	(1.0)	(-1.3, 1.9)
Metabolic and Nutritional Disorders	2	(0.7)	1	(0.3)	(-1.6, 1.0)
Cardiovascular, General Disorders	2	(0.7)	1	(0.3)	(-1.6, 1.0)
Vascular (Extracardiac) Disorders	2	(0.7)	1	(0.3)	(-1.6, 1.0)
Vision Disorders	1	(0.3)	2	(0.7)	(-1.0, 1.6)
Red Blood Cell Disorders	1	(0.3)	0	(0.0)	(-1.2, 0.5)
White Cell and RES Disorders	1	(0.3)	0	(0.0)	(-1.2, 0.5)
Urinary System Disorders	1	(0.3)	3	(1.0)	(-0.8, 2.1)
Application Site Disorders	1	(0.3)	1	(0.3)	(-1.1, 1.1)
Heart Rate and Rhythm Disorders	0	(0.0)	1	(0.3)	(-0.5, 1.1)
Total With Adverse Events (%)	114	(38.4)	146	(48.3)	(1.9, 18.0)

RES = Reticuloendothelial system.

[a] Two-sided confidence interval around the difference (amoxicillin/clavulanate 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 185 and the total number of women who received amoxicillin/clavulanate was 194.

14.3. Adverse Events of Marked Severity

The majority of adverse events were assessed as mild or moderate in severity. Seven subjects in the levofloxacin treatment group reported one or more adverse events of marked severity, including three subjects in whom the adverse event(s) (abdominal pain and diarrhea; constipation; and urticaria) were considered by the investigator to be probably related to study therapy. Fifteen subjects in the amoxicillin/clavulanate treatment group reported adverse events of marked severity, including six with GI-related symptoms (e.g., abdominal pain, nausea, or diarrhea) considered probably or definitely related to study drug. Ten of the 22 subjects with marked adverse events (four levofloxacin-treated and six amoxicillin/clavulanate-treated subjects) discontinued study drug treatment due to adverse events.

Table 14.3.1.
Subjects with Adverse Events of Marked Severity:
Subjects Evaluable for Safety (Protocol M92-040)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship To Study Drug
Levofloxacin				
	39	F	Constipation	Probable
			Insomnia	Remote
	32	F	Abdominal Pain	Probable
			Diarrhea	Probable
	21	F	Urticaria	Probable
	21	F	Influenza-Like Symptoms	None
	54	F	Vein Pain	None
	29	F	Headache	Remote
	45	F	Malaise	None
Amoxicillin/Clavulanate				
	52	F	Vomiting	None
	45	M	Rhinitis	Possible
			Dry Skin	Possible
	41	M	Asthma	Remote
			Headache	None
	27	F	Abdominal Pain	Probable
	44	F	Diarrhea	Probable
			Nausea	Probable
			Vomiting	Probable
	38	F	Headache	Remote
	21	M	Pseudomembranous Colitis	Probable
	62	F	Nausea	Probable
	20	F	Nausea	Probable
			Pruritus	Probable
			Vomiting	Probable
	23	M	Pharyngitis	Remote
	61	M	Tooth Disorder	None
	25	F	Gastroenteritis	None
	34	F	Abdominal Pain	Possible
	20	F	Dysmenorrhea	None
	27	F	Abdominal Pain	Definite
			Diarrhea	Definite
			Flatulence	Definite

‡ Subject discontinued due to constipation. (see Table 19)
* Subject discontinued study drug treatment due to the adverse event(s) listed. (See Table 19)

A smaller percentage of subjects in the levofloxacin treatment group (7.4%) than in the amoxicillin/clavulanate treatment group (21.2%) had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug. Drug-related adverse events reported by ≥1.0% of levofloxacin-treated subjects were nausea (1.7%), diarrhea (1.3%), vaginitis (1.1%), and abdominal pain (1.0%). Drug-related adverse events reported by ≥1.0% of amoxicillin/clavulanate-treated subjects were diarrhea (11.6%), vaginitis (4.1%), nausea (4.0%), genital moniliasis (3.3%), abdominal pain (1.7%), vomiting (1.7%), and flatulence (1.3%).

Two levofloxacin-treated subjects (108 and 1113) experienced a serious adverse event within one week after completing study therapy (anemia in one subject and two instances of chest pain in another). Both of these adverse events resulted in hospitalization and neither was considered by the investigator to be related to study drug administration.

No deaths occurred during the study. Twenty-seven subjects discontinued the study drug due to adverse events, including 11 (3.7%) of 297 subjects evaluable for safety in the levofloxacin treatment group and 16 (5.3%) of 302 subjects evaluable for safety in the amoxicillin/clavulanate treatment group. None of the limiting adverse events was considered serious or potentially serious. In the levofloxacin group, the subjects who discontinued due to adverse events included four subjects with urticaria, rash, or pruritus, four subjects with GI-related adverse events, one subject with both skin-and GI-related adverse events, and one subject each with asthenia/dizziness and influenza-like symptoms. In the amoxicillin/clavulanate group, all adverse event discontinuations were due to GI-related complaints except one case (fatigue).

14.4. Treatment Emergent Abnormalities in Laboratory Parameters:

Treatment emergent abnormalities in laboratory parameters will be discussed in the comprehensive safety review.

14.5. Summary of Safety Results:

Overall, levofloxacin-treated subjects reported fewer adverse events than amoxicillin/clavulanate-treated subjects; the incidence of adverse events in the levofloxacin treatment and amoxicillin/clavulanate treatment groups was 38.4% and 48.3%, respectively. The most frequently reported adverse events were nausea, diarrhea, and headache; nausea and headache were reported by similar percentages of subjects in each treatment group (6.7% and 6.1% for levofloxacin and 6.6% and 6.0% for amoxicillin/clavulanate). In contrast, diarrhea was reported more frequently in the amoxicillin/clavulanate group (19.9%) compared to the levofloxacin group (6.4%). Vaginitis and genital moniliasis were also somewhat more prevalent in the amoxicillin/clavulanate group than the levofloxacin group.

The majority of adverse events were assessed as mild or moderate in severity. Seven subjects in the levofloxacin treatment group reported one or more adverse events of marked severity, including three subjects in whom the adverse event(s) (abdominal pain and diarrhea; constipation; and urticaria) were considered by the investigator to be probably related to study therapy. Fifteen subjects in the amoxicillin/clavulanate treatment group reported adverse events of marked

severity, including six subjects with GI-related symptoms considered probably or definitely related to study drug. A smaller percentage of subjects in the levofloxacin treatment group (7.4%) than in the amoxicillin/clavulanate treatment group (21.2%) had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug.

Eleven subjects in the levofloxacin group and 16 subjects in the amoxicillin/clavulanate treatment group discontinued the study because of adverse events. In the levofloxacin group, subjects discontinued primarily due to skin- or GI-related adverse events. In the amoxicillin/clavulanate group, all adverse event discontinuations were due to GI-related complaints except one case (fatigue).

No deaths occurred during the study. There were two serious or potentially serious adverse events reported, chest pain and anemia; both events occurred in levofloxacin-treated subjects within the first week after therapy was complete and neither was considered related to study drug administration.

15. Conclusions:

15.1. Protocol M92-040 has significant flaws in the protocol design and implementation including:

15.1.1. The protocol was a completely unblinded study. This is particularly significant in light of the fact that all of the endpoints are clinical and, thus, subjective and subject to bias by both (1) **observer/expectation bias** from the investigator and (2) **reporting/recall bias** in the patient reporting the symptoms[22].

15.1.2. The windows for clinical evaluation at both the End-of-therapy and End-of-study evaluations were inappropriate to allow for a definitive test-of-cure evaluation from which could be derived a stable point estimate for the clinical cure rate. Specifically, the test-of-cure evaluation should have been conducted at a point at which the assessment could be dichotomist into a cure/failed category, eliminating the "clinically improved" category. In this protocol, the EOT evaluation was conducted too early to assess a stable cure rate and the EOS evaluation was scheduled too far out from the end of therapy to differentiate (1) clinical failures (early relapses) resulting from partial response to study drug or superinfection from (2) recurrent sinusitis (late relapses) from reinfection with the same organism or infection with another microorganism.

15.1.3. The clinical assessment categories were inappropriate. Specifically, the clinical assessment should have been a dichotomous cured/failed category. Acute bacterial sinusitis is a disease that should be fully resolved by three weeks from diagnosis, and, thus, if the appropriate time point were used for the test-of-cure evaluation, it should be evaluated as cured/failed. Any residual symptoms, though less severe than at clinical presentation and, therefore, given the clinical categorization of "improved", are by

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[22] Sackett DL. Bias in Clinical Research. J Chronic Dis 32:51-63, 1979.

strict definition a clinical failure.

15.1.4. Quantitative cultures on sinus aspirates were not included. The absense of quantitative cultures for *S. aureus* limited the rigorous assessment of *this organism* as a true pathogen, as opposed to merely a contaminant, which it is well known to frequently be. This makes accurate assessment of a microbiologic eradication rate for *S. aureus* impossible, since it will not be known if the eradicated organisms merely represented contaminants, with CFU/mL by quantitative culture below the breakpoint for a pathogenic organism.

15.1.5. There was inadequate characterization of the microbiology of the subjects who were considered clinical failures. Only 6% (4/65) patients who were clinical failures at the End-of-therapy evaluation (sponsor's assessment) and 3.4% (4/117) of those who were clinical failure at End-of-study evaluation (medical officer's assessment) had specimens taken for culture, and these were taken at the EOT visit. (Of those considered clinical failures at the End-of-study evaluation, 45% (53/117) were in the levoflxacin arm and 55% (64/117) were in the amoxicillin/clavulanate arm.) This does not allow the evaluation of whether or not there was a microorganism that was predominant in those patients who failed therapy.

An accurate assessment of the microbiology in the cohort of clinical failures is particularly important because this study was designed to evaluate the efficacy of a quinolone for infections due to *Streptococcus pneumoniae* and *Staphylococcus aureus*, two microorganisms for which there has been increasing resistance to the quinolone class of antimicrobials, as discussed in the following Section. Resistance to other quinolone agents by *Staphylococcus aureus* has been shown to occur **during therapy** with these agents. Thus, it is important to know if there was development of resistance of this organism (and, to a lesser extent, other microorganisms) in the course of antimicrobial treatment.

15.2. The use of a quinolone antimicrobials for infections involving *Streptococcus pneumoniae* and *Staphylococcus aureus* may be problematic, since resistance of these organisms to other quinolone antimicrobial agents has been shown to occur relatively rapidly. The use of levofloxacin for the treatment of sinusitis in the community will in general be empiric, thus, its coverage for organisms in which there could be pre-existing or rapid development of resistance may be suboptimal and may not be known with great accuracy.

15.2.1. Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*.

Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*, with methicillin-resistant *S. aureus* (MRSA) developing resistance at a more rapid rate than methicillin-sensitive *S. aureus* (MSSA). Ciprofloxacin-resistance in *S. aureus* is well documented, with reports resistance developing during therapy

with these agents[23]. One study surveyed the development of ciprofloxacin-resistance in methicillin-resistant *S. aureus* (MRSA) in patients treated with the antimicrobial for nonstaphylococcal infections in a VA Medical Center. These authors reported that 79% of MRSA isolates were resistant to ciprofloxacin one year after introduction of the drug, and 91% of MRSA isolates were resistant to ciprofloxacin two years after introduction of the drug[24]. Piercy et.al. reported development of resistance in 16% (6/37) of patients who were being treated with ciprofloxacin for MRSA colonization and Mulligan et.al. reported 32% (7/22) of treatment episodes were associated with the development of ciprofloxacin-resistant MRSA during the course of antimicrobial therapy[25]. Resistance among methicillin-susceptible *S. aureus* (MSSA) has been less widespread than with MRSA, but has still been reported[26].

While the mechanism of resistance of *S. aureus* to quinolones is not completely understood, there are authors who suggest that the rapid emergence of ciprofloxacin resistance in *S. aureus* may be due to the fact that a single-step point mutation alone can lead to high-level resistance[27]. For *S. aureus*, the frequency of alterations in DNA gyrase caused by single-step mutations increases from 1 in 10^2 to 1 in 10^5 when bacteria are exposed to concentrations close to the minimal inhibitory concentration. The frequency of single-step mutation to fluoroquinolone resistance in *S. aureus* ranges from 1.5 x10-5 at twice the MIC to ≤3.6 x 10 -12 at eight times the MIC; and high level resistance occurs with serial exposure of bacteria to

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[23] Daum TE, Schaberg DR. Increasing resistance of *S. aureus* to ciprofloxacin. Antimicrob Agents Chemother 34:1862-3, 1990; Blumberg HM, Rimland D, et.al. Rapid development of ciprofloxacin resistance in Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. J Infect Dis 163:1279-85, 1991; Mulligan ME, Ruane PJ, et.al. Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization. Am J Med 82 (Suppl.4A):215-9, 1987; Piercy EA, Barbaro D, et.al. Ciprofloxacin for methicillin-resistant *Staphylococcus aureus* infections. Antimicrob Agents Chemother 33:128-30, 1989; Scaefler S. Methicillin-resistant strains of *Staphylococcus aureus* resistant to the quinolones. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Widespread quinolone resistance among methicillin resistant *S. aureus*. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Ciprofloxacin resistance in epidemic methicillin-resistant *S. aureus*. Lancet 2:843, 1988.

[24] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[25] Piercy EA. Antimicrob Agents Chemother 33:128-30, 1989; Mulligan ME, Ruane PJ, et.al. Am J Med 82 (Suppl.4A):215-9, 1987.

[26] Scaefler S. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Lancet 2:843, 1988; Daum TE, Schaberg DR. Antimicrob Agents Chemother 34:1862-3, 1990.

[27] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991; Oshita Y, Hiramatsu K. A point mutation in *norA* gene is responsible for quinolone resistance in *Staphylococcus aureus*. Biochem Biophys Res Commun 172:1028-34, 1990; Yoshida H, Bogaki M, et.al. Nucleotide sequence and characterization of the Staphylococcus *norA* gene, which confers resistance to the quinolones. J Bacteriol 172:6942-9, 1990; Neu HC. Bacterial resistance to the fluoroquinolones. Rev Infect Dis 10(suppl.1):57-63, 1988; Sreedharan S, Oram M. DNA gyrase *gyrA* mutations in ciprofloxacin-resistant strains of *S. aureus*: close similarity with quinolone resistant mutations in *E. coli*. J Bacteriol 172:7260-2, 1990.

increasing concentrations of fluoroquinolones[28].

15.2.2. Quinolone-resistance has been documented to occur in *Streptococcus pneumoniae*. The mechanism for pneumococcal resistance to the quinolones is also a one-step point mutation (single amino acid substitution) in the DNA gyrase leading to high level resistance[29]. Quinolone resistance to ciprofloxacin is more prevalent than resistance to ofloxacin, with one paper in 1992 reporting 95% of pneumococcal isolates susceptible to ofloxacin and only 68% of isolates susceptible to ciprofloxacin[30]. However, it should be noted that development of resistance to antimicrobial agents is a time-dependent phenomenon, and that ciprofloxacin has been in use longer than ofloxacin. Data presented by the Center for Disease Control[31] at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy showed that there could be significant development of resistance to ofloxacin in the period of one year, such that the point prevalence for pneumococcal intermediate resistance to ofloxacin was 1% in 1993 and 9.5% in 1994. However, it should be noted that there was no absolute resistance detected in this study.

Pharmacokinetic/pharmacodymnamic data have been used to attempt to predict clinical efficacy against specific organisms. In the case of the quinolone antimicrobials, the inhibitory quotient, defined as the AUC/MIC ratio (the ratio of the Area Under the Concentration-time Curve (AUC) of the antimicrobial to the minimum inhibitory concentration (MIC) of the *S. pneumoniae* isolate) has been shown to be predictive of clinical efficacy, with an AUC/MIC value of 40 being the breakpoint for *S. pneumonaie*[32]. Levofloxacin, being the active isomer of ofloxacin, achieves higher blood levels of the active isomer, and thus has a better inhibitory quotient for *S. pneumonaie*, as described in the table below. However, it should be noted that the MIC90 of some strains of *S. pneumonaie* is now ≥4 mcg/mL for both ciprofloxacin and ofloxacin. At this higher MIC, the inhibitory quotient for levofloxacin falls below the breakpoint of 40. Thus, the margin for "MIC creep" afforded even by the higher blood levels of levofloxacin is borderline.

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[28] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[29] Piddock LJV, Wise R. The selection and frequency of streptococci with decreased susceptibility to ofloxacin and the other quinolones. J Antimicrob Chemo 22(Suppl C): 45-51, 1988.

[30] Jones RN, Reller LB, Rosati LA. Ofloxacin, a new Broad Spectrum Fluoroquinolone: Results from a Multicenter, National Comparative Activity Surveillance Study. Diag. Microbial Infect Dives 15:425-34, 1992.

[31] Butler JC, Hofman J, Elliot JA, et.al. Late breaking abstract. 35th ICAAC, San Francisco, CA, September 17-20, 1995.

[32] Dr. David C. Hooper. Presented at the 35th ICAAC, San Francisco, CA, September, 1995.

It should be noted that all these calculations are theoretical based on the pharmacokinetic/pharmacodynamic data of these compounds. For ofloxacin, there remains a discrepancy between the inadequacy of the inhibitory quotients and the clinical efficacy, with the clinical efficacy being better than would be predicted by the marginal inhibitory quotient against *S. pneumonaie*.

Table 15.2.1

Inhibitory quotients against *Streptococcus pneumonaie* for several of the Fluoroquinolone Antimicrobials: Calculated for MICs of 2 mcg/mL and 4 mcg/mL

Quinolone Antimicrobial	Inhibitory Quotient (AUC/MIC) for MIC 2 mcg/mL		Inhibitory Quotient (AUC/MIC) for MIC 4 mcg/Ml	
	MIC	AUC/MIC	MIC	AUC/MIC
Ciprofloxacin	2 mcg/mL	11.6	4 mcg/mL	5.8
Ofloxacin	2 mcg/mL	43.5	4 mcg/mL	21.8
Levofloxacin	2 mcg/mL	60.7	4 mcg/mL	30.4

15.4. Efficacy Results:

15.4.1 Clinical Efficacy Results

The **clinical cure rate** of levofloxacin was statistically equivalent to amoxicillin/clavulante in Protocol M92-040. The clinical cure rate for the levofloxacin arm was **79% (209/263)**, and that for the amoxicillin/clavulante arm was **74% (197/266)**, with the **95%** confidence interval around the difference being $_{266,\ 263}(-13.0$ to $2.2)_{74\%,\ 79\%}$. Thus, levofloxacin meets regulatory criteria for approval for the treatment of acute bacterial sinusitis based on the demonstration of statistical equivalence to an approved competitor.

Recommendations:

Recommendations for the use of levofloxacin for the treatment of acute bacterial sinusitis are discussed at the end of the review of this indication, following the discussion of Protocol N93-006.

Medical Officer's Review of NDA 20-634
Levaquin ® (levofloxacin) Tablets

Study Title: A multicenter, noncomparative study to evaluate the safety and efficacy of oral levofloxacin in the treatment of acute sinusitis (caused by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* or *Staphylococcus aureus*) in adults

Protocol: N93-006

Study dates: January 28, 1993 to April 25, 1995

1. Study Objective:

The objective of the study was to evaluate the safety and efficacy of levofloxacin 500 mg PO once a day for 10 to 14 days for the treatment of acute bacterial sinusitis caused by susceptible organisms, specifically *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*[1].

2. Protocol design:

The protocol was an unblinded, open-label, noncomparative, multicenter study. The study incorporated a microbiologic evaluation on all patients.

3. Diagnostic criteria:

The primary diagnosis of acute bacterial sinusitis was defined by clinical and radiographic signs and symptoms of acute sinusitis:

Clinical: presence for ≤ 4 weeks of at least two of the following clinical signs and symptoms of acute sinusitis: fever, headache, purulent nasal discharge, facial pain, malar tenderness, or dental pain

Radiographic: radiographic evidence on sinus x-rays (including lateral and Waters views) or CT scan of air-fluid level, opacification or mucosal thickening (≥4 mm)

Microbiologic: positive Gram stain of aspirated sinus exudate (obtained by antral puncture or endoscope).

[1] *Staphylococcus* aureus was not listed as a pathogen in the objective of the initial study protocol, but the sponsor is requesting this organism in the label.

4. Inclusion and exclusion criteria:

Multiple changes to the inclusion/exclusion criteria were made throughout the course of the study. These are as elaborated below.

4.1. Inclusion criteria:

4.1.1. Inclusion criteria as per Original Protocol dated February 12, 1993:

Subjects could be included in the study if they satisfied the following:

1. Age: 18 or older
2. Sex: male or female
3. All subjects were to be appropriate candidates for oral therapy. Patients in nursing homes could be enrolled if they were ambulatory and were able to carry out the activities of daily life.
4. Subjects with a diagnosis of acute bacterial sinusitis as evidenced by:
   - presence for ≥4 weeks of at least two of the following clinical signs and symptoms: fever, headache, purulent nasal discharge, facial pain, malar tenderness, or dental pain
   - radiographic evidence on sinus x-rays (including lateral and Waters views) or CT scan of air-fluid level, opacification or mucosal thickening (≥ 4 mm)
   - positive Gram stain of aspirated sinus exudate (obtained by antral puncture or endoscope)

   A specimen obtained by aspiration of the sinus was to be sent for routine bacteriologic culture to confirm the presumptive diagnosis of acute bacterial sinusitis for entry into the study.
5. If female, the subject must
   - have been postmenopausal for at least one year, or
   - have had a hysterectomy, or
   - have had a tubal ligation, or
   - have taken oral contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods during the study, or
   - have used another acceptable method of contraception and agree to continue with the same method during the study.

   If female and of childbearing potential, the subject must have
   - had a normal menstrual flow within one month prior to study entry, and
   - a negative pregnancy test (serum b-subunit hCG) immediately prior to entry.

   If obtaining the serum pregnancy test result would cause a delay in treatment, a subject may have entered on the basis of a negative urine pregnancy test sensitive to at least 50 mIU/mL, pending results of the serum pregnancy test. Subsequently, if the result of the serum test was positive, the subject must have been discontinued from the study and followed as indicated.
6. Completion of the confidential follow-up form
7. Reading and signing of the informed consent (and California Bill of Rights, if applicable) after the nature of the study had been fully explained.

4.1.2. Inclusion criteria as per Protocol Amendment #1 dated September 9, 1994:

The inclusion criteria were unchanged from the original protocol with the following exceptions. Additions are in bold; deletions are in italics.

4. Subjects with a diagnosis of acute bacterial sinusitis as evidenced by:
   - presence for ~~≤~~**≥**4 weeks of at least two of the following clinical signs and symptoms: fever, headache, purulent nasal discharge, facial pain, malar tenderness, or dental pain
   - radiographic evidence on sinus x-rays (including lateral and Waters views) or CT scan of air-fluid level, opacification or mucosal thickening (≥4 mm)

[Deletion: positive Gram stain of aspirated sinus exudate (obtained by antral puncture or endoscope)]

A specimen obtained by aspiration of the sinus must have been sent for routine bacteriologic culture and Gram stain to confirm the presumptive diagnosis of acute bacterial sinusitis for entry. *into the study.*

5. Subjects who had received previous antimicrobial therapy may have been enrolled if:

- **previous therapy duration was 24 hours or less**
- **previous therapy duration was greater than 24 hours, but subject did not improve or stabilize on that therapy**

4.1.3. Inclusion criteria as per Protocol Amendment #2 dated February 12, 1995:

The inclusion criteria were unchanged from Protocol Amendment #1.

4.2. Exclusion criteria:

4.2.1. Exclusion criteria as per Original Protocol dated February 12, 1993:

Subjects with any of the following criteria were not eligible for admission into the study:

1. Immunocompromised patient, such as those who were neutropenic, those with immunodeficiency disorders (such as IgG deficiency), those with active malignancies, diabetes, or those on corticosteroid or other immunosuppressive therapy
2. Subjects with an infection due to organisms known to be resistant to the study drug prior to study entry
3. Subjects with known HIV infection
4. Subjects with chronic sinusitis (defined as duration of current symptoms for more than four weeks or more than two other episodes of acute sinusitis within the previous twelve months)
5. Presence or history of serious complications of sinusitis including brain abscess, meningitis, cranial osteomyelitis, venous thrombosis, or orbital cellulitis
6. Previous allergic or serious adverse reaction to levofloxacin, or any other members of the quinolone class of antimicrobials
7. Calculated creatinine clearance less than or equal to 20 mL/min
8. Requirement of a second systemic antimicrobial agent
9. Effective systemic antimicrobial therapy within 48 hours prior to admission
10. Use of an investigational agent within 30 days prior to admission
11. Pregnancy or a nursing mother
12. Previous treatment under this protocol
13. Any disorder or disease that may interfere with the evaluation of the study drugs
14. Presence of any seizure disorder or condition requiring the administration of major tranquilizers.

4.2.2. Exclusion criteria as per Protocol Amendment #1 dated September 9, 1994:

The exclusion criteria were unchanged from the original protocol with the following exceptions. Additions are in bold; deletions are in italics.

1. Immunocompromised patient, such as those who were neutropenic, those with immunodeficiency disorders (such as IgG deficiency), those with active malignancies, **severe or unstable diabetes**, or those on corticosteroid or other immunosuppressive therapy. **(Subjects requiring a brief course of systemic steroids for this episode of sinusitis were allowed. Nasal steroids were allowed.)**
2. Subjects with an infection due to organisms known to be resistant to the study drug prior to study entry
3. Subjects with known HIV infection
4. Subjects with chronic sinusitis (defined as duration of current symptoms for more

than four weeks or more than two other episodes of acute sinusitis within the previous twelve months)

5. Presence or history of serious complications of sinusitis including brain abscess, meningitis, cranial osteomyelitis, venous thrombosis, or orbital cellulitis
6. Previous allergic or serious adverse reaction to levofloxacin, or any other members of the quinolone class of antimicrobials
7. Calculated creatinine clearance less than *[or equal to]* 20 mL/min
   When only serum creatinine was available, the following formula (based on sex, weight, and age of the subject) may have been used to estimate creatinine clearance.
   Males: Weight (kg) x [140 - age (in years)] 72 x serum creatinine (mg/100 mL)
   Females: 0.85 x above value
8. Requirement of a second systemic antimicrobial agent
9. *[Effective systemic antimicrobial therapy within 48 hours prior to admission]*
10. 9. Use of an investigational agent within 30 days prior to admission
11. 10. Pregnancy or a nursing mother
12. 11. Previous treatment under this protocol or with levofloxacin
13. 12. Any disorder or disease that may interfere with the evaluation of the study drugs
14. 13. Presence of any seizure disorder *[or condition requiring the administration of major tranquilizers.]*
14. **Unstable psychiatric conditions.**

4.2.3. Exclusion criteria as per Protocol Amendment #2 dated February 12, 1995:

The exclusion criteria were unchanged from Protocol Amendment #1.

5. Concomitant use of medications and other antimicrobial agents:

The appropriate use of antihistamines and decongestants during this study to facilitate sinus drainage was to be encouraged. Use of these medications was to be noted on the case report form (CRF). The use of other medications during the study was to be minimized. Administration of nonstudy systemic antimicrobials was to be prohibited, and aluminum-magnesium based antacids (e.g., Maalox ®) as well as mineral supplements or vitamins with iron or minerals were to be strongly discouraged because of their potential to decrease the bioavailability of study drug. However, if administration of an antacid was necessary, it was to be administered at least two hours before or after levofloxacin or amoxicillin/clavulanate potassium administration. If the administration of any other medication was required, it was to be reported on the subject's CRF.

6. Efficacy Criteria:

6.1. Clinical Efficacy Criteria:

The **primary efficacy variable** was clinical response, to be assessed by the investigator as cured, improved, failed, or unable to evaluate at the posttherapy visit two to five days after completion of the therapy. The **clinical cure rate** was to be evaluated by determining the percentage of clinically evaluable subjects who were cured, and the **clinical success rate** was to be based on the percentage of clinically evaluable subjects who were cured or improved.

6.1.1. Clinical efficacy criteria at Post-therapy Visit:

Clinical Response Rating was to be assessed at Posttherapy Evaluation (2 to 5 days after completion of therapy) and at poststudy (28 to 32 days

after the end of therapy). At the posttherapy visit, the investigator was to assess the clinical response as cured, improved, failed, or unable to evaluate. The definitions for these assessments were as follows:

Cured - Disappearance of signs and symptoms with radiographic evidence of stabilization/improvement at the posttherapy visit with no further therapy required.
Improved - Incomplete resolution of signs and symptoms or incomplete resolution of radiographic signs of acute sinusitis and no further therapy required.
Failed - No clinical response to therapy or worsening of the radiographic evidence of infection.
Unable to Evaluate - Subject did not return for follow-up evaluation.

6.1.2. Clinical efficacy criteria at Post-study evaluation:

At the poststudy visit 28 to 32 days after the end of therapy, the investigator was to again assess the clinical response for those subjects with a successful outcome (i.e., cured or improved) at posttherapy. The clinical response at poststudy was to be assessed as cured, improved, relapse, or unable to evaluate. The definitions for these assessments were as follows:

Cured - Complete resolution of signs and symptoms.
Improved - Continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period and no further therapy required.
Relapse - Resolution or improvement of signs and symptoms at posttherapy visit but reappearance or deterioration of signs and symptoms of the infection at Poststudy visit.
Unable to Evaluate - No Poststudy evaluations.

6.2. Microbiologic Efficacy Criteria:

6.2.1. Microbiologic Response:

The primary efficacy parameter of microbiologic response to treatment was to be evaluated by the Sponsor in terms of overall infection eradication rates and individual pathogen eradication rates. The microbiologic response for pathogens isolated at admission was to be determined by evaluating the posttherapy/early withdrawal culture results. A culture was to be considered valid if it was obtained within 1 to 10 days posttherapy and collected while the subject was not receiving any effective systemic antimicrobial treatment. Responses were to be categorized as follows:

Eradicated: Eradication of the admission pathogen as evidenced by failure to isolate the pathogen in a valid posttherapy/early termination culture. If clinical improvement occurs and invasive procedures for culture were contraindicated, then the pathogen was presumed eradicated.
Persisted: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/early termination culture. If a subject (I) was discontinued (due to clinical failure or a resistant pathogen) and was considered a clinical failure, or (ii) was considered a clinical failure and study therapy was not extended, or (iii) eradication of the admission pathogen was not confirmed by a valid posttherapy or early termination culture, then 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 termination culture with documented acquisition of resistance.

Unknown: No posttherapy/early termination culture results available due to lost-to-follow-up, lost culture, or culture not done when specimen was available. The response was unknown if a negative culture was obtained during therapy or while the subject was receiving an effective nonstudy antimicrobial agent for reasons other than clinical failure, unless persistence was verified or presumed.

Medical Officer's Comment: The window for obtaining posttherapy culture results was 1-10 days posttherapy. The early half of this window is too early to obtain reliable culture results after treatment with a drug with a half-life of 8-9 hours.

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.

6.2.2. Susceptibility Testing:

Susceptibility to levofloxacin was to be determined for all aerobic pathogens at admission, and at any other time when sinus aspirate specimens were obtained. The MIC susceptibility was to be the primary susceptibility criterion. If the MIC values were not available, disks were to be used to determine susceptibility. Disk susceptibility testing was to be performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) methods using 5 μg levofloxacin disks provided by the Sponsor. Minimum inhibitory concentrations for levofloxacin were to be determined for all aerobic pathogens. For full discussion of the susceptibility testing conducting during this study, the reader is referred to the microbiology review by Dr. Dick King, reviewing microbiologist.

7. Safety evaluation:

Adverse events were defined as treatment-emergent signs and symptoms, i.e., events that were not present at admission or events that represented an increase in frequency or severity of a sign or symptom already present at admission that occurred between the first dose of study drug and the posttherapy visit two to five days after therapy completion.

8. Schedule and procedures for evaluation of efficacy criteria:

The presence or absence of five **clinical signs and symptoms** of acute bacterial sinusitis (facial pain, headache, fever, purulent nasal discharge, and malar tenderness) was to be assessed at admission, at posttherapy (or early withdrawal), and at poststudy (28 to 32 days after completion of therapy). The results of **radiographic examinations** (e.g., sinus X-ray, CT, US, MRI) were to be reported as normal or abnormal at admission and posttherapy, and changes from admission to posttherapy were to be categorized by the investigator as resolved, improved, worsened, or no change. Radiographic examinations were to be repeated at the poststudy evaluation for subjects with suspected relapse. The main findings from the radiographic tests were also to be described. **Microbiology** specimen collections of sinus exudate were to be obtained at the time of admission (Day 1), by antral puncture or endoscopy, for gram stain, culture, and susceptibility testing. Specimens were also to be collected at the on-therapy visit and at the posttherapy visit if indicated, and specimens were to be collected at the poststudy visit from those subjects in whom a relapse was suspected.

8.1. Clinical Rating at Baseline/Prestudy Evaluation:

The presence or absence of five **clinical signs and symptoms** of acute bacterial sinusitis (facial pain, headache, fever, purulent nasal discharge, and malar tenderness), **radiographic evidence** of acute sinusitis (mucosal thickening, air fluid levels), and **sinus exudate collection** for microbiology (by antral puncture or endoscopy; for gram stain, culture, and susceptibility testing) were to be obtained at the time of admission (Day 1).

8.2. Clinical Response Rating at Post-therapy Evaluation (Two to Five Days After Completion of Therapy)

At the post-therapy visit two to five days after the end of therapy, the investigator was to assess the clinical response as cured, improved, failed, or unable to evaluate. The definitions for these assessments were as follows:

> **Cured** - Disappearance of signs and symptoms with radiographic evidence of stabilization/improvement at the posttherapy visit with no further therapy required.
> **Improved** - Incomplete resolution of signs and symptoms or incomplete resolution of radiographic signs of acute sinusitis and no further therapy required.
> **Failed** - No clinical response to therapy or worsening of the radiographic evidence of infection.
> **Unable to Evaluate** - Subject did not return for follow-up evaluation.

Sinus exudate collection for microbiology (by antral puncture or endoscopy; for gram stain, culture, and susceptibility testing) were to be obtained at post-therapy evaluation.

8.3. Clinical Response Rating at Poststudy Evaluation (28 to 32 Days After Completion of Therapy)

At the poststudy visit 28 to 32 days after the end of therapy, the investigator was to again assess the **clinical response** for those subjects with a successful outcome (i.e., cured or improved) at posttherapy. The clinical response at poststudy was to be assessed as cured, improved, relapse, or unable to evaluate. The definitions for these assessments were as follows:

Cured - Complete resolution of signs and symptoms.
Improved - Continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period and no further therapy required.
Relapse - Resolution or improvement of signs and symptoms at posttherapy visit but reappearance or deterioration of signs and symptoms of the infection at Poststudy visit.
Unable to Evaluate - No Poststudy evaluations.

Radiographic examinations were to be repeated at the poststudy evaluation for subjects with suspected relapse. The main findings from the radiographic tests were also to be described. **Sinus exudate collection** for microbiology (by antral puncture or endoscopy; for gram stain, culture, and susceptibility testing) were to be obtained at post-therapy evaluation for cases of suspected relapse.

9. Safety evaluation/ Adverse Event Evaluation:

Serious adverse events were defined as those events that presented a significant threat to the well-being of the subject. Serious adverse events included any event that was fatal, life-threatening, permanently or significantly disabling, required hospitalization or prolonged hospitalization, resulted in long-term outpatient treatment (greater than six months), or was a congenital anomaly, cancer, or overdose. Investigators were instructed to report all serious adverse events immediately to RWJPRI. A 5-mL venous blood sample for determination of levofloxacin plasma concentration was to be obtained at the time of a serious adverse event. However, due to practical limitations, these blood samples were not obtained as planned.

10. Evaluability Criteria:

10.1. Evaluability criteria as per Sponsor:

The Sponsor made multiple changes in the evaluability criteria during the conduct of this study. These are delineated below.

10.1.1. Evaluability criteria as per Original Protocol dated February 12, 1993:

1. **Safety Analysis**: To be evaluable for the safety analysis, a subject must take the study medication and must relay safety information.
2. **Efficacy Analysis**

A subject will be evaluable for microbiological efficacy unless categorized into one of the following groups:

a. Unevaluable for safety
b. Infection not bacteriologically proven. No pathogen identified in the admission culture.
c. Resistant to study drug. An admission pathogen was resistant to the study drug
d. Insufficient course of therapy. Subject does not take the study drug for at least seven days. Subjects who take study drug for less than seven days because they were judged a clinical failure by the investigator were evaluable.
e. Effective concomitant therapy. Subject takes an effective systemic antimicrobial agent between time of admission culture and within 48 hours prior to start of therapy, or following therapy prior to test-of-cure culture (posttherapy).If the subject takes an effective systemic antimicrobial because they have been judged a clinical failure by the investigator, they were evaluable.
f. Inappropriate bacteriologic cultures
    1) Admission culture was greater than 48 hours prior to the start of therapy
    2) Posttherapy culture was not between 2-6 days posttherapy. If the subject was discontinued as a clinical failure and the posttherapy visit was performed on the last day of therapy, the subject was considered evaluable.
    3) Adequate microbiological data was not available
g. Lost to follow-up but relays safety information
h. Other protocol violation, e.g.,
    1) Subject fails specific entrance criteria
    2) Subject re-enters study
    3) Subject does not take at least 70% of assigned study drug
    4) Subject takes study drug for more than 14 days (unless due to persistent pathogen)

Additionally, a subject will be evaluable for clinical efficacy unless the clinical diagnosis was unconfirmed or the subject was classified by categories a, d, e, g, and/or h above.

10.1.2. Evaluability criteria as per Protocol Amendment #1 dated September 9, 1994:

1. **Safety Analysis**: Unchanged from Original Protocol.
2. **Efficacy Analysis**

A subject will be evaluable for microbiological efficacy unless categorized into one of the following groups:

a. Unevaluable for safety
b. Infection not bacteriologically proven. No pathogen identified in the admission culture.

[c. Resistant to study drug. An admission pathogen was resistant to the study drug]

c. Insufficient course of therapy
    - Subject does not take the study drug for at least seven days.
    - Subjects who take study drug for *[less than seven days because they were judged a clinical failure by the investigator were evaluable]*. **greater than 48 hours but for less than 7 days because they were judged a clinical failure by the investigator were evaluable. The pathogen(s) was(were) presumed to persist in these situations.**
d. Effective concomitant therapy
    - Subject takes an effective systemic antimicrobial agent between time of

admission culture and *[within 48 hours prior to start of therapy, or following therapy prior]* to test-of-cure culture (posttherapy).

- If the subject takes an effective systemic antimicrobial because they have been judged a clinical failure by the investigator, they are evaluable.

e. Inappropriate bacteriologic cultures
   1) Admission culture was greater than 48 hours prior to the start of therapy
   2) Posttherapy culture/evaluation was not between 2-10 days posttherapy. If the subject was discontinued as a clinical failure and the posttherapy visit was performed on the last day of therapy, the subject was considered evaluable.
   3) Adequate microbiological data was not available

f. Lost to follow-up but relays safety information

g. Other protocol violation, e.g.,
   [1) Subject fails specific entrance criteria]
   1) Subject re-enters study
   2) Subject does not take at least 70% of assigned study drug
   [4) Subject takes study drug for more than 14 days (unless due to a persistent pathogen)]

Additionally, a subject will be evaluable for clinical efficacy unless the clinical diagnosis was unconfirmed or the subject was classified by categories a, d, e, g, c, d, e.2, f, and/or h g above.

10.1.3. Evaluability criteria as per Protocol Amendment #2 dated February 12, 1995:

The evaluability criteria were unchanged from Protocol Amendment #1 with the following exception:

e. Inappropriate bacteriologic cultures
   1) Admission culture was greater than 48 hours prior to the start of therapy
   2) Posttherapy culture/evaluation was not between *[2-10 days]* 1-10 days posttherapy. If the subject was discontinued as a clinical failure and the posttherapy visit was performed on the last day of therapy, the subject was considered evaluable.
   3) Adequate microbiological data was not available

10.2. Evaluability criteria as per Medical Officer:

10.2.1. Clinical evaluability Criteria:

1. The subject met the inclusion criteria
2. The subject did **NOT** meet any of the exclusion criteria at the time of enrollment
3. A **posttherapy/end-of therapy/EOT** (2-10 days post therapy) and a **poststudy/end-of-study/EOS** (28-30 days posttherapy) clinical evaluation were performed. The exception was for patients who were declared clinical failures at the posttherapy visit, but did not have a poststudy follow-up, here the failure declared at post-therapy was carried forward.
4. A symptomatic response could be evaluated at both the **posttherapy** and **poststudy** time points.
5. In terms of **defining the time point for test-of cure**, the amended protocol as specified that clinical evaluation at the **posttherapy/EOT** (2-10 days posttherapy) visit was to be the primary clinical endpoint. The medical officer chose to use the **poststudy/EOS** (28-32 days posttherapy) evaluation as the primary clinical endpoint: the rationale for this decision are delineated in the following paragraphs.

   5.1. With regard to establishing time point for follow-up after treatment of acute bacterial sinusitis, both (1) the **natural history of the disease** and (2) the **half-life of the antimicrobial agent** under investigation need to be taken into account.

5.1.1. In regard to the **natural history of acute bacterial sinusitis**, there are multiple sources in both the medical and otolaryngology literature that would suggest that acute sinusitis should resolve within 3 weeks:

> "Symptoms of acute maxillary sinusitis should resolve within 5 days when treatment with appropriate antibiotics and decongestants is begun."[2]
>
> "Acute sinusitis should be fully resolved within three weeks."[3]
>
> "Most patients recover from acute sinusitis within three weeks. For some patients, the problem remains unresolved, and the sinus mucosa undergoes changes that prolong the infection."[4]
>
> "Acute suppurative sinusitis is any infectious process in a para nasal sinus lasting from 1 day to 3 weeks."[5]
>
> "Those with acute sinusitis whose symptoms persist despite an adequate course of antimicrobial treatment should be treated with sinus lavage."[6]

5.1.2. The windows for follow-up after an episode of acute bacterial sinusitis will be the same for patients treated with any **antimicrobial agent with a relatively short half-life**. It is only in the case of a prolonged half-life that the window for follow-up needs to be extended because blood levels and tissue levels persist far beyond the last dose of the antimicrobial drug. For levofloxacin, whose serum half-life is 6.34-6.39 hours in the clinical tablet, the window of follow-up can be the same as for other antimicrobial agents with relatively short half-lives.

5.1.2.1. The **IDSA Guidelines** recommend standard follow-up after an episode of acute bacterial sinusitis as follows:

> "Patients should be follow-up clinically and with imaging for at least 2 weeks after completion of antimicrobial therapy to assess relapse or recurrence, clinical complications, and adverse effects of the antimicrobial regimen."[7]

5.1.2.2. Recent **regulatory precedent** for the appropriate time point for test of cure has been established in other reviews of antimicrobial agents with

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[2] Frazier LM, Corey GR. Acute Bacterial Sinusitis. NCMJ 47(3):115-7, 1986.

[3] Richtsmeier WJ, Medical and Surgical Management of Sinusitis in Adults. Ann Otol Rhinol Laryngol 101:46-50, 1992.

[4] Godley FA. Chronic Sinusitis: An Update. Am Fam Phys 45(5):2190-8, 1992.

[5] Melen I. Chronic Sinusitis: Clinical and Pathophysiological Aspects. Acta Otolaryngol Suppl 151:45-8, 1994.

[6] Gwaltney JM. Therapeutic approach to sinusitis: Antiinfectious therapy as the baseline of management. Otolaryngol Head Neck Surg 103:876, 1990.

[7] Chow AW, et.al. General Guidelines for the evaluation of New Anti-Infective Drugs for the Treatment of Respiratory Tract Infections: Sinusitis. Clin Infect Dis 15(Suppl 1): 77, 1992.

short half-lives for the indication of acute bacterial sinusitis :

> Review of NDA 50-621/S-4,14,15,16 (Suprax®, cefixime tablets) a window of 8-22 days post-therapy for the follow-up of acute bacterial sinusitis. "Considering the relatively short half-lives of the two study drugs (The half-life of cefixime averages 3-4 hours, but ranges up to 9 hours; and the half-life of amoxicillin is 1.3 hours and that of clavulanate is 1.0 hour), the MO considered posttherapy follow-up from days +8 to +21 adequate to detect significant relapses. If a patient was seen with relapse on day +22 or later, this visit was considered unevaluable by the MO, [who felt that] relapse occurring after day +21 should not be held against either study drug. However, if a patient returned for follow-up beyond day +21 with a clinical assessment of cure, this patient would be considered evaluable."[8]

> Review of NDA 50-664/Amendment #1 to S-003 and NDA 50-665/Amendment #1 to S-003 (CEFZIL®, cefprozil tablets) required that a patient would be unevaluable if they were "not seen at least 10 days after completion of course of therapy, [which] correlates with IDSA guidelines that stress follow-up evaluations to be done at least 10-14 days after antimicrobial therapy for sinusitis is completed." The exception to this was that "patients could be considered a failure if at any earlier visit deemed as being so."[9]

Thus, the basis for the decision to use **the EOS evaluation (28-32 days posttherapy) as the primary clinical endpoint** was based on the fact that: (1) the original (2-5 days posttherapy) and the extended (2-10 days post-therapy) windows for the EOT visit were to early in the course of the disease to be definitive time points for test-of-cure, since the accepted duration of (treated) bacterial sinusitis is three weeks, and (2) while the EOS evaluation (28-32 days posttherapy) may not be the optimal time point for test of cure (because relapses at this late a time point may not be definitively attributed to the study drug), this later time point was superior to the earlier time point for the test-of-cure evaluation, since it is beyond the time point at which acute sinusitis should have fully resolved and thus is a more stable point estimate.

6. In regards to **categorization of the clinical response**, the sponsor defined the clinical response at both the EOT and the EOS visits according to the "cured-improved-failed-relapsed" scale delineated in sections 7.2 and 7.3.1 above. The medical officer considered that, since both the medical and otolaryngology literature would suggest that acute sinusitis should completely resolve within 3 weeks, the category of "improved" was not applicable to the evaluation at the EOS visit. Thus, the **clinical evaluation at the EOS visit was changed to a dichotomous variable "cure\failed"**, predominantly on the presence or absence of the ANY of the **major/cardinal signs/symptoms of acute bacterial sinusitis** as defined in the inclusion criteria of the study protocol:

> cure-complete resolution of all symptoms, including fever, facial pain headache, malar tenderness and purulent discharge, indicative of acute

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[8] Leissa B. Medical Officer's Review of NDA 50-621, Suppl.004, 014, 015, 016, p.B4-B5, p. C14, final draft 05-Dec-91.

[9] Rakowsky A. Medical Officer's Review of NDAs 50-664 and 50-665, Supplement 003, p.08, final draft 21 May-95.

sinusitis.
fail- the persistence (treatment failure) or recurrence (early or late relapse) of any of the symptoms of acute sinusitis, including persistent purulent nasal discharge in isolation from other symptomatology.

The basis for this decision are documented in the following paragraphs taken from the ENT and medical literature:

"Symptoms of acute maxillary sinusitis should resolve within 5 days when treatment with appropriate antibiotics and decongestants is begun."[10]

"Acute sinusitis should be fully resolved within three weeks."[11]

"Most patients recover from acute sinusitis within three weeks. For some patients, the problem remains unresolved, and the sinus mucosa undergoes changes that prolong the infection."[12]

"Acute suppurative sinusitis is any infectious process in a paranasal sinus lasting from 1 day to 3 weeks."[13]

"Those with acute sinusitis whose symptoms persist despite an adequate course of antimicrobial treatment should be treated with sinus lavage."[14]

Furthermore, symptoms indicative of treatment failure in acute sinusitis may be subtle: the only symptom present in a case of treatment failure may be the persistence of purulent nasal discharge. Gwaltney summarizes the issue in the following: "It should be emphasized that clinical improvement was seen in the face of bacteriologic failure in patients in whom the infecting bacteria was resistant to the antibiotic given. Particularly, facial and "sinus" discomfort tended to resolve despite continued high concentrations and exudate in the sinus cavity, presumably because these complaints were associated with initial stretching of the sinus membrane in the early stages of infection. Persistent nasal discharge and abnormal tonal quality of the voice appeared to be more sensitive signs of continuing disease."[15]

7. In regards to **categorization of minor symptoms/signs** (such as isolated congestion and post nasal drip) that were not cardinal signs and symptoms of acute bacterial sinusitis (as defined by the inclusion criteria of the protocol) the medical officer attempted to determine if these were attributable to (1) pre-

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[10] Frazier LM, Corey GR. Acute Bacterial Sinusitis. NCMJ 47(3):115-7, 1986.

[11] Richtsmeier WJ, Medical and Surgical Management of Sinusitis in Adults. Ann Otol Rhinol Laryngol 101:46-50, 1992.

[12] Godley FA. Chronic Sinusitis: An Update. Am Fam Phys 45(5):2190-8, 1992.

[13] Melen I. Chronic Sinusitis: Clinical and Pathophysiological Aspects. Acta Otolaryngol Suppl 151:45-8, 1994.

[14] Gwaltney JM. Therapeutic approach to sinusitis: Antiinfectious therapy as the baseline of management. Otolaryngol Head Neck Surg 103:876, 1990.

[15] Gwaltney JM. The microbial etiology and antimicrobial therapy of adults with acute community acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 90:457-62, 1992.

existing allergic rhinitis or chronic sinusitis or (2) represented a cohort of patient who were treatment failures progressing into subacute/chronic sinusitis.

There exists debate in the literature regarding the pathophysiology of chronic sinusitis. There are authors who argue that chronic sinusitis arises primarily from chronic obstruction of the sinus ostia secondary to anatomic abnormalities of the osteomeatal complex through which the sinuses drain into the nose[16]. Others argue that it generally arises from untreated, partially treated or treatment failure of acute sinusitis[17]. Patients with chronic sinusitis rarely present with spiking fevers, purulent discharge and peripheral leukocytosis. Instead, they present with a constellation of symptoms which usually includes not only the "triad" of chronic sinusitis (sinus congestion, postnasal drip, and fatigue), but also retrobulbar pressure/headaches, daily facial pain, daily headaches for several weeks, ear pain, and ear blockage[18]. Of particular note, "Nasal airway obstruction and post-nasal drip may be the only complaints"[19]. Because of the subtly of symptoms comprising the syndrome of chronic sinusitis, the medical officer applied the following criteria to the analysis of the "minor symptoms" of nasal congestion and postnasal drip remaining at the EOS visit:

7.1. if the subject had a history of allergic rhinitis AND has resolution of all major symptoms of sinusitis, these symptoms were attributed to the allergic rhinitis

7.2. if the subject had ANY other symptoms of acute sinusitis, these symptoms were considered indicative of clinical failure

7.3. patients with congestion and/or PND **WITHOUT** other signs and symptoms of sinusitis or a history of allergic rhinitis were evaluated as a separate subset to determine whether, if this cohort was treated as clinical failures that were progressing into a subacute/chronic sinusitis, this would affect the relative cure rates of the two treatment arms

8. In regards to the use of concomitant antibiotic therapy **from the time of enrollment through the end-of study visit**, the following criteria were applied:

8.1. A patient was **fully clinically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

- Within 48 hours prior to enrollment in the protocol
- During the treatment period
- From the end of the treatment period to the poststudy evaluation
- At the evaluation for clinical relapse

8.2. if the patient received **pretherapy** antimicrobial treatment with another antibiotic, the patient was clinically evaluable ***only*** if there was a pathogen isolated on admission culture. If **no**

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[16] Messerklinger W. On the drainage of the normal frontal sinus of man. Acta Otolaryngol 63:176-81, 1967; Stammberger H. Endoscopic endonasal surgery-concepts in the treatment of recurrent sinusitis. Otolaryngol Head Neck Surg 94:143-56, 1986; Stammberger H. Nasal and paranasal sinus endoscopy. Endoscopy 18:213-8, 1986.

[17] Kern EB. Suppurative (bacterial) sinusitis. Postgrad Med 81(4):194-210, 1987.

[18] Godley FA. Chronic Sinusitis: An Update. Am Fam Phys 45(5):2190-2199, 1992;

[19] Kern AB. Postgrad Med. 81(4): 198.

pathogen was isolated on admission culture, the patient was both clinically and microbiologically unevaluable.

8.3. if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **clinically unevaluable.**

8.4. if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **clinically evaluable (only) as a treatment failure.**

9. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

9.1. for patients designated as a clinical cure at EOS, a minimum of 7 days or 70% of the minimum dose specified by the protocol

9.2. for patients designated a clinical failure at EOS, a minimum of 72 hours of study drug was to have been taken

9.3. for the levofloxacin arm, no more than 2 missed doses within the dosing interval requiring extension of the dosing interval to complete the full 10-14 doses of therapy

10. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

10.2.2. Microbiologic evaluability criteria as per medical Officer:

1. Pretherapy sinus culture, **obtained EITHER by direct aspirate or by endoscopy,** was positive for:

Subgroup 1: All microorganisms isolated on admission culture
Subgroup 2: One of four pathogenic organisms, including *Streptococcus pneumoniae, Haemophilus influenzae, Branhamella catarrhalis,* and *Staphylococcus aureus.*
Subgroup 3: One of three pathogenic organisms, including *Streptococcus pneumoniae, Haemophilus influenzae,* and *Branhamella catarrhalis.*

2. Patients met criteria for clinical evaluability at ALL time points during the study
3. Any secretions that were suitable for culture were cultured. The use of the category "presumed eradication" was reserved only for those cases in which there was no residual secretions to culture
4. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit,** the following criteria were applied:

4.1. A patient was **fully microbiologically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

- During the treatment period
- From the end of the treatment period to the poststudy evaluation
- At the evaluation for clinical relapse

4.2. if the patient received **pretherapy** antimicrobial treatment with another antibiotic, the patient was microbiologically

evaluable if there was a pathogen isolated on admission culture. If no pathogen was isolated on admission culture, the patient was both clinically and microbiologically unevaluable.

4.3. if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **microbiologically unevaluable.**

4.4. if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **microbiologically evaluable (only) as a persistent pathogen.**

5. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

(I) for patients designated as a microbiologic eradication, a minimum of 7 days or 70% of the minimum dose specified by the protocol
(ii) for patients designated a microbiologic persistence, a minimum of 72 hours of study drug was to have been taken
(iii) no more than 2 missed doses within the dosing interval requiring extension of the dosing interval to complete the full 10-14 doses of therapy

7. With regards to distinguishing *S. aureus* as a pathogen from *S. aureus* as a contaminant, the medical officer acknowledges that the best method is by quantitative culture, with isolates of $>10^3$ CFU/mL being considered pathogens, and those below this breakpoint being considered contaminants. There were no quantitative cultures obtained in the conduct of this protocol, thus, the medical officer and team leader chose to use evaluate only the isolates of *S. aureus* that were obtained as monomicrobial isolates as pathogens. Isolates of *S. aureus* from polymicrobial infections were considered contaminants for the purposes of this analysis.

8. In evaluating isolates of *Staphylococcus aureus (as a contaminant vs. a pathogen)*, the medical officer applied the following criteria:

8.1. In regards to *S. aureus* as a pathogen, the medical officer is aware that controversy exists in the literature. However, recent literature reviews[20] and Division of Anti-Infective Drug Product

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[20] Gwaltney JM, Scheld M, et.al., The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 90:457-62, 1992; Winther B, Gwaltney JM. Therapeutic approach to sinusitis: Antiinfectious Therapy as the baseline of management. Otolaryngol Head Neck Surg 103:876, 1990; Calhoun K. Diagnosis and management of sinusitis in the allergic patient. Otolaryngol Head Neck Surg 107:850-4, 1992; Gleckman RA. Acute Bacterial Sinusitis. Hospital Practice pp. 92-100. January 30, 1986; Frazier LM, Corey GR. Acute Bacterial Sinusitis. NCMJ 47(3):115-7, 1986; Gwaltney JM, Sinusitis. In Mandell GL, Dolin R, Bennett JE, eds. Principles and Practice of Infectious Diseases, 4th Edition, New York, Churchill Livingstone, 1995, 585-90; Kennedy DW. Medical Management of Sinusitis: Educational Goals and Management Guidelines. In: International Conference on Sinus Disease: Terminology Staging, Therapy. Ann Otol Rhino Laryngol 104(10 part 2):22-30, 1995; Jousimies-Somer HR, Savolainen S, et.al., Macroscopic Purulence, Leukocyte Counts, and Bacterial Morphotypes in Relation to Culture Findings in Acute Bacterial Sinusitis. J Clin Microbiol 26(10):1926-33, 1988; Berg O, Carenfelt C. Bacteriology of Maxillary Sinusitis in Relation to Character of Inflammation and Prior Treatment. Scand J Infect Dis 20:511-16, 1988..

Advisory Committee[21] have considered *S. aureus* to be a pathogen in acute bacterial sinusitis, including maxillary sinusitis. The frequency of *S. aureus* as a pathogen in maxillary sinusitis is less than in frontal and sphenoid sinusitis, where it is a major pathogen.[22] *S. aureus* is considered as a pathogen in up to 8% of cases of maxillary sinusitis, but is the responsible pathogen in over 50% of the orbital and intracranial complications of maxillary sinusitis[23]. Thus, when *S. aureus* is a pathogen in maxillary sinusitis, it is generally more aggressive than other pathogenic bacteria. Given these lines of evidence, the medical officer considered *S. aureus* to be a pathogen in acute bacterial sinusitis, both in the maxillary and other sinuses.

8.2. *S. aureus* may also be present as a contaminant when isolated from the maxillary sinus by either endoscopy or aspirate, and the rate of isolation as contaminant is greater with endoscopy than with direct aspiration. A recent DAIDP Advisory Committees[24] considered a breakpoint of $\geq 10^6$ CFU/mL to distinguish pathogens from contaminants in cultures of sinus secretions obtained by either endoscopy or sinus aspirate. However, quantitative cultures were not included as part of Protocol N93-006, and, thus, these data were not available to distinguish *S. aureus* as a pathogen from *S. aureus* as a contaminant. While the MO and Team Leader MO are aware that recent advisory committees have considered *S. aureus* to be a pathogen in polymicrobial infections when isolated $\geq 10^3$ CFU/mL, a decision was made to only consider as clinically evaluable for this review those cases in which *S. aureus* was isolated in monomicrobial infections. If *S. aureus* was isolated as part of a polymicrobial infection, it was considered a contaminant for the purposes of this analysis.

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[21] 53rd Anti-Infective Drugs Advisory Committee, November 17, 1994, Versailles Rooms III and IV, Bethesda Holiday Inn, 8120 Wisconsin Ave, N.E. Washington, D.C., 20002

[22] Bamberger DM. Antimicrobial Treatment of Sinusitis. Sem Resp Infect 6(2): 77-84, 1991.

[23] Frazier LM, Corey GR. Acute Bacterial Sinusitis. NCMJ 47(3): 115-7, 1986,

[24] 53rd Anti-Infective Drugs Advisory Committee, November 17, 1994, Versailles Rooms III and IV, Bethesda Holiday Inn, 8120 Wisconsin Ave, N.E. Washington, D.C., 20002

11. Investigators and Study Sites:

This protocol was conducted by a total of 34 investigators at a total of 50 study sites. All of the study sites were within the continental United States.

Table 11
Clinical Investigators and Study Sites: Protocol N93-006

Investigator	Study Site(s)
Glenn A. Amsbaugh, M.D.	York ENT Associates, York, PA; USA
Kent E. Anthony, M.D.	R/D Clinical Research, Inc., Nassau Bay, TX; USA
Patrick D. Bianchi, M.D.	Community Medical Arts Center, Tallassee, AL; Eclectic, AL; USA
Merrill A. Biel, M.D., Ph.D.	Minneapolis Ear, Nose & Throat Clinic, Minneapolis, MN; USA
James E. Carrabre, M.D.	Chanhassen Medical Center, Chanhassen, MN; USA Ridgeview Medical Center, Waconia, MN; USA
James M. Chow, M.D.	Loyola University, Maywood, IL; USA
Gregory V. Collins, M.D.	Charlotte Clinical Research, Charlotte, NC; USA
Anthony F. Cutrona, M.D.	Western Reserve Care System, Northside Medical Center, Youngstown, OH; USA Western Reserve Care System, Southside Medical Center, Youngstown OH; Boardman, OH; USA
Michael Dennington, M.D.	Aurora, CO; USA
Stephen H. Dyke, M.D.	New England Clinical Research Center, Hampton, NH; USA
David R. Edelstein, M.D.	Manhattan Eye, Ear & Throat Hospital, New York, NY; USA
Jeffrey R. Fenwick, M.D.	Trident Ear, Nose, Throat, Head and Neck Surgery Associates, P.A., Charleston, SC; USA
Joseph V. Follett, M.D.	Internal Medicine Group, P.C., Cheyenne, WY; USA Southeast Wyoming Ear, Nose & Throat Clinic P.C., Cheyenne, WY; USA
Linda J. Gorin, M.D.	Memorial City Medical Center , Houston , TX; USA
Thomas M. Kidder, M.D.	Medical College of Wisconsin, Milwaukee, WI; USA
Terry Klein, M.D.	Mid-Kansas Ear, Nose & Throat Assoc. PA, Wichita, KA; USA Family Medicine East Chartered, Wichita, KA; USA
Elliot J. Kopp, M.D. and Douglas Freeman, M.D.	Raleigh ENT, Raleigh, NC; USA Carolina Ear, Nose & Throat, Raleigh, NC; USA N.C. Arthritis & Allergy Care Center, Raleigh, NC; USA
Terrence J. Lee, M.D.	Asheville Infectious Disease Consultants, Asheville, NC; USA
Joseph Liotti, D.O.	Future Health Care Research Center, West Orange, NJ; USA Saint Barnabus Outpatient Centers, West Orange, NJ; USA
Thomas W. Littlejohn, III, M.D.	Winston-Salem, NC, Piedmont Research Associates, Winston-Salem, NC; USA Salem Family Practice, Winston-Salem, NC; USA Maplewood Family Practice, Winston-Salem, NC; USA Salem Chest Specialists, Winston-Salem, NC; USA Salem Ear, Nose, and Throat, Winston-Salem, NC; USA
Douglas G. Mann, M.D.	Plastic Surgical, Ear, Nose and Throat Associates, Media, PA; USA Plastic Surgical Ear, Nose, and Throat Associates, Chester, PA; USA
B. Chandler May, M.D.	Santa Barbara, CA; USA
Steven P. McClean, M.D.	Seattle, WA; USA Renton, WA; USA

Table 11
Clinical Investigators and Study Sites:
Protocol N93-006 (continued from previous page)

Investigator	Study Site(s)
Richard R. Moyer, M.D.	Mesaba Clinic, Hibbing, MN; USA
Erik Nielsen, M.D.	The Graduate Hospital, Philadelphia, PA; USA
Jay P. Piccirillo, M.D.	Washington University School of Medicine: Jewish Hospital, St. Louis, MO; USA Washington University School of Medicine: Barnes Hospital, St. Louis, MO; USA
Louis Portugal, M.D. and Richard G. Fiscella, R.Ph., M.P.H.	University of Illinois Hospital, Chicago, IL; USA
Donald W. Pulver, M.D.	Rochester, NY; USA
J. Daniel Scott, M.D.	R/D Clinical Research, Inc., Lake Jackson, TX; USA
T. Austin Sydnor, M.D.	Charlottesville, VA; USA Harrisonburg, VA; USA Roanoke, VA; USA Newport News, VA; USA Warrenton, VA; USA
Suzanne Weakley, M.D.	Houston, TX; USA
Welby I. Winstead, M.D.	Louisville, KY; University of Louisville, Louisville, KY; USA

12. Efficacy as per sponsor:

12.1. Study Population:

12.1.1. Analysis Groups:

Treatment evaluations are based on several analysis groups to assess efficacy and consistency across different, standard approaches. The discussion and displays in the body of the report focus mainly on the efficacy analyses based on (I) subjects classified as microbiologically evaluable according to the protocol-specified evaluability criteria and (ii) subjects classified as clinically evaluable according to the protocol-specified evaluability criteria. Supportive efficacy analyses include analyses based on all subjects enrolled, i.e., Intent-to-Treat. Supportive efficacy analyses also include an additional analysis group – Modified Intent-to-Treat Subjects with an Admission Pathogen – representing those subjects in the Intent-to-treat group who had a pathogen isolated at admission.

Table 12.1.1
Number of Subjects by Analysis Group and Study Center
(Protocol N93-006)

	Levofloxacin		
Investigator[a]	Intent-to-Treat	Clinically Evaluable	Microbiologically Evaluable
Amsbaugh[4]	2	2 (100.0)	2 (100.0)
Anthony[1]	29	29 (100.0)	11 (37.9)
Bianchi	1	1 (100.0)	0 (0.0)
Carrabre	1	1 (100.0)	0 (0.0)
Chow	2	2 (100.0)	0 (0.0)
Collins	2	2 (100.0)	0 (0.0)
Dennington[1]	12	11 (91.7)	7 (58.3)
Dyke[3]	11	6 (54.5)	5 (45.5)
Edelstein[1]	3	3 (100.0)	3 (100.0)
Follett[4]	10	9 (90.0)	3 (30.0)
Kidder[2]	5	4 (80.0)	3 (60.0)
Klein[1]	3	3 (100.0)	1 (33.3)
Kopp[1]	66	53 (80.3)	26 (39.4)
Lee	2	0 (0.0)	0 (0.0)
Liotti	1	1 (100.0)	0 (0.0)
Littlejohn[4]	19	18 (94.7)	11 (57.9)
May	1	1 (100.0)	0 (0.0)
McClean[4]	14	13 (92.9)	7 (50.0)
Moyer	1	1 (100.0)	0 (0.0)
Portugal	2	2 (100.0)	0 (0.0)
Pulver[3]	3	3 (100.0)	2 (66.7)
Scott[1]	11	11 (100.0)	5 (45.5)
Sydnor[1]	111	107 (96.4)	40 (36.0)
Weakley[1]	17	17 (100.0)	12 (70.6)
Total	**329**	**308 (91.2)**	**138 (41.9)**

Numbers shown in parentheses are percentage of total subject population in that category.

12.1.2. Demographics of Intent-to-Treat Cohort:

Three hundred twenty nine subjects were enrolled in this study at 24 of the 50 centers. All but one of the three hundred twenty nine subjects received levofloxacin 500 mg PO q24h (one subject took levofloxacin 500 mg PO q12h in error). Of the three hundred twenty nine subjects enrolled in the study, 12 (3.6%) discontinued therapy prematurely and 317 (96.4%) completed the full course of study drug as prescribed by the investigator. Of the 12 subjects who discontinued therapy prematurely, 6 (1.8%) did so because of an adverse event, 2 (0.6%) because of clinical failure as judged by the investigator, 1 (0.3%) withdrew for personal reasons, 1 (0.3%) withdrew for participation in another clinical study (not known to investigator at the time of enrollment), 1 (0.3%) withdrew because of perceived worsening of symptoms, and 1 (0.3%) withdrew because of a history of chronic sinusitis (not known to investigator at the time of enrollment).

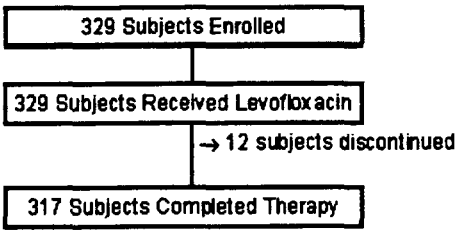
Table 12.1.2
Demographic and Baseline Characteristics:
Intent-to-treat Cohort (Protocol N93-006)

	Levofloxacin (N=329)
	No. (%)
Sex	
Men	137 (41.6)
Women	192 (58.4)
Race	
Caucasian	305 (92.7)
Black	14 (4.3)
Oriental	1 (0.3)
Hispanic	7 (2.1)
Other	2 (0.6)
Age (Years)	
≤45	222 (67.5)
46-64	88 (26.7)
≥65	19 (5.8)
Mean±SD	41.6±13.0
Range	[redacted]
Weight (lbs.)	
N	325
Mean±SD	171.9±43.4
Range	[redacted]
Missing	4
Height (ins.)	
N	325
Mean±SD	67.2±4.10
Range	[redacted]
Missing	4

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.1.3. Discontinuation from study:
Subjects could be discontinued from the study due to adverse events, significant protocol violation, intercurrent illness, treatment failure, or at the request of the subject.

Figure 12.1.3
Discontinuation/Completion Information: Intent-to-treat Cohort
(Protocol N93-006)



12.1.4. Evaluable Patient Population: Based on their evaluability criteria, the sponsor obtained 300 clinically evaluable and 138 microbiologically evaluable patients from the intent-to-treat cohort.

Table 12.1.4
Number of Subjects by Analysis Group and Study Center
(Protocol N93-006)

	Levofloxacin		
Investigator[a]	Intent-to-Treat	Clinically Evaluable	Microbiologically Evaluable
Amsbaugh[a]	2	2 (100.0)	2 (100.0)
Anthony[†]	29	29 (100.0)	11 (37.9)
Bianchi	1	1 (100.0)	0 (0.0)
Carrabre	1	1 (100.0)	0 (0.0)
Chow	2	2 (100.0)	0 (0.0)
Collins	2	2 (100.0)	0 (0.0)
Dennington[†]	12	11 (91.7)	7 (58.3)
Dyke[‡]	11	6 (54.5)	5 (45.5)
Edelstein[†]	3	3 (100.0)	3 (100.0)
Follett[a]	10	9 (90.0)	3 (30.0)
Kidder[‡]	5	4 (80.0)	3 (60.0)
Klein[†]	3	3 (100.0)	1 (33.3)
Kopp[†]	66	53 (80.3)	26 (39.4)
Lee	2	0 (0.0)	0 (0.0)
Liotti	1	1 (100.0)	0 (0.0)
Littlejohn[a]	19	18 (94.7)	11 (57.9)
May	1	1 (100.0)	0 (0.0)
McClean[a]	14	13 (92.9)	7 (50.0)
Moyer	1	1 (100.0)	0 (0.0)
Portugal	2	2 (100.0)	0 (0.0)
Pulver[‡]	3	3 (100.0)	2 (66.7)
Scott[†]	11	11 (100.0)	5 (45.5)
Sydnor[†]	111	107 (96.4)	40 (36.0)
Weakley[†]	17	17 (100.0)	12 (70.6)
Total	**329**	**300 (91.2)**	**138 (41.9)**

Numbers shown in parentheses are percentage of total subject population in that category.

12.1.5. Demographics of the Evaluable Patient Population:

Demographic summaries of sex, age, race, height, and weight are provided for all patients in the clinically and microbiologically evaluable groups.

Table 12.1.5
Demographic and Baseline Characteristics:
Sponsor's Clinically and Microbiologically Evaluable Subjects
(Protocol N93-006)

	Levofloxacin	
	Clinically Evaluable (N=300)	Microbiologically Evaluable (N=138)
Sex		
Men	121	59
Women	179	79
Race		
Caucasian	278	125
Black	13	6
Oriental	1	1
Hispanic	6	5
Other	2	1
Age (Years)		
≤45	205	103
46-64	79	29
≥65	16	6
N	300	138
Mean±SD	41.4±12.7	39.0±12.2
Range	[redacted]	[redacted]
Weight (lbs)		
N	296	135
Mean±SD	171.5±42.7	164.5±38.4
Range	[redacted]	[redacted]
Missing	4	3
Height (ins)		
N	296	135
Mean±SD	67.1±4.02	67.0±3.86
Range	[redacted]	[redacted]
Missing	4	3

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.2. Clinical Efficacy analysis

The clinical efficacy analyses focus mainly on the group of subjects evaluable for clinical efficacy. The clinical response rates (cured, improved, failed, and unable to evaluate) at posttherapy were summarized by study center, collection method, and admission pathogen for subjects evaluable for clinical efficacy. Supporting summaries and analyses are provided for the intent-to-treat subjects, modified intent-to-treat subjects with an admission pathogen, and microbiologically evaluable subjects. To allow for a dichotomous analysis, the clinical response categories of "cured" and "improved" were combined into one category of "Clinical Success." For the intent-to-treat and modified intent-to-treat with an admission pathogen groups, the clinical response category "failed" was combined with "unable to evaluate" into one category of "Clinical Failure." Transitions from admission to posttherapy of the signs and symptoms of sinusitis are presented for clinically evaluable and intent-to-treat subjects, modified intent-to-treat subjects with an admission pathogen, and microbiologically evaluable subjects. Based on these data, the percentages of subjects with resolution of these signs and symptoms are presented for the clinically evaluable

subjects. In addition, changes from admission to posttherapy in radiographic findings are presented for the clinically and microbiologically evaluable subjects. Clinical response rates at the poststudy evaluation (cured, improved, relapse, and unable to evaluate) for those subjects who were not failed at posttherapy are summarized by study center and by pathogen for all analysis groups. A separate listing is provided of clinically evaluable subjects with a poststudy clinical response of relapse.

12.3. Microbiologic efficacy analysis

Microbiologic response of sinus pathogens to treatment at the posttherapy visit represents the primary efficacy variable in this study. The microbiologic efficacy analyses focus mainly on the group of subjects evaluable for microbiologic efficacy. Summaries and analyses are provided for the microbiologically evaluable group, for the clinically evaluable group, and for modified intent-to-treat subjects with an admission pathogen, and are presented by study center and method of collection (antral puncture or endoscope). Admission susceptibilities to levofloxacin are summarized for all pathogens isolated from subjects. The overall pathogen and infection eradication rates (eradicated versus persisted) are summarized. To allow for a dichotomous assessment, the microbiologic response categories of "persisted" and "unknown" were combined into one category of "persisted". In addition to the overall eradication rates described above, eradication rates are also provided according to whether eradication of the pathogen or infection was documented (i.e., confirmed by culture results) or presumed (i.e., not confirmed by culture results). Subjects who developed an infection while on therapy that was associated with clinical signs and symptoms are considered to have had a superinfection.

12.4. Combined Clinical and Microbiologic Efficacy analysis:

As confirmatory information, a cross-tabulation of microbiologic response versus clinical response is provided for subjects evaluable for microbiologic efficacy.

12.5. Clinical Results

This section of the report focuses on results of the secondary efficacy analyses of clinical response, based primarily on the group of subjects evaluable for clinical efficacy. The results from the intent-to-treat, modified intent-to-treat with an admission pathogen, and microbiologically evaluable groups were generally consistent with those from the clinically evaluable group.

12.5.1. Clinical Response to Treatment

12.5.1.1. Overall Clinical Response

12.5.1.1.1. Clinical Response Posttherapy (Two to Five Days After Completion of Therapy)

Among the 300 clinically evaluable subjects, 175 (58.3%) were cured and 90 (30.0%) were improved. Thirty-five (11.7%) of the clinically evaluable subjects failed treatment. In the microbiologically evaluable group, levofloxacin treatment resulted in 63.0% cure, 27.5% improvement, and 9.4% failure. In the intent-to-treat group, levofloxacin treatment resulted in 57.1% cure, 29.5% improvement, and 13.4% failure. Among modified intent-to-treat subjects with an admission pathogen, levofloxacin treatment resulted in 60.4% cure, 27.3% improvement, and 12.3% failure.

Table 12.5.1.1.1.A
Clinical Response at Posttherapy (2-5 days) Evaluation by Study Center: Sponsor's Clinically Evaluable Patients (Protocol N93-006)

	Levofloxacin			
Investigator	N	Cured	Improved	Failed
Amsbaugh	2	1 (50.0)	1 (50.0)	0 (0.0)
Anthony	29	17 (58.6)	11 (37.9)	1 (3.4)
Bianchi	1	1 (100.0)	0 (0.0)	0 (0.0)
Carrabre	1	0 (0.0)	1 (100.0)	0 (0.0)
Chow	2	1 (50.0)	0 (0.0)	1 (50.0)
Collins	2	0 (0.0)	2 (100.0)	0 (0.0)
Dennington	11	0 (0.0)	6 (54.5)	5 (45.5)
Dyke	6	4 (66.7)	0 (0.0)	2 (33.3)
Edelstein	3	2 (66.7)	1 (33.3)	0 (0.0)
Follett	9	1 (11.1)	7 (77.8)	1 (11.1)
Kidder	4	4 (100.0)	0 (0.0)	0 (0.0)
Klein	3	1 (33.3)	2 (66.7)	0 (0.0)
Kopp	53	26 (49.1)	18 (34.0)	9 (17.0)
Liotti	1	1 (100.0)	0 (0.0)	0 (0.0)
Littlejohn	18	9 (50.0)	5 (27.8)	4 (22.2)
May	1	0 (0.0)	1 (100.0)	0 (0.0)
McClean	13	7 (53.8)	5 (38.5)	1 (7.7)
Moyer	1	1 (100.0)	0 (0.0)	0 (0.0)
Portugal	2	1 (50.0)	1 (50.0)	0 (0.0)
Pulver	3	2 (66.7)	1 (33.3)	0 (0.0)
Scott	11	9 (81.8)	1 (9.1)	1 (9.1)
Sydnor	107	79 (73.8)	19 (17.8)	9 (8.4)
Weakley	17	8 (47.1)	8 (47.1)	1 (5.9)
Total	**300**	**175 (58.3)**	**90 (30.0)**	**35 (11.7)**

Numbers shown in parentheses are percentages for that category.
* A window of 1-10 days posttherapy was used for determination of evaluability.

To allow for a dichotomous assessment of clinical response, the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success". Among clinically evaluable subjects, levofloxacin treatment resulted in 88.3% clinical success at the posttherapy evaluation. In the intent-to-treat group, the clinical success rate was 86.6%. Clinical success rates in modified intent-to-treat in subjects with an admission pathogen and microbiologically evaluable subjects were 87.7% and 90.6%, respectively. Clinical cure and success rates were generally comparable across the various sex, age, and race subgroups.

Table 12.5.1.1.1.B
Clinical Success/Failure Rates at Posttherapy (2-5 days) by Study Center: Sponsor's Clinically Evaluable Patients (Protocol N93-006)

	Levofloxacin				
Investigator	N	Success		Failure	
Amsbaugh	2	2	(100.0)	0	(0.0)
Anthony	29	28	(96.6)	1	(3.4)
Bianchi	1	1	(100.0)	0	(0.0)
Cerrabre	1	1	(100.0)	0	(0.0)
Chow	2	1	(50.0)	1	(50.0)
Collins	2	2	(100.0)	0	(0.0)
Dennington	11	6	(54.5)	5	(45.5)
Dyke	6	4	(66.7)	2	(33.3)
Edelstein	3	3	(100.0)	0	(0.0)
Follett	9	8	(88.9)	1	(11.1)
Kidder	4	4	(100.0)	0	(0.0)
Klein	3	3	(100.0)	0	(0.0)
Kopp	53	44	(83.0)	9	(17.0)
Liotti	1	1	(100.0)	0	(0.0)
Littlejohn	18	14	(77.8)	4	(22.2)
May	1	1	(100.0)	0	(0.0)
McClean	13	12	(92.3)	1	(7.7)
Moyer	1	1	(100.0)	0	(0.0)
Portugal	2	2	(100.0)	0	(0.0)
Pulver	3	3	(100.0)	0	(0.0)
Scott	11	10	(90.9)	1	(9.1)
Sydnor	107	98	(91.6)	9	(8.4)
Weakley	17	16	(94.1)	1	(5.9)
Total	**300**	**265**	**(88.3)**	**35**	**(11.7)**

Numbers shown in parentheses are percentages for that category.
*A window of 1-10 days posttherapy was used for determination of evaluability.

12.5.1.1.2. Clinical Response Poststudy (28 to 32 Days After Completion of Therapy)

Clinical response rates at the poststudy evaluation are summarized and cross-tabulated against clinical response rates at the posttherapy visit in the table below for clinically evaluable subjects who had a poststudy evaluation performed. Of the 264 levofloxacin-treated subjects who were cured or improved at the posttherapy evaluation and had poststudy evaluations done approximately four weeks later, 21 (8.0%) had relapsed clinically by the time of the poststudy evaluation, including six (3.4%) of the 175 who had been cured and 15 (16.9%) of the 89 who had improved. More than half of the subjects who had improved at the posttherapy evaluation were found to be cured at the poststudy follow-up visit.

Table 12.5.1.1.2
Clinical Success/Failure Rates at Posttherapy (2-5 days) by Study Center: Sponsor's Clinically Evaluable Patients (Protocol N93-006)

		Levofloxacin Poststudy (N=264)*					
Posttherapy	N	Cured		Improved		Relapse	
Cured	175	167	(95.4)	2	(1.1)	6	(3.4)
Improved	89	49	(55.1)	25	(28.1)	15	(16.9)
Total	264	216	(81.8)	27	(10.2)	21	(8.0)

* Thirty-six subjects either failed at the posttherapy evaluation (35) or did not have poststudy evaluations performed (1) and are not included in this analysis.
Numbers shown in parentheses are percentages for that category.

13.5.1.1.3. Clinical Relapse Rate at Poststudy (28 to 32 Days After Completion of Therapy)

The 21 subjects (8% of clinically evaluable subjects) who had a relapse at the poststudy evaluation are listed in the table below. Thirteen of the subjects were microbiologically evaluable and showed microbiologic eradication of their pathogen at the posttherapy visit; the admission pathogens for these subjects were *S. aureus*, *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *H. parainfluenzae*, and *S. milleri*. *S. aureus* was the most commonly isolated pathogen at admission among subjects with a clinical relapse. Only one of these 13 subjects (709) had a culture performed at the poststudy visit; this culture was positive for the admission pathogen(*S. aureus*) as well as for *A. calcoaceticus* and *E. agglomerans*.

Table 12.5.1.1.3.
Subjects with Clinical Relapse at Poststudy (28 to 32 Days)
Sponsor's Clinically Evaluable Patients (Protocol N93-006)

Subject	Investigator	Admission Pathogen	Clinical Response at Posttherapy	Microbiologic Response at Posttherapy
	Littlejohn	*Staphylococcus aureus*	Improved	Eradicated
	Follett	No Pathogen	Improved	N/A[a]
	Follett	No Pathogen	Improved	N/A
	Follett	*Staphylococcus aureus*	Improved	Eradicated[b]
	May	No Pathogen	Improved	N/A
	McClean	*Moraxella (Branhamella) catarrhalis* *Staphylococcus aureus*	Cure	Eradicated Eradicated
	Anthony	*Haemophilus influenzae*	Improved	Eradicated
	Anthony	No Pathogen	Improved	N/A
	Anthony	No Pathogen	Cure	N/A
	Kopp	*Haemophilus parainfluenzae*	Cure	Eradicated
	Amsbaugh	*Haemophilus parainfluenzae*	Cure	Eradicated
	Dennington	*Streptococcus pneumoniae*	Improved	Eradicated
	Dennington	*Staphylococcus aureus*	Improved	Eradicated
	Dennington	*Staphylococcus aureus* *Streptococcus pneumoniae*	Improved	Eradicated Eradicated
	Klein	*Streptococcus milleri*	Improved	Eradicated
	Sydnor	No Pathogen	Improved	N/A
	Sydnor	*Moraxella (Branhamella) catarrhalis* *Haemophilus influenzae*	Improved	Eradicated Eradicated
	Sydnor	*Moraxella (Branhamella) catarrhalis* *Staphylococcus aureus*	Cure	Eradicated Eradicated
	Sydnor	No Pathogen	Improved	N/A
	Sydnor	No Pathogen	Improved	N/A
	Sydnor	*Haemophilus influenzae*	Cure	Eradicated

[a] N/A = Not applicable; no admission pathogen was identified.
[b] This subject also had a culture obtained at the poststudy visit that was positive for *S. aureus*, *A. calcoaceticus* and *E. agglomerans*.

12.5.1.2. Clinical Response by Pathogen

Among pathogens isolated, *H. influenzae*, *S. pneumoniae*, and *S. aureus* were the most prevalent. Clinical success rates (cured + improved) for these three pathogens collected by antral puncture ranged from 93.1% (*H. influenzae*) to 100% (*S. pneumoniae*). Success rates were generally comparable among the same pathogens collected by endoscope. The clinical response rates by pathogen for the other efficacy analysis groups were consistent with those from the clinically evaluable group.

Table 12.5.1.2.
Clinical Response Rate by Pathogen at Posttherapy (2-5 days) Categorized by Method of Specimen Collection: Sponsor's Clinically Evaluable Patients (Protocol N93-006)

		Levofloxacin		
Collection Method/Pathogen[b]	N[c]	Cured	Improved	Failed
Antral puncture				
Haemophilus influenzae	29	20 (69.0)	7 (24.1)	2 (6.9)
Streptococcus pneumoniae	29	24 (82.8)	5 (17.2)	0 (0.0)
Staphylococcus aureus	22	15 (68.2)	6 (27.3)	1 (4.5)
Moraxella (Branhamella) catarrhalis	14	8 (57.1)	5 (35.7)	1 (7.1)
Streptococcus sanguis	6	3 (50.0)	2 (33.3)	1 (16.7)
Haemophilus parainfluenzae	5	5 (100.0)	0 (0.0)	0 (0.0)
Endoscope				
Haemophilus influenzae	7	5 (71.4)	2 (28.6)	0 (0.0)
Streptococcus pneumoniae	3	2 (66.7)	1 (33.3)	0 (0.0)
Staphylococcus aureus	11	5 (45.5)	4 (36.4)	2 (18.2)
Moraxella (Branhamella) catarrhalis	1	1 (100.0)	0 (0.0)	0 (0.0)
Streptococcus sanguis	0	0 –	0 –	0 –
Haemophilus parainfluenzae	1	1 (100.0)	0 (0.0)	0 (0.0)

Numbers shown in parentheses are percentages for that category.
[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] N≥5 for both methods combined.
[c] Number of subjects who had that pathogen, alone or in combination with other pathogens.

12.5.1.3. Clinical Signs and Symptoms at Post-Therapy

Among clinically evaluable subjects, there was clearing of individual symptoms from admission to posttherapy for 73.6% (purulent nasal discharge) to 97.0% (fever) of the subjects, as presented in the table below.

Table 12.5.1.3
Resolution of Clinical Signs and Symptoms at Posttherapy (2-5 days)
Sponsor's Clinically Evaluable Subjects (Protocol N93-006)

	Levofloxacin	
Signs/Symptoms	Resolved[b]	(%)
Facial Pain	199/249	(79.9%)
Headache	191/241	(79.3%)
Fever	64/ 66	(97.0%)
Purulent Nasal Discharge	206/280	(73.6%)
Malar Tenderness	159/189	(84.1%)
Dental Pain	126/136	(92.6%)

[a] Sign/symptom present at admission and absent at posttherapy evaluation.
[b] Denominator represents number of subjects with that sign or symptom at admission.

12.5.1.4. Radiographic Findings

Of the 294 clinically evaluable levofloxacin-treated subjects with abnormal admission radiographic findings who underwent a posttherapy radiographic examination, 243 (82.7%) showed either resolution (37.4%) or improvement (45.2%). Thirty-five (11.9%) subjects showed no change from admission to posttherapy, and 16 (5.4%) showed worsening. Similar results were seen in the microbiologically evaluable subjects.

Table 12.5.1.4.
Radiographic Findings at Poststudy (2-5 Days)
Sponsor's Clinically and Microbiologically Evaluable Patients
(Protocol N93-006)

Posttherapy Radiographic Findings	Clinically Evaluable (N=294)[a]		Microbiologically Evaluable (N=136)[b]	
	No.	%	No.	%
Resolved	110	(37.4%)	53	(39.0%)
Improved	133	(45.2%)	63	(46.3%)
No Change	35	(11.9%)	14	(10.3%)
Worsened	16	(5.4%)	6	(4.4%)

[a] One clinically evaluable subject [redacted] had normal radiographic findings at admission, and five subjects did not have posttherapy radiographic data.
[b] One microbiologically evaluable subject [redacted] had normal radiographic findings at admission, and one subject [redacted] did not have posttherapy radiographic data.

12.6. Microbiologic Results

Microbiologic response at posttherapy was the primary efficacy variable in this study. The analyses of microbiologic response, based primarily on the group of subjects evaluable for microbiologic efficacy, are presented in detail in this section, with results of other analysis groups provided in the Supporting Data section at the end of the text and briefly described here. The results from other analysis groups were generally consistent with those from the microbiologically evaluable group.

12.6.1. *In Vitro* Susceptibility

One hundred fifty-four subjects had pathogens isolated at admission, including 151 pathogens with known susceptibility and 27 pathogens with unknown susceptibility. There were 148 (98.0%) pathogens with known susceptibility that were susceptible or moderately susceptible to levofloxacin. Pathogens resistant to levofloxacin represented 2.0% of all isolates with known susceptibility.

Table 12.6.1
***In Vitro* Susceptibility of All Pathogens Isolated At Admission: Sponsor's Modified Intent-to-treat Patients with an Admission Pathogen (Protocol N93-006)**

Susceptibility of Pathogen	No. (%)* of Pathogens	
Susceptible	147	(97.4%)
Moderately Susceptible	1	(0.7%)
Resistant	3	(2.0%)
Unknown	27	
Total No. Pathogens	178	

*Percentages were based on numbers of pathogens with known susceptibilities. Pathogens were isolated from 154 subjects.

12.6.2. Microbiologic Eradication Rates

12.6.2.1. Microbiologic Eradication Rates by Subject

Among microbiologically evaluable subjects, the overall eradication rate was 92.0% (comprised of 78.3% presumed eradication and 13.8% documented eradication), with comparable results seen for pathogens collected by antral puncture or by endoscope. Overall, 11 (8.0%) subjects did not have their infection eradicated. Eradication rates were generally similar across age and race subgroups; however, eradication rates were somewhat higher in women (76/79 = 96.2%) than in men (51/59 = 86.4%). Among modified intent-to-treat subjects with an admission pathogen, levofloxacin treatment resulted in 87.0% eradication and 13.0% persistence (including 4.5% unknown).

Table 12.6.2.1
Microbiologic Eradication Rates by Subject
Sponsor's Clinically and Microbiologically Evaluable Subjects
(Protocol N93-006)

	Levofloxacin								
	Antral Puncture			Endoscope			Total		
Investigator	N	Eradicated[a]		N	Eradicated[a]		N	Eradicated[a]	
Amsbaugh	1	1	(100.0)	1	1	(100.0)	2	2	(100.0)
Anthony	11	10	(90.9)	0	0	(–)	11	10	(90.9)
Dennington	7	4	(57.1)	0	0	(–)	7	4	(57.1)
Dyke	0	0	(–)	5	4	(80.0)	5	4	(80.0)
Edelstein	3	3	(100.0)	0	0	(–)	3	3	(100.0)
Follett	1	1	(100.0)	2	2	(100.0)	3	3	(100.0)
Kidder	0	0	(–)	3	3	(100.0)	3	3	(100.0)
Klein	1	1	(100.0)	0	0	(–)	1	1	(100.0)
Kopp	26	22	(84.6)	0	0	(–)	26	22	(84.6)
Littlejohn	5	5	(100.0)	6	5	(83.3)	11	10	(90.9)
McClean	3	2	(66.7)	4	4	(100.0)	7	6	(85.7)
Pulver	0	0	(–)	2	2	(100.0)	2	2	(100.0)
Scott	5	5	(100.0)	0	0	(–)	5	5	(100.0)
Sydnor	40	40	(100.0)	0	0	(–)	40	40	(100.0)
Weakley	12	12	(100.0)	0	0	(–)	12	12	(100.0)
Total	**115**	**106**	**(92.2)**	**23**	**21**	**(91.3)**	**138**	**127**	**(92.0)**

[a] Eradication of all pathogens isolated for a subject at admission.
[b] A window of 1-10 days posttherapy was used for determination of evaluability.
[c] Numbers shown in parentheses are percentages for that category.

12.6.2.2. Microbiologic Eradication Rates by Pathogen

The overall microbiologic eradication rate by pathogen was 91.3%; this eradication rate was similar for pathogens identified by antral puncture (91.2%) and endoscope (92.0%). The most prevalent pathogens were aerobes (similar numbers of gram-positive and gram-negative pathogens were obtained); a small number of gram-negative and gram-positive anaerobic pathogens were also identified. Eradication rates were similar for both types of aerobes; levofloxacin treatment eradicated 92.7% of the gram-positive aerobic pathogens and 90.8% of the gram-negative aerobic pathogens. Too few anaerobic pathogens were isolated to yield meaningful eradication rates. The most common pathogens isolated, *H. influenzae* and *S. pneumoniae*, were eradicated by levofloxacin in 97.2% and 100% of cases, respectively (both collection methods combined). The other most commonly identified pathogens were eradicated from 83.3% (*S. sanguis*) to 100% (*H. parainfluenzae*) of cases. Similar results were obtained for pathogens isolated by antral puncture or by endoscope. No subject with susceptibility data available at posttherapy had microbiologic persistence of a pathogen that acquired resistance. *Of the 13 microbiologically evaluable subjects with a clinical relapse at poststudy, only three subjects had a culture done at the poststudy visit; the remainder of the subjects who were microbiologically evaluable were presumed eradicated based on clinical response. Two of these three subjects showed eradication of their infection at both the posttherapy and poststudy visit; the other subject (709) showed eradication of her infection at the posttherapy visit and a relapse at poststudy (this latter subject was also a clinical*

relapse). The eradication rates across centers were comparable. Eradication rates were also comparable across the various age and race subgroups; however, pathogen eradication rates were somewhat higher in women (96.7%) than men (84.3%), consistent with the infection eradication rates presented in the previous section.

Table 12.6.2.2
Microbiologic Eradication Rates by Pathogen
Sponsor's Clinically and Microbiologically Evaluable Subjects
(Protocol N93-006)

	Antral Puncture		Endoscope		Total	
Pathogen Category/Pathogen	N	Eradicated[a]	N	Eradicated[a]	N	Eradicated[a]
Pathogen Category						
Gram-negative aerobic pathogens	66	59 (89.4)	10	10 (100.0)	76	69 (90.8)
Gram-negative anaerobic pathogens	1	1 (100.0)	0	0 (-)	1	1 (100.0)
Gram-positive aerobic pathogens	67	63 (94.0)	15	13 (86.7)	82	76 (92.7)
Gram-positive anaerobic pathogens	2	1 (50.0)	0	0 (-)	2	1 (50.0)
Total by pathogen	136	124 (91.2)	25	23 (92.0)	161	147 (91.3)
Total by subject	115	106 (92.2)	23	21 (91.3)	138	127 (92.0)
Pathogen[c]						
Haemophilus influenzae	29	28 (96.6)	7	7 (100.0)	36	35 (97.2)
Streptococcus pneumoniae	29	29 (100.0)	3	3 (100.0)	32	32 (100.0)
Staphylococcus aureus	22	21 (95.5)	11	10 (90.9)	33	31 (93.9)
Moraxella (Branhamella) catarrhalis	14	13 (92.9)	1	1 (100.0)	15	14 (93.3)
Streptococcus sanguis	6	5 (83.3)	0	0 (-)	6	5 (83.3)
Haemophilus parahaemolyticus	5	5 (100.0)	1	1 (100.0)	6	6 (100.0)

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Numbers shown in parentheses are percentages for that category.
[c] The most prevalent pathogens (N≥5) are presented in this summary.

12.6.3. Superinfection

No subjects in this study developed superinfections.

12.7. Summary of Sponsor's Key Efficacy Results

Clinical success rates for the clinically evaluable and intent-to-treat groups, and microbiologic eradication rates for microbiologically evaluable subjects and modified intent-to-treat subjects with an admission pathogen are summarized in Table 20. Comparable results were seen across analysis groups for both clinical and microbiologic endpoints, and show response rates of approximately 90%. Moreover, there is concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency and reliability of these response measures.

Table 12.7.
Summary of Sponsor's Key Efficacy Results
Sponsor's and Intent-to-treat, Clinically evaluable,
and Microbiologically Evaluable Groups (Protocol N93-006)

Table 20: Summary of Key Efficacy Results
(Study N93-006)

Clinical and Microbiologic Response 2 to 5 Days Posttherapy[a]

Response/Group	Clinical Success or Microbiologic Eradication Rate[b]	
Clinical Response		
Clinically Evaluable	265/300	(88.3)
Intent-to-Treat	285/329	(86.6)
Microbiologic Response		
Antral Puncture		
Microbiologically Evaluable	106/115	(92.2)
Modified Intent-to-Treat Subjects With an Admission Pathogen	112/126	(88.9)
Endoscope		
Microbiologically Evaluable	21/ 23	(91.3)
Modified Intent-to-Treat Subjects With an Admission Pathogen	22/ 28	(78.6)
Total		
Microbiologically Evaluable	127/138	(92.0)
Modified Intent-to-Treat Subjects With an Admission Pathogen	134/154	(87.0)

Microbiologic Response Versus Clinical Response 2 to 5 Days Posttherapy[a,c]

Microbiologic Response	N	Clinical Response: Cured	Improved	Failed
Antral Puncture				
Eradicated	106	74 (69.8)	31 (29.2)	1 (0.9)
Persisted	9	0 (0.0)	0 (0.0)	9 (100.0)
Endoscope				
Eradicated	21	13 (61.9)	7 (33.3)	1 (4.8)
Persisted	2	0 (0.0)	0 (0.0)	2 (100.0)
Total				
Eradicated	127	87 (68.5)	38 (29.9)	2 (1.6)
Persisted	11	0 (0.0)	0 (0.0)	11 (100.0)

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Denominator for clinical success rate = cured + improved + failed (+ unable to evaluate for intent-to-treat group). Denominator for microbiologic eradication rate = eradication + persistence (+ unknown for modified intent-to-treat subjects with an admission pathogen).
[c] Based on microbiologically evaluable group.

13. Efficacy as per Medical Officer:
13.1. Patient Population:

Of the sponsor's intent-to-treat cohort, the medical officer considered 84% (277/329) clinically evaluable. Of the 329 clinically evaluable patients, the medical officer determined that 38% (105/329) of these were microbiologically evaluable. Of the clinically evaluable patients, 62% (172/277) were microbiologically unevaluable. The reasons for both clinical and microbiologic nonevaluability are summarized in a series of tables under section 13.1.2. The breakdown of the intent-to-treat cohort into evaluable subgroups is summarized in Table 13.1, below.

Table 13.1
FDA Clinically and Microbiologically Evaluable Patients:
Subgroups of Sponsor's Intent-to-treat Cohort (Protocol N93-006)

Intent-to-treat Cohort (Total N) 329			
FDA Clinically Evaluable 277 277/329 (84%)		**FDA Clinically Nonevaluable** 52 52/329 (16%)	
FDA Microbiologically Evaluable N (%)	**FDA Microbiologically Nonevaluable N(%)**	**FDA Microbiologically Evaluable N(%)**	**FDA Microbiologically Nonevaluable N(%)**
105 105/277 (38%) 105/329 (32%)	172 172/277 (62%) 172/329 (52%)	0	52 52/329 (16%)

13.1.1. Demographics of FDA Clinically and Microbiologically Evaluable Cohorts

Of the 277 patients in the FDA clinically evaluable patient cohort, 168 (61%) were female and 109 (39%) were male. This is similar to the distribution found in the intent-to-treat cohort, as summarized in Table 12.1.2. In the cohort of 105 patients who were both clinically and microbiologically evaluable, there were 63 (60%) males and 42 (40%) females. The distribution among racial groups was similar for both cohorts, and this was similar to the distribution in the intent-to-treat cohort. Likewise, the age distribution in the clinically and clinically/microbiologically evaluable cohorts was similar to that in the intent-to-treat cohort.

Table 13.1.1
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts (Protocol N93-006)

		FDA Clinically Evaluable Patients N (%)	FDA Clinically and Microbiologically Evaluable Patients N (%)
TOTAL		277	105
Sex	M	109/277 (39%)	63/105 (60%)
	F	168/277 (61%)	42/105 (40%)
Race	Caucasian	257/277 (93%)	98/105 (93%)
	Black	12/277 (4.3%)	5/105 (3.5%)
	Hispanic	5/277 (2%)	5/105 (3.5%)
	Asian	1/277 (<1%)	--
	Other	2/277 (<1%)	--
Age (yrs)	≤45	186/277 (67%)	79/105 (75%)
	46-64	77/277 (28%)	23/105 (22%)
	≥65	14/277 (5%)	3/105 (3%)

13.1.2. Reasons for Nonevaluability

13.1.2.1. Reasons for Clinical Nonevaluability

Of the sponsor's intent-to-treat cohort, the medical officer considered 84% (277/329) clinically evaluable. The reasons for nonevaluability in the remaining 16% are summarized in the tables below.

Table 13.1.2.1.A
Reasons for Clinical Nonevaluability:
ALL FDA Nonevaluable Patients (Protocol N93-006)

Reason for Nonevaluability	N	Subgroups of Reasons for Nonevaluability
Inappropriate clinical evaluation date	11	(No EOS evaluation)
Insufficient Course of therapy	6	
Clinical Diagnosis Unconfirmed	0	
Unevaluable for safety	1	No admission laboratory studies
Protocol violation	8	History of Chronic Sinusitis (5) History of Recurrent Sinusitis (2) History of Seizure Disorder (1)
Exceeded 14 days of therapy	17	Exceeded 14 days of therapy: unevaluable as clinical cure
Effective Concomitant Antibiotic	5	Prestudy antibiotic with no pathogen on admission culture(3) Therapy with PCN for alternative diagnosis (2)
Insufficient clinical evaluation	1	Residual dizziness persisting at both EOT and EOS evaluations was not appropriately evaluated
Medication noncompliance	3	Missed more than 2 doses (2) Took medication BID (1)
Contradictory data	1	Clinical cure with *S. pneumo* superinfection on repeat culture
TOTAL Reasons **TOTAL Patients**	53 52	

Patient [redacted] had two reasons for nonevaluability-extended therapy and prestudy antibiotic

Table 13.1.2.1.B.
Reasons for Clinical Nonevaluability:
Patients Evaluable by Sponsor but Nonevaluable by FDA (Protocol N93-006)

Reason for Nonevaluability	N	Subgroups of Reasons for Nonevaluability
Unevaluable for safety	1	No admission laboratory studies
Protocol violation	7	History of Chronic Sinusitis (5) History of Recurrent Sinusitis (1) History of Seizure Disorder (1)
Exceeded 14 days of therapy	16	Exceeded 14 days of therapy: unevaluable as clinical cure
Concomitant Antibiotic	4	Prestudy antibiotic with no pathogen on admission culture(3) Therapy with PCN for alternative diagnosis (1)
Inappropriate clinical evaluation	1	Residual dizziness persisting at both EOT and EOS evaluations was not appropriately evaluated
Medication noncompliance	2	Missed more than 2 doses (2)
No End-of-study visit	1	
Contradictory data	1	Clinical cure with *S. pneumo* superinfection on repeat culture
TOTAL Reasons **TOTAL Patients**	33 32	

Patient [redacted] had two reasons for nonevaluability-extended therapy and prestudy antibiotic

13.1.2.2. Reasons for Microbiologic Nonevaluability

Of the 329 clinically evaluable patients, the medical officer determined that 38% (105/329) of these were microbiologically evaluable. Of the clinically evaluable patients, 62% (172/277) were microbiologically unevaluable. Because of the controversy surrounding the inclusion of Staphylococcus aureus as a pathogen, the medical officer divided the evaluable patient cohort into three subgroups of microbiologic evaluability:

FDA Microbiologically Evaluable Patients: All Microorganisms
FDA Microbiologically Evaluable Patients: Major Four Pathogens
FDA Microbiologically Evaluable Patients: Major Three Pathogens

The reasons for microbiologic nonevaluability for each of these subgroups are as summarized in the table below.

13.2. Clinical Efficacy:

Using the medical officer's clinical evaluability criteria delineated in Section 10.2.1 of this review, a total of 277 clinically evaluable patients were selected from the intent-to-treat cohort. The overall cure rate at the post-study evaluation was 71% for this cohort. Cure rates by investigator are summarized in the table below.

Table 13.2
Poststudy Clinical Cure Rates By Investigator:
FDA Clinically Evaluable Subjects (Protocol N93-006)

	Levofloxacin	
Investigator	N	Cure[a]
Amsbaugh	2	0 (0)
Anthony	26	18 (69)
Bianchi	1	1 (100)
Carrabre	1	1 (100)
Chow	1	1 (100)
Collins	2	2 (100)
Dennington	12	3 (25)
Dyke	8	3 (38)
Edelstein	3	3 (100)
Follett	8	4 (50)
Kidder	5	3 (60)
Klein	3	2 (67)
Kopp	40	24 (60)
Lee	1	1 (100)
Liotti	1	0 (0)
Littlejohn	16	12 (75)
May	1	0 (0)
McClean	13	10 (77)
Moyer	1	1 (100)
Portugal	2	1 (50)
Pulver	3	2 (66)
Scott	10	9 (90)
Sydnor	100	81 (81)
Weakley	17	16 (94)
Total	277	198 (71)

[a]Poststudy clinical outcome is defined by the reviewing medical officer as either cure or failure (i.e., no improvement category is used). Numbers shown in parentheses are percentages for that category.

Table 13.1.2.2
Reasons for Microbiologic Nonevaluability:
Three FDA Evaluable Patient Cohorts
All Admission Pathogens, Major Four Pathogens, Major Three Pathogens
(Protocol N93-006)

	Clinically Evaluable/ Microbiologically Unevaluable	Clinically and Microbiologically Unevaluable
No Admission Pathogen	149	
Admission Pathogen not an "Accepted Pathogen"**		
Evaluable Pathogens: *S. pneumo, S. aureus, H. flu, M. cat.*	23**	
Evaluable Pathogens: *S. pneumo, H. flu, M. cat.*	52***	
Drug Therapy		17
Insufficient duration of therapy		5
Extended therapy, unevaluable as clinical cure		11
Concurrent Antimicrobial Therapy		1
Protocol Violation		7
History of Chronic Sinusitis		3
History of Recurrent Sinusitis		2
History of Seizure Disorder		1
Other		1
Inappropriate Clinical Evaluation		3
Total: Microbiologically Nonevaluable Patients		
FDA Evaluable Patients: All Microorganisms	149	25
FDA Evaluable Patients: Major Four Pathogens	172	25
FDA Evaluable Patients: Major Three Pathogens	213	25
Total: Microbiologically Nonevaluable Patients		
FDA Evaluable Patients: All Microorganisms	174/277 (63%)	
FDA Evaluable Patients: Major Four Pathogens	197/277 (71%)	
FDA Evaluable Patients: Major Three Pathogens	238/277 (86%)	

** Admission microorganism was not one of the four organisms accepted as pathogens in acute bacterial sinusitis for purposes of this review. This review contains three analyses of efficacy data with (1) all pathogens, (2) only the subgroup of patients with the accepted four pathogens *(S. pneumo, S. aureus, H. flu, M. cat)* and (3) only the subgroup of patients with the accepted three pathogens (*S. pneumo, H. flu, M. cat*).

*** Total number of patients with *S. aureus* isolated on admission was 41, of these, 22 were microbiologically evaluable, 7 were microbiologically unevaluable, and 12 were isolated as part of polymicrobial infections and, therefore considered contaminants for the purposes of this analysis.

13.2. Microbiologic Efficacy

Study N93-006 also entailed a microbiologic evaluation. According to the DAIDP "Points-to-Consider", this study should establish acceptable microbial and clinical outcome in at least 25 patients with *H. influenzae*, in at least 25 patients with *S. pneumoniae*, and in at least 15 patients with *M. catarrhalis*. The "Points-to-Consider" Document does not address the issue of *S. aureus* as a pathogen, nor does it give required numbers for the number of evaluable patients.

Using the medical officer's clinical and microbiologic evaluability criteria delineated in Sections 10.2.1 and 10.2.2 of this review, a total of 105 patients were both clinically and microbiologically evaluable. The sponsor was able meet the "points-to-consider" recommendations for the number of pathogens for *Streptococcus pneumoniae* and *Haemophilus influenzae*, but not for *Moraxella catarrhalis*.

The cure rates by pathogen for the three major pathogens of sinusitis and *S. aureus* are listed below. The clinical cure rates are acceptable for both *H. influenzae* and *S. pneumonaie*, but are suboptimal for both *Moraxella* and *S. aureus*.

Table 13.2.A
Poststudy Clinical Cure Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Protocol N93-006)

	Levofloxacin	
Pathogen	N[a]	Cure[b]
Haemophilus influenzae	34	25 (74)
Moraxella catarrhalis	13	8 (62)
Staphylococcus aureus	22	11 (50)
Streptococcus pneumoniae	29	26 (90)

[a]N=number of subjects who had that pathogen alone or in combination with other pathogens. (Note: *Staphylococcus aureus* was considered a pathogen when isolated alone; in polymicrobial infections, *S. aureus* was considered a contaminant. Eleven patients considered clinically evaluable by FDA had *S. aureus* as part of a polymicrobial infection. *S. aureus* data for these patients is not included in this table.)

[b]Poststudy clinical outcome is defined by the reviewing medical officer as either cure or failure (i.e., no improvement category is used). Numbers shown in parentheses are percentages for that category.

As noted previously, there were no quantitative cultures included as part of this protocol. Therefore, it is unknown whether or not the cure rates and eradication rates for *S. aureus* represent isolates with a CFU count that were actually below the breakpoint for *S. aureus* as a pathogen.

The microbiologic eradication rates by pathogen for the three major pathogens of sinusitis and *S. aureus* are listed below. The clinical cure rates are acceptable for both *H. influenzae* and *S. pneumonaie*, but are suboptimal for both *Moraxella* and *S. aureus*.

Table 13.2.B
Overall Microbiologic Eradication Rates
by Pathogen Category and Pathogen:
FDA Microbiologically Evaluable Subjects (Protocol N93-006) [a]

Pathogen Category/Pathogen	Levofloxacin	
	N[b]	Eradicated[c] N (%)
Pathogen Category		
Gram-positive aerobic pathogens	63	50 (79)
Gram-negative aerobic pathogens	70	51 (73)
Gram-positive anaerobic pathogens	2	1 (50)
Gram-negative anaerobic pathogens	1	1 (100)
Total by pathogen	136	103 (76)
Total by subject	131	96 (73)
Pathogen		
Haemophilus influenzae	34	25 (73)
Moraxella catarrhalis	13	8 (62)
Staphylococcus aureus	22	11 (50)
Streptococcus pneumoniae	29	27 (93)

[a]The sponsor presents microbiologic results separately by collection method (i.e., antral puncture and endoscope). Since results are very similar, FDA presents results for both collection methods combined.

[b]N=number of subjects who had that pathogen alone or in combination with other pathogens. (Note: *Staphylococcus aureus* was considered a pathogen when isolated alone; in polymicrobial infections, *S. aureus* was considered a contaminant. Eleven patients considered clinically evaluable by FDA had *S. aureus* as part of a polymicrobial infection. *S. aureus* data for these patients is not included in this table.)

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

As noted previously, there were no quantitative cultures included as part of this protocol. Therefore, it is unknown whether or not the cure rates and eradication rates for *S. aureus* represent isolates with a CFU count that were actually below the breakpoint for *S. aureus* as a pathogen. Of the 329 patients in the intent-to-treat cohort, 84% (276/329) were evaluated by needle aspirate and 23% (64/276) were evaluated by endoscopy. Of the 277 FDA clinically evaluable patients, 84% (233/277) were evaluated by needle aspirate and 15% (41/277) were evaluated by

endoscopy. In the intent-to-treat cohort, the rate of isolation for S. aureus was 9.8% (27/276) by aspirate and 22% (14/64) by endoscopy. Similarly, in the FDA evaluable patient cohort, the rate of isolation for S. aureus was 9.4% (22/233) for aspirate and 29% (12/41) for endoscopy. Thus, in the intent-to-treat cohort, up to 12% of the *S. aureus* isolates obtained by endoscopy may represent contaminants rather than true pathogens, and up to 20% of the *S. aureus* isolate obtained by endoscopy in the FDA evaluable cohort could represent contaminants rather than true pathogen. These calculations should be qualified by the fact that there are small numbers of patients in the endoscopy group, thus these estimates may not be representative of a larger sample of endoscopically obtained isolates.

When a similar analysis was conducted for the FDA microbiologically evaluable patient cohort, the analysis was done both on a per patient and per isolate basis. The rate of isolation of *S. aureus* by needle aspiration was 27% (22/81 patients), on a per patient basis, and 20% (23/116 procedures), on a per procedure basis; and the rate of isolation of *S. aureus* by endoscopy was 50% (12/24 patients), on a per patient basis, and 34% (12/35 procedures) on a per procedure basis. Thus the rate of contamination in the endoscopically obtained samples could range up to 23% on a per patient basis and 14% on a per procedure basis.

13.4. Overall Success Rates: Analysis by Subgroups of FDA Microbiologically Evaluable Patients

The overall success rates for the three subgroups of microbiologically evaluable patients are summarized in Table 13.4, below. The overall success rate for patients with all pathogens isolated at admission was 70%, for those with the major three pathogens and *S. aureus* was 68% and for those with only the major three pathogens was 75%. This emphasizes the deleterious effect of the low cure/eradication rate for *S. aureus* on the overall success rate for treatment of the major pathogens of acute bacterial sinusitis.

Table 13.4
Overall Success Rates[a] by Study Center:
FDA Microbiologically AND Clinically Evaluable Subjects
(Protocol N93-006)

Investigator	**All Microorganisms** isolated on Admission Culture		**Admission Pathogens** *S. pneumoniae* *M. catarrhalis* *H. influenzae* *S. aureus*		**Admission Pathogens** *S. pneumoniae* *M. catarrhalis* *H. influenzae*	
	N	Overall Success[b]	N	Overall Success[b]	N	Overall Success[b]
Amsbaugh	2	0 (0)	1	0 (0)	0	0 (0)
Anthony	8	4 (50)	6	3 (50)	4	2 (50)
Dennington	8	1 (13)	8	0 (0)	3	0 (0)
Dyke	6	2 (33)	5	1 (20)	2	1 (50)
Edelstein	3	3 (100)	2	2 (100)	1	1 (100)
Follett	3	2 (67)	2	1 (50)	0	0 (0)
Kidder	3	2 (67)	3	2 (67)	3	2 (67)
Klein	1	0 (0)	0	0 (0)	0	0 (0)
Kopp	17	9 (53)	12	6 (50)	10	4 (40)
Lee	1	1 (100)	1	1 (100)	1	1 (100)
Littlejohn	11	9 (82)	11	9 (82)	8	8 (100)
McClean	7	5 (71)	7	5 (71)	4	3 (75)
Pulver	2	1 (50)	2	1 (50)	2	1 (50)
Scott	5	5 (100)	2	2 (100)	2	2 (100)
Sydnor	38	33 (87)	31	26 (87)	25	22 (88)
Weakley	12	12 (100)	9	9 (100)	6	6 (100)
Total	127	89 (70)	102	69 (68)	71	53 (75)

[a]Overall success is defined as clinical cure (as assessed by the reviewing medical officer) and microbiologic eradication (also as assessed by the reviewing medical officer).

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

13.5. Overall Success Rates: Analysis by Pathogen

The overall success rates for FDA clincially and microbiologically evaluable patients are summarized by pathogen for the four pathogens requested by the sponsor in the proposed package labelling in Table 13.5, below. As discussed above under Section 13.4, the overall success rate for patients with the major three pathogens (*Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae)* and *S. aureus* was 68%; and the overall success rate for those with only the major three pathogens (*Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae)* was 75%. The overall success rate for patients with *H. influenzae* was 73%, for those with *M. catarrhalis* was 62%, for those with *S. aureus* was 50%, and for those with *S. pneumoniae* was 93%. Thus, the overall success rate for patients with one of the four pathogens requested by the sponsor varied greatly by individual pathogen, and the very low clinical success rates among cases of sinusitis due to *M. catarrhalis* and *S. aureus* contributed to the low overall success rate for levofloxacin in the treatment of acute bacterial sinusitis caused by one of these four pathogens. Likewise, the overall success rate for patients with one of the three major pathogens varied greatly by individual pathogen, and the very low clinical success rate among cases of sinusitis due to *M. catarrhalis* contributed to the low overall success rate for levofloxacin in the treatment of acute bacterial sinusitis caused by one of the three major pathogens.

Table 13.5
Overall Success Rates* by Admission Pathogen:
FDA Microbiologically AND Clinically Evaluable Subjects
(Protocol N93-006)

Admission Pathogens	N	Overall Success*
Haemophilus influenzae	34	25 (73)
Moraxella catarrhalis	13	8 (62)
Staphylococcus aureus	22	11 (50)
Streptococcus pneumoniae	29	27 (93)
All Four Pathogens	102	69 (68)
All Pathogens except *S. aureus*	71	53 (75)

*Overall Success is defined as clinically cured AND microbiologically eradicated

14. Safety Results as per Sponsor

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any postadmission data were available. All of the 329 subjects enrolled in this study were evaluated for safety.

14.2. Overview of Safety Data

The most frequently reported adverse events (regardless of relationship to study drug) occurred in the gastrointestinal (GI) system (17.0% incidence)and consisted primarily of diarrhea, nausea, flatulence, and abdominal pain. The most common adverse event, diarrhea, was reported by 7.3% of levofloxacin-treated subjects. Adverse events in the other body systems occurred in fewer than 5% of subjects, with insomnia (4.6% incidence) the second most common adverse event in this study. Eight (2.4%) subjects had adverse events considered marked in severity. Twenty-nine (8.8%) subjects had adverse events considered by the investigator to be probably or definitely drug-related.

Six (1.8%) of 329 subjects evaluable for safety discontinued due to adverse events. Three subjects discontinued because of skin-related adverse events (rash, pruritus, and/or edema) and three discontinued because of GI-related adverse events (diarrhea, nausea, or abdominal pain); one subject who discontinued because of a GI event also discontinued due to dizziness and lightheadedness. One serious adverse event (myocardial infarction) was reported; this event was moderate in severity and considered by the investigator to be unrelated to study drug administration. No deaths occurred during the study. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs occurred infrequently.

14.3. Treatment-Emergent Adverse Events

One hundred twenty-nine (39.2%) of 329 subjects evaluated for safety reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. These are summarized by body system in Table 14.3.A, on the following page. The body system with the highest reported incidence of adverse events was the gastrointestinal (GI) system in which 56 (17.0%) of the subjects reported an adverse event. Adverse events in the other body systems occurred in fewer than 10% of subjects.

Adverse events (primary terms) reported for at least 2.0% of subjects are presented in the Table 14.3.B, on the following page. The most frequently reported adverse events were diarrhea (7.3%), insomnia (4.6%), nausea (4.3%), and flatulence (2.7%). Psychiatric/ CNS adverse events, consisting primarily of insomnia, occurred at a rate of 4.7%.

Table 14.3.A
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol N93-006)

	N=329	
Body System	N	%
Gastrointestinal System Disorders	56	(17.0)
Psychiatric Disorders	21	(6.4)
Body as a Whole – General Disorders	19	(5.8)
Central & Peripheral Nervous System Disorders	17	(5.2)
Respiratory System Disorders	16	(4.9)
Skin and Appendages Disorders	15	(4.6)
Musculo-Skeletal System Disorders	11	(3.3)
Resistance Mechanism Disorders	8	(2.4)
Hearing and Vestibular Disorders	6	(1.8)
Vision Disorders	4	(1.2)
Reproductive Disorders, Female*	3	(1.6)
Special Senses Other, Disorders	2	(0.6)
Cardiovascular Disorders, General	1	(0.3)
Myo-, Endo-, Pericardial & Valve Disorders	1	(0.3)
Vascular (Extracardiac) Disorders	1	(0.3)
Total With Adverse Events (%)	**129**	**(39.2)**

*Percentage for this body system is based on the total number of women evaluable for safety (N=192).

Table 14.3.B
Incidence of Frequently Reported Adverse Events (≥2%) Summarized by Primary Term: Subjects Evaluable for Safety (Protocol N93-006)

	Levofloxacin (N=329)	
Body System/Primary Term	No. Subjects	% Subjects
All Body Systems	**129**	**39.2**
Gastrointestinal System Disorders		
Diarrhea	24	7.3
Nausea	14	4.3
Flatulence	9	2.7
Abdominal Pain	7	2.1
Psychiatric Disorders		
Insomnia	15	4.6
Central & Peripheral Nervous System Disorders		
Headache	8	2.4
Dizziness	7	2.1
Body As A Whole – General Disorders		
Pain	7	2.1

*Primary term reported by ≥2.0% of subjects.

The majority of adverse events were assessed as mild or moderate in severity. Eight (2.4%) subjects reported one or more adverse events of marked severity; no marked adverse event of a specific type was reported by more than one subject. Pruritus and erythematous rash in one subject were considered by the investigator to be definitely related to study drug administration and genital moniliasis in another subject was considered probably related; none of the other markedly severe adverse events was considered drug-related. One of the eight subjects with marked adverse events discontinued study drug treatment due to adverse events. In general, the profile of adverse events in these different subgroups was comparable to that observed in the study population as a whole. The percentage of subjects 65 years of age or older who reported at least one adverse event was higher than in the overall study population (52.6% vs. 39.2%, respectively), but the significance of the finding is unclear given the small number (N=19) of subjects in this age subgroup.

Table 14.3.C
Subjects with Adverse Events of Marked Severity:
Subjects Evaluable for Safety (Protocol N93-006)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship To Study Drug*
Levofloxacin				
	43	F	Dizziness	Remote
	44	F	Earache	None
	30	M	Pruritus Erythematous Rash	Definite Definite
	64	M	Headache Fatigue	Remote Remote
	41	M	Insomnia	Remote
	46	F	Pain[b]	None
	55	F	Arthralgia	Possible
	30	F	Genital Moniliasis	Probable

*Based on investigator's assessment.
[b]Facial Pain.
[a] Subject discontinued due to these adverse events. (see Table 24)

No deaths occurred during the study. Six (1.8%) of the subjects enrolled in the study discontinued due to adverse events. Three discontinued because of skin-related adverse events (rash, pruritus, and/or edema) and three discontinued because of GI-related adverse events (nausea, abdominal pain, or diarrhea). One subject (504) who discontinued because of a GI adverse event (nausea) also discontinued due to dizziness and lightheadedness.

One subject [redacted] experienced a serious adverse event (myocardial infarction) on Day 28, 14 days after completing therapy. This adverse event was considered by the investigator to be unrelated to study drug administration.

15. Medical Officer's Conclusions from Study N93-005:

15.1. Clinical Efficacy

15.1.1. **The clinical cure rate for levofloxacin in FDA evaluable patients with a diagnosis of acute bacterial sinusitis was 79% in protocol M92-040 and 71 % in protocol N93-006.** Protocol M92-040 was an active-controlled study comparing levofloxacin to amoxicillin/clavulanate, and in this study the confidence intervals around the difference in cure rates between the two arms overlapped zero (95% CI -13.0 to 2.2). Thus, levofloxacin can be considered statistically equivalent to amoxicillin/clavulanate in the treatment of acute bacterial sinusitis.

15.1.2 **Protocol N93-006 has significant flaws in the protocol design including:**

15.1.2.1. The protocol was a completely unblinded study. This is particularly significant in light of the fact that the clinical endpoints are subjective and, thus, subject to bias from both (1) the **observer/expectation bias** of the investigator and (2) the **reporting/recall bias** of the patient reporting the symptoms[25].

15.1.2.2. The windows for clinical evaluation at both the End-of-therapy and End-of-study evaluations were inappropriate to allow for a definitive test-of-cure evaluation from which could be derived a stable point estimate for the clinical cure rate. Specifically, the test-of-cure evaluation should have been conducted at a point at which the assessment could be dichotomized into a cure/failed category, eliminating the "clinically improved" category. In this protocol, the EOT evaluation was conducted too early to assess a stable cure rate and the EOS evaluation was scheduled too far out from the end of therapy to differentiate (1) clinical failures (early relapses) resulting from partial response to study drug or superinfection from (2) recurrent sinusitis (late relapses)from reinfection with the same organism or infection with another organism

15.1.2.3. **The clinical assessment categories were inappropriate.** Specifically, the clinical assessment should have been a dichotomous cured/failed category. Acute bacterial sinusitis is a disease that should be fully resolved by three weeks from diagnosis, and, thus, if the appropriate time point were used for the test-of-cure evaluation, should be evaluated as cured/failed. Any residual symptoms, though less severe than at clinical presentation and, therefore, given the clinical categorization of "improved", are by strict definition a clinical failure.

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[25] Sackett DL. Bias in Clinical Research. J Chronic Dis 32:51-63, 1979.

15.1.3. Protocol N93-006 has significant flaws in the protocol implementation including:

15.1.3.1. In adequate documentation of the dates of previous episodes of acute sinusitis, history of chronic sinusitis, and history of recurrent sinusitis. Multiple examples were present of patients with (1) a history of chronic sinusitis or (2) the present infection being an acute exacerbation of chronic sinusitis being included in the sponsor's evaluable patient cohort.

15.1.3.2. Omission of culture of persistent sinus secretions at the follow-up visits (both EOT and EOS), with overuse of the designation of "presumed eradication" in cases where documentation of microbiologic outcome was possible.

15.1.3.3. Inadequate of numbers of microbiologically evaluable pathogens for some pathogens. Study N93-006 also entailed a microbiologic evaluation. According to the DAIDP "Points-to-Consider", this study should establish acceptable microbial and clinical outcome in at least 25 patients with *H. influenzae*, in at least 25 patients with *S. pneumoniae*, and in at least 15 patients with *M. catarrhalis*. The "Points-to-Consider" Document does not address the issue of *S. aureus* as a pathogen, nor does it give required numbers for the number of evaluable patients.

15.1.3.4. **There was inadequate characterization of the microbiology of the subjects who were considered clinical failures.** According to the sponsor's analysis, only 37% (13/35) of patients who were clinical failures at the End-of-therapy evaluation and 23% (3/13) who were relapses at post-study were evaluated by culture. According to the medical officers analysis, only 48% (38/79) of those who were clinical failures at End-of-study evaluation had specimens taken for culture. According to the Sponsor's analysis, of the 13 microbiologically evaluable subjects with a clinical relapse at poststudy, only three subjects had a culture done at the poststudy visit; the remainder of the subjects who were microbiologically evaluable were presumed eradicated based on clinical response. Two of these three subjects showed eradication of their infection at both the posttherapy and poststudy visit; the other subject [redacted] showed eradication of her infection at the posttherapy visit and a relapse at poststudy (this latter subject was also a clinical relapse).

An accurate assessment of the microbiology in the cohort of clinical failures is particularly important because this study was designed to evaluate the efficacy of a quinolone for infections due to *Streptococcus pneumoniae* and *Staphylococcus aureus*, two microorganisms for which there has been increasing resistance to the quinolone class of antibiotics. As discussed below, *S. aureus* has been shown to develop resistance to quinolone antibiotics DURING THE COURSE OF THERAPY. Thus, it is important to characterize the population of microorganisms comprising the clinical failures and to assess if there was development of resistance in the course of

antibiotic treatment.

15.2. The use of a quinolone antibiotics for infections involving *Streptococcus pneumoniae* and *Staphylococcus aureus* may be problematic, since resistance of these organisms to other quinolone antimicrobial agents has been shown to occur relatively rapidly. The use of levofloxacin for the treatment of sinusitis in the community will in general be empiric, thus, its coverage for organisms in which there could be pre-existing or rapid development of resistance may be suboptimal and may not be known with great accuracy.

15.2.1. Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*.

Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*, with methicillin-resistant *S. aureus* (MRSA) developing resistance at a more rapid rate than methicillin-sensitive *S. aureus* (MSSA). Ciprofloxacin-resistance in *S. aureus* is well documented, with reports resistance developing during therapy with these agents[26]. One study surveyed the development of ciprofloxacin-resistance in methicillin-resistant *S. aureus* (MRSA) in patients treated with the antibiotic for nonstaphylococcal infections in a VA Medical Center. These authors reported that 79% of MRSA isolates were resistant to ciprofloxacin one year after introduction of the drug, and 91% of MRSA isolates were resistant to ciprofloxacin two years after introduction of the drug[27]. Piercy et.al. reported development of resistance in 16% (6/37) of patients who were being treated with ciprofloxacin for MRSA colonization and Mulligan et.al. reported 32% (7/22) of treatment episodes were associated with the development of ciprofloxacin-resistant MRSA during the course of antibiotic therapy[28]. Resistance among methicillin-susceptible *S. aureus* (MSSA) has been less widespread than with MRSA, but has still been reported[29].

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[26] Daum TE, Schaberg DR. Increasing resistance of *S. aureus* to ciprofloxacin. Antimicrob Agents Chemother 34:1862-3, 1990; Blumberg HM, Rimland D, et.al. Rapid development of ciprofloxacin resistance in Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. J Infect Dis 163:1279-85, 1991; Mulligan ME, Ruane PJ, et.al. Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization. Am J Med 82 (Suppl.4A):215-9, 1987; Piercy EA, Barbaro D, et.al. Ciprofloxacin for methicillin-resistant Staphylococcus aureus infections. Antimicrob Agents Chemother 33:128-30, 1989; Scaefler S. Methicillin-resistant strains of Staphylococcus aureus resistant to the quinolones. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Widespread quinolone resistance among methicillin resistant S. aureus. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Ciprofloxacin resistance in epidemic methicillin-resistant *S. aureus*. Lancet 2:843, 1988.

[27] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[28] Piercy EA. Antimicrob Agents Chemother 33:128-30, 1989; Mulligan ME, Ruane PJ, et.al. Am J Med 82 (Suppl.4A):215-9, 1987.

[29] Scaefler S. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Lancet 2:843, 1988; Daum TE, Schaberg DR. Antimicrob Agents Chemother 34:1862-3, 1990.

While the mechanism of resistance of *S. aureus* to quinolones is not completely understood, there are authors who suggest that the rapid emergence of ciprofloxacin resistance in *S. aureus* may be due to the fact that a single-step point mutation alone can lead to high-level resistance[30]. For *S. aureus*, the frequency of alterations in DNA gyrase caused by single-step mutations increases from 1 in 10^2 to 1 in 10^5 when bacteria are exposed to concentrations close to the minimal inhibitory concentration. The frequency of single-step mutation to fluoroquinolone resistance in *S. aureus* ranges from 1.5 x 10-5 at twice the MIC to ≤3.6 x 10 -12 at eight times the MIC; and high level resistance occurs with serial exposure of bacteria to increasing concentrations of fluoroquinolones[31].

15.2.2. **Quinolone-resistance has been documented to occur in *Streptococcus pneumoniae*.** The mechanism for pneumococcal resistance to the quinolones is also a one-step point mutation (single amino acid substitution) in the DNA gyrase leading to high level resistance[32]. Quinolone resistance to ciprofloxacin is more prevalent than resistance to ofloxacin, with one paper in 1992 reporting 95% of pneumococcal isolates susceptible to ofloxacin and only 68% of isolates susceptible to ciprofloxacin[33]. However, it should be noted that development of resistance to antimicrobial agents is a time-dependent phenomenon, and that ciprofloxacin has been in use longer than ofloxacin. Data presented by the Center for Disease Control[34] at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy showed that there could be significant development of resistance to ofloxacin in the period of one year, such that the point prevalence for pneumococcal intermediate resistance to ofloxacin was 1% in 1993 and 9.5% in 1994. However, it should be noted that there was no absolute resistance detected in this study.

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[30] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991; Oshita Y, Hiramatsu K. A point mutation in *norA* gene is responsible for quinolone resistance in *Staphylococcus aureus*. Biochem Biophys Res Commun 172:1028-34, 1990; Yoshida H, Bogaki M, et.al. Nucleotide sequence and characterization of the Staphylococcus *norA* gene, which confers resistance to the quinolones. J Bacteriol 172:6942-9, 1990; Neu HC. Bacterial resistance to the fluoroquinolones. Rev Infect Dis 10(suppl.1):57-63, 1988; Sreedharan S, Oram M. DNA gyrase *gyrA* mutations in ciprofloxacin-resistant strains of *S. aureus*: close similarity with quinolone resistant mutations in *E. coli*. J Bacteriol 172:7260-2, 1990.

[31] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[32] Piddock LJV, Wise R. The selection and frequency of streptococci with decreased susceptibility to ofloxacin and the other quinolones. J Antimicrobial Chemo 22(suppl C):45-51, 1988.

[33] Jones RN, Reller LB, Rosati LA. Ofloxacin, a new Broad Spectrum Fluoroquinolone: Results from a Multicenter, National Comparative Activity Surveillance Study. Diag. Microbial Infect Dives 15:425-34, 1992.

[34] Butler JC, Hofman J, Elliot JA, et.al. Late breaking abstract. 35th ICAAC, San Francisco, CA, September 17-20, 1995.

Pharmacokinetic/pharmacodynamic data have been used to attempt to predict the clinical efficacy of antimicrobial agents against specific microorganisms. In the case of the quinolone antimicrobials, the inhibitory quotient, defined as the AUC/MIC ratio (the ratio of the Area Under the Concentration-time Curve (AUC) of the antibiotic to the minimum inhibitory concentration (MIC) of the S. pneumoniae isolate) has been shown to be predictive of clinical efficacy, with an AUC/MIC value of 40 being the breakpoint for *S. pneumonaie*[35]. Levofloxacin, being the active isomer of ofloxacin, achieves higher blood level of the active isomer, and thus has a better inhibitory quotient for *S. pneumonaie*, as described in the table below. However, it should be noted that the MIC90 of some strains of *S. pneumonaie* is now ≥4 mcg/mL for both ciprofloxacin and ofloxacin. At this higher MIC, the inhibitory quotient for levofloxacin falls below the breakpoint of 40. Thus, the margin for "MIC creep" afforded even by the higher blood levels of levofloxacin is borderline.

It should be noted that all these calculations are theoretical based on the pharmacokinetic/pharmacodynamic data of these compounds. For ofloxacin, there remains a discrepancy between the inadequacy of the inhibitory quotients and the clinical efficacy, with the clinical efficacy being better than would be predicted by the marginal inhibitory quotient against *S. pneumonaie*.

Table 15.2.1

Inhibitory quotients against *Streptococcus pneumonaie* for several of the Fluoroquinolone Antibiotics: Calculated for MICs of 2 mcg/mL and 4 mcg/mL

Quinolone Antimicrobial	Inhibitory Quotient (AUC/MIC) for MIC 2 mcg/mL		Inhibitory Quotient (AUC/MIC) for MIC 4 mcg/mL	
	MIC	AUC/MIC	MIC	AUC/MIC
Ciprofloxacin	2 mcg/mL	11.6	4 mcg/mL	5.8
Ofloxacin	2 mcg/mL	43.5	4 mcg/mL	21.8
Levofloxacin	2 mcg/mL	60.7	4 mcg/mL	30.4

[35] Dr. David C. Hooper . Presented at the 35th ICAAC, San Francisco, CA, September, 1995.

15.3. There is inadequate data regarding the CNS levels of levofloxacin. This is particularly important in assessing the adequacy of this drug for coverage against CNS seeding in bacteremic pneumococcal pneumonia. However, also for CNS coverage in sinusitis (particularly *S. pneumoniae* and *S. aureus*, given that the venous drainage of the sinus is posterior into the venous drainage of the CNS.

According to the biopharmaceutics reviewer, the pharmacokinetics and distribution of levofloxacin are comparable to that of ofloxacin, such that extrapolation of the CSF penetration of ofloxacin to levofloxacin can be used to calculate the theoretical CSF penetration of levofloxacin. The CNS penetration ofloxacin is generally 40-50% of its blood level. Theoretically, if the CNS levels of levofloxacin were 50% of the blood levels of the drug, the inhibitory quotient (AUC/MIC) within the CNS for S. pneumoniae (at an MIC of 2 MIC/mL) would be approximately 30, which is below the breakpoint of 40 which correlates with clinically efficacy for the quinolones. Thus, the coverage for *S. pneumoniae* within the CNS could, hypothetically, be marginal, particularly for pneumococcal bacteremia. Again, this is based on a theoretical calculation using a breakpoint calculated by Hooper for use win predicting the clinical efficacy of the fluoroquinones. The reader is referred to Section 15.2.2. for a discussion of the use of the inhibitory quotient in extrapolating pharmacokinetic/pharmacodynamic data to clinical efficacy.

15.4. The clinical efficacy (i.e. the clinical cure rate) of levofloxacin was statistically equivalent to amoxicillin/clavulanate in Protocol M92-040. The clinical cure rate for the levofloxacin arm was 79% (209/263), and that for the amoxicillin/clavulanate arm was 74% (197/266), with the 95% confidence interval around the difference being -13.0 to 2.2. Thus, levofloxacin meets statistical criteria for approval for the treatment of acute bacterial sinusitis. The clinical cure rate in Protocol N93-006 was 71 %, thus, comparable to the levofloxacin arm in Protocol M92-040.

Recommendations:

1. Clinical Efficacy:

Protocol M92-040 demonstrated that clinical cure rate of levofloxacin (79%) in the treatment of acute bacterial sinusitis meets statistical criteria for equivalence to the comparison arm of amoxicillin/clavulanate (74%). The clinical cure rate in study N93-006 (71%) was comparable to the levofloxacin treatment arm in Protocol M92-040. When the levofloxacin-treated patients in protocol MR92-040 and N93-006 were combined into a single cohort, the clinical cure rate was 75%. The 95% confidence interval around the difference in treatment arms for the combined cohort was $_{266,\ 540}(-7,\ 5)_{74\%,\ 75\%}$ Thus, based on the data in the NDA database, which meet regulatory criteria for approval, the Division is justified in granting this indication for the use of levofloxacin.

Table I
Combined Analysis of Protocols MR92-040 and N93-006
Poststudy Clinical Cure Rates and Confidence Intervals By Protocol:
FDA Clinically Evaluable Subjects

Protocol	Levofloxacin		Amoxicillin/ Clavulanate		95% Confidence Interval[b]
	N	Cure[a]	N	Cure[a]	
MR92-040	263	209 (79)	266	197 (74)	(-12, 2)
N93-006	277	198 (71)	---	--- ---	-----
Total	540	407 (75)	266	197 (74)	(-7, 5)

[a]Poststudy clinical outcome is defined by the reviewing medical officer as either "cured" or "failed": there was no intermediate clinical outcome category of "improved".

2. Microbiologic Efficacy:

There exists discrepancies in the eradication rates for the pathogens requested by the sponsor (*S. pneumoniae, M. catarrhalis, H. influenzae, S. aureus*). The clinical cure rates and microbiologic eradication rates for *S. pneumoniae* and *H. Influenzae* are adequate, but the clinical cure a rates for *M. catarrhalis* and *S. aureus* are suboptimal. There was only one study with microbiologic evaluation in the pivotal studies submitted for this indication, and that was Protocol N93-006. Therefore, the microbiologic efficacy results for that protocol would be considered the summary microbiologic results for this indication. These results are summarized in Tables II and III, on the following page. Following the summary table, there is a discussion of the recommendations for each pathogen requested by the sponsor in the proposed labeling for this indication.

Table II
Overall Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Protocol N93-006) [a]

Pathogen Category/Pathogen	Levofloxacin	
	N[b]	Eradicated[c] N (%)
Pathogen Category		
Gram-positive aerobic pathogens	63	50 (79)
Gram-negative aerobic pathogens	70	51 (73)
Gram-positive anaerobic pathogens	2	1 (50)
Gram-negative anaerobic pathogens	1	1 (100)
Total by pathogen	136	103 (76)
Total by subject	131	96 (73)
Pathogen		
Haemophilus influenzae	34	25 (73)
Moraxella catarrhalis	13	8 (62)
Staphylococcus aureus	22	11 (50)
Streptococcus pneumoniae	29	27 (93)

[a]The sponsor presents microbiologic results separately by collection method (i.e., antral puncture and endoscope). Since results are very similar, FDA presents results for both collection methods combined.

[b]N=number of subjects who had that pathogen alone or in combination with other pathogens. (Note: *Staphylococcus aureus* was considered a pathogen when isolated alone; in polymicrobial infections, *S. aureus* was considered a contaminant. Eleven patients considered clinically evaluable by FDA had *S. aureus* as part of a polymicrobial infection. *S. aureus* data for these patients is not included in this table.)

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

Table III
Overall Success Rates* by Admission Pathogen: FDA Microbiologically AND Clinically Evaluable Subjects (Protocol N93-006)

Admission Pathogen(s)	N	Overall Success*
Haemophilus influenzae	34	25 (73)
Moraxella catarrhalis	13	8 (62)
Staphylococcus aureus	22	11 (50)
Streptococcus pneumoniae	29	27 (93)
All Microorganisms isolated at Admission	127	89 (70)
Four Pathogens *(H. flu., M. cat., S. aureus., S. pneumo.)*	102	69 (68)
Three Major Pathogens *(H.flu., M. cat., S. pneumo.)*	71	53 (75)

*Overall Success is defined as clinically cured AND microbiologically eradicated

[b]N=number of subjects who had that pathogen alone or in combination with other pathogens. (Note: *Staphylococcus aureus* was considered a pathogen when isolated alone; in polymicrobial infections, *S. aureus* was considered a contaminant. Refer to footnote to Table II, above.

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

2.1 Streptococcus pneumoniae:

The point estimate for a 93% eradication rate of *Streptococcus pneumoniae* would, generally, support the inclusion of this organism in the labeling. However, the issues surrounding the resistance of this organism to the quinolone antimicrobials need to be considered, since the use of this antimicrobial in general medical practice for the treatment of acute bacterial sinusitis will, in general, be empiric.

Acknowledging the limitation of comparing eradication rates and *in vitro* susceptibility rates, the eradication rate of *S. pneumoniae* in Protocol N93-006 is below the historic susceptibility rate of 95% for ofloxacin against *S. pneumoniae* that existed at time that this advisory committee made this recommendation for the class labeling change for the quinolones. However, this eradication rate is well above the comparable susceptibility rate of 68% for ciprofloxacin against *S. pneumoniae* during that same period. The Medical Officer recommends that the microbiologist examine the *in vitro* susceptibilities of *S. pneumoniae* in light of the historical data on other quinolne antimicrobials. If the resistance rates to levofloxacin are comparable to those for ofloxacin at time of this advisory committee recommendation, a warning statement regarding resistance of this organism to the fluoroquinolones should definitely be included in the label.

2.2. Haemophilus influenzae:

The eradication rate (73%) of this organism is acceptable to support its inclusion in the labeling.

2.3. Moraxella catarrhalis:

The small numbers of *Moraxella* present in the evaluable patient pool may not give a stable point estimate for the eradication rate of this microorganism; nevertheless, the eradication rate of 62% is suboptimal. The inclusion of this organism in the labeling is equivocal.

2.4. Staphylococcus aureus:

The clinical cure (50%) and eradication rate (50%) for *S. aureus* are not adequate to support its inclusion in the labeling. In addition, the lack of quantitative cultures makes rigorous interpretation of the cure/eradication rates for this organism impossible.

Given the eradication rates in the NDA database, the Division is justified in granting *H. influenzae* and, depending on the *in vitro* susceptibility rates, *S. pneumoniae* for the product labeling. The medical officer will defer to the team leader in granting *M. catarrhalis* for the labeling, because of the low number of organisms and the poor eradication. The team leader may wish to recommend a repeat study with adequate numbers of *M. catarrhalis* for inclusion of this organism in the labeling. The medical officer cannot recommend the inclusion of *S. aureus* in the labeling because of (1) the low eradication rate (2) the absence of quantitative culture in the protocol. The extensive discussion above regarding the resistance of both *S.* aureus and *S. pneumoniae* to quinolone

antimicrobial emphasizes the Medical Officer's concerns regarding the long term efficacy of levofloxacin for this indication.

3. Subsequent clinical study for the treatment of *Staphylococcus aureus* in acute bacterial sinusitis:

The Medical Officer recommends that the Sponsor not be granted a claim for *Staphylococcus aureus* based on the above reasons. The Medical Officer also raises concerns about the use of quinolone antimicrobial for the treatment of presumed or documented *S. aureus* in either the maxillary or frontal/sphenoid/ethmoid sinuses because of (1) the low susceptibility rates of *S. aureus* to levofloxacin documented in this database, (2) the rapid development of resistance (at times during therapy) of *S. aureus* to the other quinolones, and (3) the high CNS complication rates of *S. aureus* sinusitis. If the sponsor would like *S. aureus* included in the label for this indication, the Medical Officer recommends a rigorous subsequent study with, at minimum, (1) quantitative cultures to distinguish between *S. aureus* as a contaminant and *S. aureus* as a pathogen and (2) rigorous characterization of the microbiology of clinical and microbiologic failures to assess for the development of resistance in *S. aureus* during the course of therapy.

4. Phase 4 agreement requiring surveillance for the development of resistance to levofloxacin:

The extensive discussion above regarding the resistance of both *S. aureus* and *S. pneumoniae* to these agents emphasizes the medical officer's concerns regarding the long term efficacy of levofloxacin for this indication. The Medical officer would recommend that a condition of the approval be a Phase 4 surveillance program to document the development of resistance to this antimicrobial so that product labeling can be updated accordingly.

4.1. Streptococcus pneumoniae:

According to an DAIDP advisory committee recommendation in October 1991, there exist significant concern about the resistance of *S. pneumonaie* to the quinolone antimicrobials, such that there was a recommendation of a labeling change warning of the development of resistance in *S. pneumoniae* and recommending that the "quinolones not be used as first line agent for the treatment of infection due to presumed or confirmed [pneumonia] *S. pneumonaie*". As per the discussion of inhibitory quotients of several of the quinolone antimicrobials for *S. pneumonaie*, there does not exist a large safety margin for levofloxacin in regards to the achievable blood levels (AUC) and the MIC of this organism. In addition, the eradication rate of *S. pneumoniae* in Protocol N93-006 is below the historic susceptibility rate of 95% for ofloxacin against *S. pneumoniae* that existed at time that this advisory committee made this recommendation for the class labeling change for the quinolones.

4.2. Staphylococcus aureus:

Although the Medical Officer cannot recommend the use of levofloxacin for the treatment of acute bacterial sinusitis due to *S. aureus*, the fact that the organism is a minor pathogen in this disorder, and, when present, a very aggressive pathogen, raises concern over the empiric use of this antimicrobial for coverage of *S. aureus* in the sinuses. Accurate data on the development of resistance in this organism is important to the labeling, as this drug will most frequently be used empirically in the treatment of community-acquired acute bacterial sinusitis.

5. A statement regarding the lack of data on the CNS penetration of levofloxacin should be included in the product labeling.

This is particularly important in light of the fact that, in clinical practice, this drug will be used empirically for the coverage *Streptococcus pneumoniae* and *Staphylococcus aureus* in the treatment of sinusitis. The inhibitory quotient in the CSF may be suboptimal at baseline and inadequate upon development of even intermediate resistance.

Medical Officer's Review of NDA 20-634
Levaquin® (levofloxacin) Tablets

Indication: Acute Exacerbation of Chronic Bronchitis

Overview of Clinical Studies:

1. **Pivotal studies conducted primarily in the United States:**
   1.1. **Study K90-070**: A multicenter, randomized, open-label study to compare the safety and efficacy of oral levofloxacin (488mg PO QD for 5-7 days) with cefaclor (250mg PO TID for 7-10 days) in the treatment of acute exacerbation of chronic bronchitis in adults
   1.2. **Study M92-024**: A multicenter, randomized, open-label study to compare the safety and efficacy of oral levofloxacin (500mg PO QD for 5-7 days) with cefuroxime (250mg PO BID for 7-10 days) in the treatment of acute exacerbation of chronic bronchitis in adults
2. **Supportive foreign study:**
   2.1. **3355E-CLN026** : Multicenter, double-blind, randomized, active-controlled study comparing levofloxacin (300mg PO QD for 7 days) with amoxicillin (500mg PO TID for 7 days) in the treatment of acute exacerbation of chronic bronchitis in adults

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Protocol: K90-070

Study Title: A multicenter, randomized study to compare the safety and efficacy of oral levofloxacin with cefaclor in the treatment of acute exacerbation of chronic bronchitis in adults

Study dates: DATE STUDY INITIATED: January 7, 1992
DATE STUDY COMPLETED: July 13, 1994

1. Study Objective:

The objective of this study was to compare the safety and efficacy of 488 mg levofloxacin administered orally once daily for 5 to 7 days with that of 250 mg cefaclor administered orally three times daily for 7 to 10 days in the treatment of acute bacterial exacerbation of chronic bronchitis due to susceptible organisms in adult outpatients.

2. Protocol design:

This was a randomized, open-label, active-control, multicenter study. Subjects who met the entry criteria were assigned randomly to receive levofloxacin for 5 to 7 days or cefaclor for 7 to 10 days. Efficacy evaluations were based on the assessments of clinical symptoms, chest examination signs, and overall clinical response (cured, improved, failed, or unable to evaluate) and on microbiologic eradication of the suspected pathogen(s) isolated at admission (baseline) and of the subject's infection considering all pathogens isolated. Clinical symptoms and chest examination signs were to be assessed at admission and five to seven days after the end of therapy (posttherapy), with an overall clinical response rating

at the posttherapy visit. Cultures, gram stains, and susceptibility testing of respiratory specimens were to be performed at admission and posttherapy. Microbiologic response was the primary efficacy parameter and was based primarily on the group of subjects evaluable for microbiologic efficacy as noted below. Clinical response in the group of subjects evaluable for clinical efficacy (see below) represented the secondary efficacy parameter for this study. Safety evaluations consisted of treatment-emergent adverse events reported during the study period and of clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, and physical examinations performed at baseline and posttherapy.

3. Diagnostic criteria:

The primary diagnosis of acute bacterial exacerbation of chronic bronchitis was defined by clinical and radiographic signs and symptoms of acute bacterial exacerbation of chronic bronchitis:

3.1. **Clinical**: Subjects with a diagnosis of acute bacterial exacerbation of chronic bronchitis, as evidenced by **all of the following:**

- history of chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema)
- recent increase in cough
- change in character and/or increase in production of sputum
- physical findings consistent with a diagnosis of acute bacterial exacerbation of chronic bronchitis.

3.2. **Radiographic**: The patient should have had a chest radiograph without an acute inflammatory infiltrate consistent with pneumonia

3.3. **Microbiologic**: An appropriate sputum specimen must have been available for entry into the study.

4. Inclusion and exclusion criteria:

4.1. Inclusion criteria:

4.1.1. Inclusion criteria as per Original Protocol dated October 18, 1991:

Subjects may have been included in the study if they satisfied the following criteria:

1. Age: 18 or older
2. Sex: male or female
3. All subjects were to be appropriate candidates for oral therapy. Patients in nursing homes may have been enrolled if they were ambulatory and were able to carry out the activities of daily life.
4. Diagnosis of pneumonia as evidenced by:

• history • physical findings • chest x-ray, and/or • laboratory tests

Subjects with an exacerbation of chronic bronchitis, as evidenced by a recent increase in cough and change in character of sputum production, may be entered.

Medical Officer's Comment: The inclusion of pneumonia in the original inclusion criteria is a reflection of the fact that this protocol was originally written as a Lower Respiratory Tract Infection (LRI) protocol, under which community-acquired pneumonia and acute exacerbation of chronic bronchitis are both included under the umbrella category of LRI.

5. If female, the subject must

- have been post-menopausal for at least one year, or
- have had a hysterectomy, or
- have had a tubal ligation, or
- have taken oral contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods during the study, or
- have used another acceptable method of contraception and agreed to continue with the same method during the study.

If female and of childbearing potential, the subject must have
- had a normal menstrual flow within one month prior to study entry, and
- a negative pregnancy test (serum β-subunit HCG) immediately prior to entry.

If obtaining the serum pregnancy test result would cause a delay in treatment, a subject may have been entered on the basis of a negative urine pregnancy test sensitive to at least 50 mIU/mL, pending results of the serum pregnancy test. Subsequently, if the result of the serum test was positive, the subject must have been discontinued from the study and followed as indicated.

6. Completion of the confidential follow-up form
7. Reading and signing of the informed consent (and California Bill of Rights, if applicable) after the nature of the study had been fully explained.

4.1.2. Inclusion criteria as per Protocol Amendment #1 dated June 10, 1992:

Subjects may have been included in the study if they satisfied the following:

1. Age: 18 or older
2. Sex: male or female
3. All subjects were to be appropriate candidates for oral therapy. Patients in nursing homes may have been enrolled if they were ambulatory and were able to carry out the activities of daily life.
4. Subjects with a diagnosis of acute bacterial exacerbation of chronic bronchitis, as evidenced by all of the following:
   - history of chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema)
   - recent increase in cough
   - change in character and/or increase in production of sputum
   - physical findings consistent with a diagnosis of acute bacterial exacerbation of chronic bronchitis.

   An appropriate sputum specimen must have been available for entry into the study.
5. Subjects who had received previous antimicrobial therapy may have been enrolled in the protocol if:
   - previous therapy duration was 24 hours or less
   - previous therapy duration was greater than 24 hours, but subject did not improve or stabilize on that therapy
6. Criteria regarding female subjects:
   - 6.1. If female, the subject must
     - have been post-menopausal for at least one year, or
     - have had a hysterectomy, or
     - have had a tubal ligation, or
     - have taken oral contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods during the study, or
     - have used another acceptable method of contraception and agreed to continue with the same method during the study.
   - 6.2. If female and of childbearing potential, the subject must have
     - had a normal menstrual flow within one month prior to study entry, and
     - had a negative pregnancy test (serum β-subunit HCG) immediately prior to entry.
   - 6.3. If obtaining the serum pregnancy test result would cause a delay in

treatment, a subject may have been entered on the basis of a negative urine pregnancy test sensitive to at least 50 mIU/mL, pending results of the serum pregnancy test. Subsequently, if the result of the serum test was positive, the subject must have been discontinued from the study and followed as indicated.

7. Completion of the confidential follow-up form
8. Reading and signing of the informed consent (and California Bill of Rights, if applicable) after the nature of the study had been fully explained.

4.1.3. Inclusion criteria as per Protocol Amendment #2 dated April 21, 1993:

Inclusion criteria unchanged from Protocol Amendment #1 dated June 18, 1992.

4.1.4. Inclusion criteria as per Protocol Amendment #3 dated March 9, 1994:

Inclusion criteria unchanged from Protocol Amendment #1 dated June 18, 1992, with the exception of the following addition:

5. Subjects who had received previous antimicrobial therapy may have been enrolled if:
   - previous therapy duration was 24 hours or less
   - previous therapy duration was greater than 24 hours, but subject did not improve or stabilize on that therapy

4.1.5. Inclusion criteria as per Protocol Amendment #4 dated July 14, 1994:

Inclusion criteria unchanged from Protocol Amendment #3 dated March 9, 1993.

4.2. Exclusion criteria:

4.2.1. Exclusion criteria as per Original Protocol dated October 18, 1991:

Subjects with any of the following criteria were not to be eligible for admission into the study:

1. Severity of illness requiring parenteral antimicrobial therapy
2. Subjects with an infection due to organisms known to be resistant to the study drug prior to study entry
3. Previous allergic or serious adverse reaction to l-ofloxacin, cefaclor, or any other members of the quinolone or cephalosporin classes of antimicrobials, or a severe reaction to penicillin. Subjects with previous allergies or serious adverse reactions to erythromycin or macrolide classes of antimicrobials should not be placed on these alternative regimens
4. Serum creatinine greater than 2.0 mg/dL
5. Diagnosis of acute bronchitis or cystic fibrosis
6. Requirement of a second systemic antimicrobial agent
7. Effective systemic antimicrobial therapy within 48 hours prior to admission
8. Use of an investigational agent within 30 days prior to admission
9. Pregnancy or a nursing mother
10. Previous treatment under this protocol
11. Any disorder or disease that might interfere with the evaluation of the study drugs
12. Presence of any seizure disorder or condition requiring the administration of major tranquilizers.

4.2.2. Exclusion criteria as per Protocol Amendment #1 dated

June 10, 1992:

The exclusion criteria were changed from Protocol Amendment #1 as follows. Deletions are in parentheses and additions are in bold.

1. Severity of illness requiring parenteral antimicrobial therapy
2. Subjects with an infection due to organisms known to be resistant to the study drug prior to study entry
3. **Previous allergic or serious adverse reaction to levofloxacin, cefaclor, or any other members of the quinolone or cephalosporin classes of antimicrobials, or a severe reaction to penicillin**

[Deletion: Subjects with previous allergies or serious adverse reactions to erythromycin or macrolide classes of antimicrobials should not be placed on these alternative regimens]

4. **Calculated creatinine clearance less than or equal to 50 mL/min**
5. *Diagnosis* of acute bronchitis, **pneumonia (as evidenced by acute infiltrates on the admission chest x-ray obtained within 12 hours prior to study entry)**, or cystic fibrosis
6. Requirement of a second systemic antimicrobial agent
7. Effective systemic antimicrobial therapy within 48 hours prior to admission
8. Use of an investigational agent within 30 days prior to admission
9. Pregnancy or a nursing mother
10. Previous treatment under this protocol
11. Any disorder or disease that may interfere with the evaluation of the study drugs
12. Presence of any seizure disorder or condition requiring the administration of major tranquilizers.

4.2.3. Exclusion criteria as per Protocol Amendment #2 dated April 21, 1993:

The exclusion criteria were unchanged from Protocol Amendment #1, with exception of the following addition. Deletions are in parentheses and additions are in bold.

12. *[Presence]* **History** of *[any]* seizure disorder or condition requiring the administration of major tranquilizers.

4.2.4. Exclusion criteria as per Protocol Amendment #3 dated March 9, 1994:

The exclusion criteria were unchanged from Protocol Amendment #2, with exception of the following: deletions are in parentheses and additions are in bold.

4. **Calculated creatinine clearance less than or equal to 50 mL/min**
   [Deletion: Serum creatinine greater than 2.0 mg/Dl]
5. Diagnosis of acute bronchitis, **pneumonia (as evidenced by acute infiltrates on the admission chest x-ray obtained within 12 hours prior to study entry)**, or cystic fibrosis
6. Requirement of a second systemic antimicrobial agent
   [Deletion: 7. Effective systemic antimicrobial therapy within 48 hours prior to admission]
7. Use of an investigational agent within 30 days prior to admission
8. Pregnancy or a nursing mother
9. Previous treatment under this protocol
10. Any disorder or disease that may interfere with the evaluation of the study drugs
    [Deletion: 12. Presence History of any seizure disorder or condition requiring the administration of major tranquilizers.]
11. **Presence of seizure disorder**
12. **Unstable psychiatric conditions.**

4.2.5. Exclusion criteria as per Protocol Amendment #4 dated

July 14, 1994:
The exclusion criteria were unchanged from Protocol Amendment #3 dated March 9, 1994.

5. Medications:

5.1. Dosage and Administration of Study Medications:

5.1.1. Dosage and Administration of Study Medications as per Original Protocol dated October 18, 1991:

Each subject were to be assigned a study number in strict sequential order. All subjects randomized to l-ofloxacin were to receive 488 mg (five 97.6 mg tablets) q24h. Subjects randomized to the control group were to receive cefaclor 500 mg (two 250 mg capsules) q8h. Total duration of therapy was to be 7-10 days for exacerbation of chronic bronchitis (and, according to the original protocol, 10-14 days for pneumonia). For cefaclor subjects only, erythromycin base (Ery-Tab •, Abbott Laboratories, North Chicago, IL) 500 mg PO qid may have been added if *M. pneumonia* or *L. pneumophila* was suspected. If these pathogens are confirmed by culture or by DFA (*Legionella*), these patients may have been continued on erythromycin alone.

5.1.2. Dosage and Administration of Study Medications as per Protocol Amendments:

5.1.2.1. Amendment #1 dated June 1, 1992 (additions in bold face type, deletions in brackets):

Each subject was to be assigned a study number in strict sequential order. All subjects randomized to *[Deletion: l-]* **levofloxacin** were to receive 488 mg (five 97.6 mg tablets) q24h **for 5-7 days**. Subjects randomized to the control group were to receive cefaclor **250** *[500 mg (two 250 mg capsules)]* q8h **for 7-10 days**.

[Present in original protocol, but deleted from this amendment: Total duration of therapy [for either study drug] will be 7-10 days for exacerbation of chronic bronchitis and 10-14 days for pneumonia. For cefaclor subjects only, erythromycin base (Ery-Tab ®, Abbott Laboratories, North Chicago, IL) 500 mg PO qid may have been added if M. pneumonia or L. pneumophila is suspected. If these pathogens are confirmed by culture or by DFA (Legionella), these patients may have been continued on erythromycin alone.]

5.1.2.2. Amendment #2 dated April 21, 1993 (additions in bold face type, deletions in brackets):

Dosage and administration of study medication was unchanged form Protocol Amendment #1 dated June 1, 1992.

5.1.2.3. Amendment #3 dated March 9, 1994 (additions in bold face type, deletions in brackets):

Each subject was to be assigned a study number in strict sequential order. All subjects randomized to **levofloxacin** was to receive 488 mg (five 97.6 mg tablets) q24h **for 5-7 days**. Subjects randomized to the control group were to receive cefaclor **250** *[500] mg [(two 250 mg capsules)]* q8h **for 7-10 days. If, in the opinion of the investigator, a subject required a longer duration of therapy, the RWJPRI medical monitor should have been**

contacted.

5.1.2.4. Amendment #4 dated July 14, 1994:

Dosage and Administration were unchanged from Amendment #3 dated March 9, 1994.

5.2. Administration of concomitant medications and other antimicrobial agents during the treatment and follow-up phases:

The use of other medications during the study was to be kept to a minimum. Administration of nonstudy systemic antimicrobials was to be prohibited and aluminum-magnesium based antacids (e.g., Maalox®) and mineral supplements or vitamins with iron or minerals were to be strongly discouraged because they might decrease bioavailability of study drug. However, if administration of an antacid was necessary, it was to be administered at least two hours before or after levofloxacin or cefaclor administration. If the administration of any other medication (e.g., aspirin) was required, it was to be reported on the subject's CRF.

6. Efficacy Criteria per Sponsor:

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

7. Schedule and procedures for Efficacy and Safety Evaluations

7.1. Clinical Efficacy Evaluation:

7.1.1. Clinical Signs and Symptoms

Clinical symptoms of acute bacterial exacerbation of chronic bronchitis, including chills, chest pain, shortness of breath, increased cough, sputum increase, and purulent sputum, were indicated by the investigator as present or absent at admission and at the posttherapy visit five to seven days after the end of therapy. Clinical signs of bronchitis obtained from a chest examination (diminished breath sounds, rales, rhonchi, and wheezes) were to be graded by the investigator as none, mild, moderate, or severe at admission and at the posttherapy visit five to seven days after the end of therapy.

7.1.2. Clinical Response Rating

At the posttherapy visit five to seven days after the end of therapy, the investigator was to assess clinical response as cured, improved, failed, or unable to evaluate. These assessments were defined as follows:

Cure: Resolution of signs and symptoms associated with active infection.
Improved: Incomplete resolution of signs and symptoms and no additional antimicrobial therapy required.
Failure: No response to therapy.
Unable to evaluate: Not able to evaluate because subject lost to follow-up.

7.2. Microbiologic Efficacy Evaluation:

7.2.1. Specimen Collection

7.2.1.1. Respiratory Secretions

Specimens were to be obtained from respiratory secretions including deep expectorated or suctioned sputum, transtracheal aspirates, bronchial brushings, or washings. Respiratory specimens were to be collected within 48 hours prior to admission for culture, gram stain, and susceptibility tests. If the subject could produce sputum, specimens were to be obtained at the posttherapy visit (five to seven days after the end of therapy) for culture, susceptibility testing, and gram stain.

7.2.1.2. Blood Culture

Blood cultures were to be obtained at admission if bacteremia was suspected. Cultures were to be repeated at later time points if bacteremia was found at admission.

7.2.1.3. Serology

Prior to the first amendment, serology studies for *Mycoplasma pneumoniae, Legionella pneumophila,* and *Chlamydia pneumoniae* were to be performed at admission for all subjects. A fourfold rise or fall in titer of antibodies from admission to posttherapy or a single diagnostic titer was to be considered evidence of an infection.

7.2.2. Susceptibility Testing

Susceptibility to levofloxacin and cefaclor was to be determined for all aerobic pathogens at admission, and, if indicated, at five to seven days posttherapy. The MIC susceptibility was the primary susceptibility criterion. If the MIC values were not available, disks were to be used to determine susceptibility. Disk susceptibility testing was to be performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) methods using 5 μg levofloxacin disks provided by RWJPRI for levofloxacin susceptibility and cefaclor disks provided by the study center for cefaclor susceptibility.

7.3. Efficacy Criteria

7.3.1. Microbiologic Response

The primary efficacy parameter of microbiologic response to treatment was evaluated by RWJPRI in terms of pathogen and infection eradication rates. The microbiologic response for pathogens isolated at admission was determined by evaluating the posttherapy/withdrawal culture results. A culture was considered valid if it was obtained at least one day posttherapy and collected while the subject was not receiving any effective concomitant antimicrobial treatment. Results were to be categorized as follows:

Eradicated: Eradication of the admission pathogen as evidenced by failure to isolate the pathogen in a valid posttherapy/withdrawal culture. If clinical improvement occurred such that no sputum was produced and invasive procedures for culture were contraindicated, then the pathogen was presumed eradicated.

Persisted: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/withdrawal culture. If a subject was to be discontinued due to clinical failure or a resistant pathogen and was considered a clinical failure or was considered a clinical failure and study

therapy was not extended or eradication of the admission pathogen was not confirmed by a valid posttherapy/withdrawal culture, then the pathogen was to be presumed to persist.

Persisted with Acquisition of Resistance: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/ withdrawal culture with documented acquisition of resistance.

Unknown: No posttherapy/withdrawal culture results available due to lost-to-follow-up, lost culture, or culture not done when specimen was available. The response was unknown if the culture was performed on the last day of therapy or if the culture was done while the subject was receiving an effective antimicrobial agent for reasons other than clinical failure, unless persistence was verified or presumed.

7.3.2. Clinical Response

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

7.4. Safety Evaluation

7.4.1. Treatment-Emergent Adverse Events

Adverse events were defined as treatment-emergent signs and symptoms, i.e., events that were not present at admission or events that represented an increase in severity or frequency of a sign or symptom already present at admission. Each subject was to be assessed at each visit after admission for possible adverse events that might have occurred throughout the study period. The investigator was to record all adverse events on the CRFs and grade their severity as mild, moderate, or marked. The investigator also was to assess the relationship of the adverse event to trial treatment using the following ratings: none, remote, possible, probable, or definite. Other information recorded on the subject's CRF included: the date of onset of the event, control measures taken (i.e., discontinuation of study drug, or administration of remedial therapy), the outcome (resolved, persisted, or unknown), and the date of resolution of the event. Serious adverse events were defined as those events that presented a significant threat to the well-being of the subject. Serious adverse events included any event that was fatal, life-threatening, permanently or significantly disabling, required hospitalization or prolonged hospitalization, resulted in long-term outpatient treatment (greater than six months), or was a congenital anomaly, cancer, or overdose. Investigators were instructed to report all serious adverse events immediately to RWJPRI. For subjects randomized to levofloxacin, a 5cc venous blood sample for determination of levofloxacin plasma concentration was to be obtained at the time of a serious adverse event. However, due to practical limitations, these blood samples were not consistently obtained as planned.

7.4.2. Clinical Laboratory Tests

The following standard clinical laboratory evaluations were to be performed before dosing (admission) and at the posttherapy visit. A central laboratory was used.

Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, red blood cell (RBC) count, and platelet count.

Blood Chemistry: glucose, blood urea nitrogen (BUN), total bilirubin, total protein, albumin, uric acid, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), creatinine, calcium, inorganic phosphorus, sodium, potassium, chloride, and bicarbonate.

Urinalysis: pH, specific gravity, and microscopic examination for red blood cells, white blood cells, and nonamorphous crystals.

8. Discontinuation from study:

Subjects could 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, including evaluation of signs and symptoms, physical examination and vital signs, culture, susceptibility testing, and gram stain of respiratory secretions, if indicated, and clinical laboratory tests were to be performed. The investigator recorded the reason for premature discontinuation on the subject's CRF.

9. Evaluability Criteria:

9.1. Evaluability criteria as per Sponsor:

9.1.1. Original evaluability criteria as outlined in Original Protocol dated October 18, 1991:

To be evaluable for clinical efficacy, subjects were not to be classified in any of the following categories:

1. Safety Analysis

To be evaluable for the safety analysis, a subject must have taken the study medication and must have relayed safety information.

2. Efficacy Analysis

A subject were to be evaluable for efficacy unless categorized into one of the following groups:

1. Unevaluable for safety
2. Infection not bacteriologically proven. No pathogen identified in the admission respiratory or blood cultures, and there was no evidence of *Mycoplasma pneumoniae*, *Legionella pneumophila*, or *Chlamydia pneumoniae* based on serology results
3. Insufficient course of therapy. Subject did not take the study drug for at least five days. Subjects who took study drug for less than five days because they were judged a clinical failure by the investigator were evaluable. The pathogen(s) was (were) presumed to persist in these situations.
4. Effective concomitant therapy. Subject took an effective systemic antimicrobial agent between time of admission culture and within 48 hours prior to start of therapy, or following therapy prior to test-of-cure culture (post-therapy). If the subject took an effective systemic antimicrobial because they had been judged a clinical failure by the investigator, they were evaluable. The pathogen(s) was (were) presumed to persist.

5. Inappropriate bacteriologic cultures as defined by:

5.1) Admission culture was greater than 48 hours prior to or greater than 48 hours following the start of therapy
5.2) Post-therapy culture was not between 1-8 days post-therapy. If the subject was discontinued due to a persistent pathogen or clinical failure and the post-therapy culture was obtained on the last day of therapy, the subject was considered evaluable.
5.3) Adequate microbiological data were not available. If the subject was a clinical failure and persistence of the pathogen(s) isolated on admission was (were) not confirmed by culture results, the pathogen(s) was (were) presumed to persist.

6. Lost to follow-up but relays safety information
7. Other protocol violation, e.g.,

7.1) Subject fails specific entrance criteria
7.2) Subject re-enters study
7.3) Subject does not take at least 70% of assigned study drug
7.4) Subject takes study drug for more than 20 days (unless due to a persistent pathogen)

8. Subjects with no initial pathogen but a fourfold or greater rise or a single diagnostic titer of antibodies for *Mycoplasma pneumoniae*, *Legionella pneumophila* or *Chlamydia pneumoniae* are evaluable for efficacy unless any of the following criteria were met:

8.1) Subject was not evaluable for safety
8.2) Insufficient course of therapy
8.3) Effective concomitant therapy
8.4) Lost to follow-up but relayed safety information
8.5) Other protocol violation

9. All subjects evaluable for efficacy were evaluable for clinical response. The microbiological response of the pathogen was based on the clinical response of the subject. For this indication, an evaluable subject may have a microbiological response of "unknown."

Medical officer's Comment: The original efficacy criteria specify taking the post-therapy follow-up culture at anywhere for 1-8 days post-therapy. Given that the half-life of levofloxacin is 6.1-7.5 hours, the cultures done on days 1-3 may result in false eradications because of suppression of regrowth by residual levels of antibiotic and/or the post-antibiotic effect. Five half-lives of this drug (the time required for plasma levels to fall to <5% of peak) sum to slightly over 1.5 days, so that a conservative estimate of two days for elimination of drug and a subsequent twenty four hours to allow for any post-antibiotic effect would lead to a conservative window of >3 days post-therapy for test-of-cure cultures to fully reflect true eradications and not merely suppression of regrowth.

9.1.2. Evaluability criteria as outlined in Protocol Amendment #1 dated June 10, 1992:

Evaluability criteria in this amendment were unmodified from the original protocol with the exception of the omission of the following statements listed here in brackets:

1. Under "Efficacy Analysis, Part b. Infection not bacteriologically proven": No pathogen identified in the admission respiratory or blood cultures [and there is no evidence of *Mycoplasma pneumoniae*, *Legionella pneumophila*, or *Chlamydia pneumoniae* based on serology results]
2. Under "Efficacy Analysis, Part e. Inappropriate bacteriologic cultures":
   1) Admission culture is greater than 48 hours prior to or greater [than 48

hours following] the start of therapy
2) Post-therapy culture is not between *[Deletion: 1-8 (original protocol)]* 2-10 days post-therapy

3. Under "Efficacy Analysis, Part g. Other protocol violation, e.g.,

[Deletion: Subjects with no initial pathogen but a four-fold or greater rise or a single diagnostic titer of antibodies for Mycoplasma pneumoniae, Legionella pneumophila or Chlamydia pneumoniae are evaluable for efficacy unless any of the following criteria were met]:

[Deletion: Subject is not evaluable for safety]

[Deletion: Insufficient course of therapy- Lost to follow-up but relayed safety information]

[Deletion: Other protocol violation]

4. *[Deletion: All subjects evaluable for efficacy are evaluable for clinical response. The microbiological response of the pathogen is based on the clinical response of the subject. For this indication, an evaluable subject may have a microbiological response of "unknown."]*

5. *[Deletion: Effective concomitant therapy]*

9.1.3. Evaluability criteria as outlined in Protocol Amendment #2, dated April 21, 1993:

Evaluability criteria in this amendment were modified from the Amendment #1 with the addition of the single statement highlighted in bold.

2. Efficacy Analysis

A subject will be evaluable for **microbiological** efficacy unless categorized into one of the following groups:

9.1.4. Evaluability criteria as outlined in Protocol Amendment #3, dated March 9, 1994:

Evaluability criteria in this amendment were modified from the Amendment #1 with the addition of the statements in bold and the omission of the statements in brackets:

1. Safety Analysis

To be evaluable for the safety analysis, a subject must have taken the study medication and must have relayed safety information.

2. Efficacy Analysis

A subject was to be evaluable for **microbiological** efficacy unless categorized into one of the following groups:

1. Unevaluable for safety
2. Infection not bacteriologically proven. No pathogen was identified in the admission respiratory or blood cultures. *[and there was no evidence of Mycoplasma pneumoniae, Legionella pneumophila, or Chlamydia pneumoniae based on serology results]*

[c. Resistant to study drug. In a monomicrobial infection, the admission pathogen was resistant to the assigned study drug. If the infection was caused by more than one pathogen and at least one pathogen was susceptible to the assigned study drug, the case was to be considered evaluable.]

3. Insufficient course of therapy. Subject did not take the study drug for at least five days. Subjects who had taken study drug for **greater than 48 hours** but for less than five days because they were judged a clinical failure by the investigator were to be evaluable. The pathogen(s) was (were) presumed to persist in these situations.
4. Effective concomitant therapy. Subject were not to have taken an effective systemic antimicrobial agent between time of admission culture [and within 48 hours prior to start of therapy, or following therapy prior] to test-of-cure culture (post-therapy). If the subject took an effective systemic antimicrobial because they were judged a clinical failure by the investigator, they were evaluable. The pathogen(s) was (were) presumed to persist.

5. Inappropriate bacteriologic cultures as defined by:

5.1) Admission culture was greater than 48 hours prior to [or greater than 48 hours following] the start of therapy
5.2) Post-therapy culture/evaluation was not between *[Deletion: 1-8 (original protocol)]*, 2-10 **(amendment #1)]** 1-10 days post-therapy. If the subject was discontinued due to a persistent pathogen or clinical failure and the post-therapy culture was obtained on the last day of therapy, the subject was considered evaluable
5.3) Adequate microbiological data was not available. If the subject was a clinical failure and persistence of the pathogen(s) isolated on admission was (are) not confirmed by culture results, the pathogen(s) was (were) presumed to persist.

6. Lost to follow-up but relays safety information
7. Other protocol violation, e.g.,

[Deletion: 7.1) Subject fails specific entrance criteria]
7.1) Subject re-enters study
7.2) Subject did not take at least 70% of assigned study drug
[Deletion: 7.4) Subject takes study drug for more than 20 days (unless due to a persistent pathogen)]

[Deletion: 8.Subjects with no initial pathogen but a fourfold or greater rise or a single diagnostic titer of antibodies for Mycoplasma pneumoniae, Legionella pneumophila or Chlamydia pneumoniae are evaluable for efficacy unless any of the following criteria were met:]

[8.1. Subject is not evaluable for safety
[8.2. Insufficient course of therapy]
[8.3. Effective concomitant therapy]
[8.4. Lost to follow-up but relayed safety information]
[8.5. Other protocol violation]

[All subjects evaluable for efficacy are evaluable for clinical response. The microbiological response of the pathogen is based on the clinical response of the subject. For this indication, an evaluable subject may have a microbiological response of "unknown."]

9.1.4. Evaluability criteria as outlined in Protocol Amendment #4, dated July 14, 1994:

Evaluability criteria in this amendment were unmodified from the Amendment #3 with the addition of the statements in bold and the omission of the statements in brackets:

3. Insufficient course of therapy
Subject does not take *[deletion: the study drug]* **levofloxacin for at least four days or cefaclor for at least five days.** Subjects who take study drug for greater than 48 hours but for less than five days because they are judged a clinical failure by the investigator are evaluable. The pathogen(s) is(are) presumed to persist in these situations.

10.2. Evaluability criteria as per Medical Officer:

10.2.1. Clinical Evaluablility Criteria as per Medical Officer:

1. The subject met the inclusion criteria
2. The subject did **NOT** meet any of the exclusion criteria at the time of enrollment
3. A **posttherapy/end-of therapy/EOT** clinical evaluation was pērformed. The exception was for patients who were declared clinical failures prior to the posttherapy visit, but did not have a posttherapy follow-up visit, here the failure declared on-therapy was carried forward.
4. A symptomatic response could be evaluated at the **posttherapy** time point.
5. With regard to establishing time point for follow-up after treatment of acute bacterial exacerbation of chronic bronchitis, both (1) the **natural history of the disease** and (2) the **half-life of the antimicrobial agent** under investigation need to be taken into account. The windows for follow-up after an episode of acute bacterial exacerbation of chronic bronchitis will be the same for patients treated with any **antimicrobial agent with a relatively short half-life**. It is only in the case of a prolonged half-life that the window for follow-up needs to be extended because blood levels and tissue levels persist far beyond the last dose of the antimicrobial drug. For levofloxacin, whose serum half-life is 6.34-6.310 hours in the clinical tablet, the window of follow-up can be the same as for other antibiotics with relatively short half-lives.

   5.1. The **IDSA Guidelines** recommend standard follow-up after an episode of acute bacterial exacerbation of chronic bronchitis as follows:

   > "Assessment after completion of therapy and follow-up: Patients should undergo clinical and microbiologic assessment within 48 hours, 7-14 days, and 21-28 days after completion of therapy. Clinical assessment should include assessment of cough, dyspnea, sputum volume and sputum purulence."[1]

   5.2. Recent **regulatory precedent** for the appropriate time point for test of cure has been established in other reviews of antimicrobial agents with short half-lives for the indication of acute bacterial exacerbation of chronic bronchitis, and these confirm the need for late post-therapy follow-up to determine a stable point-estimate for clinical cure at the test-of-cure evaluation[2].

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[1] Guidelines for the Evaluation of Anti-infective Drug Products. Clin Infect Dis 15(suppl 1):s78, 1992.

[2] Dr. Rosemary Roberts, Merepenam NDA Review. NDA Number 50706, Division HFD-520.

The original protocol specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but with an End-of-Study evaluation at 3-6 weeks post-therapy to provide a late follow-up assessment and stable estimate for the test-of-cure. Protocol Amendment #1 also specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but the late follow-up at 3-6 weeks was deleted from the protocol under this amendment. **Therefore, acknowledging that the 5-7 day posttherapy visit is suboptimal for establishing a stable point estimate of the test-of-cure, the medical officer had no choice but to use the only existing time point for the follow-up clinical evaluation as the time point for the primary clinical endpoint for the purposes of this analysis.**

6. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

   6.1. A patient was **fully clinically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

   - Within 48 hours prior to enrollment in the protocol
   - During the treatment period
   - From the end of the treatment period to the poststudy evaluation
   - At the evaluation for clinical relapse

   6.2. If the patient received an antimicrobial agent prior to enrollment in the study, but there was **a pathogenic organism isolated on admission culture**, the patient was considered **clinically evaluable**

   6.3. If the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **clinically unevaluable**.

   6.4. If the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **clinically evaluable (only) as a treatment failure**.

7. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

   7.1. For patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 5 days or 100% of the minimum dose specified by the amended protocol

   7.2. For patients in the cefaclor arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol

   7.3. For patients in either the levofloxacin arm or the cefaclor designated a clinical failure at EOT, a minimum of 72 hours of study drug was to have been taken

evaluation and culture
- At the evaluation for clinical relapse

4.2. if the patient received **pretherapy** antimicrobial treatment with another antibiotic, the patient was microbiologically evaluable if there was a pathogen isolated on admission culture. If no pathogen was isolated on admission culture, the patient was both clinically and microbiologically unevaluable.

4.3. if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **microbiologically unevaluable.**

4.4. if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **microbiologically evaluable (only) as a persistent pathogen.**

5. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

5.1. for patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 5 days or 100% of the minimum dose specified by the amended protocol

5.2. for patients in the cefaclor arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol

5.3. for patients in either the levofloxacin arm or the cefaclor designated a clinical failure at EOT, a minimum of 72 hours of study drug was to have been taken

5.4. for the levofloxacin arm, no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 5-7 doses of therapy, as specified by the amended protocol.

5.5. for patients in the cefaclor arm, no more than two missed doses requiring extension of the dosing interval to complete the full 7-10 days of therapy specified by the protocol

6. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

The original protocol specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but with an End-of-Study evaluation at 3-6 weeks post-therapy to provide a late follow-up assessment and stable estimate for the test-of-cure. Protocol Amendment #1 also specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but the late follow-up at 3-6 weeks was deleted from the protocol under this amendment. **Therefore, acknowledging that the 5-7 day posttherapy visit is suboptimal for establishing a stable point estimate of the test-of-cure, the medical officer had no choice but to use the only existing time point for the follow-up clinical evaluation as the time point for the primary clinical endpoint for the purposes of this analysis.**

6. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

   6.1. A patient was **fully clinically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

   - Within 48 hours prior to enrollment in the protocol
   - During the treatment period
   - From the end of the treatment period to the poststudy evaluation
   - At the evaluation for clinical relapse

   6.2. If the patient received an antimicrobial agent prior to enrollment in the study, but there was **a pathogenic organism isolated on admission culture**, the patient was considered **clinically evaluable**

   6.3. If the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **clinically unevaluable**.

   6.4. If the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **clinically evaluable (only) as a treatment failure**.

7. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

   7.1. For patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 5 days or 100% of the minimum dose specified by the amended protocol

   7.2. For patients in the cefaclor arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol

   7.3. For patients in either the levofloxacin arm or the cefaclor designated a clinical failure at EOT, a minimum of 72 hours of study drug was to have been taken

7.4. For the levofloxacin arm, no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 5-7 doses of therapy, as specified by the amended protocol.

7.5. For patients in the cefaclor arm, no more than two missed doses requiring extension of the dosing interval to complete the full 7-10 days of therapy specified by the protocol

8. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

10.2.2. Microbiologic evaluability criteria as per Medical Officer:

1. A subject met criteria for clinical evaluability at all time points during the study
2. Pretherapy sputum culture was positive for a microorganism known to be pathogenic in acute exacerbation of chronic bronchitis
3. Any residual secretions present at the EOT visit were sent for culture. The medical officer would not accept the category of "presumed eradication" in cases in which there were persistent secretions that were not cultured. The medical officer felt that it was incumbent upon the sponsor and investigators to document eradication when and where possible.

   3.1. Only in cases where there were no residual secretions would the designation "clinical cure/presumed eradication" be accepted.
   3.2. If there residual **purulent** secretions that were not cultured, the medical officer defaulted to "presumed persistence".
   3.3. If there residual **nonpurulent** secretions that were not cultured, the medical officer defaulted to "microbiologically unevaluable".
   3.4. In cases of clinical failure, a microbiologic assessment of "presumed persistence" was universally applied.

4. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

   4.1. a patient was **fully microbiologically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

   - For the 48 hour period prior to enrollment (see exception under item (ii) below)
   - During the treatment period
   - From the end of the treatment period to the posttherapy

evaluation and culture
- At the evaluation for clinical relapse

4.2. if the patient received **pretherapy** antimicrobial treatment with another antibiotic, the patient was microbiologically evaluable if there was a pathogen isolated on admission culture. If no pathogen was isolated on admission culture, the patient was both clinically and microbiologically unevaluable.

4.3. if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **microbiologically unevaluable**.

4.4. if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **microbiologically evaluable (only) as a persistent pathogen**.

5. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

5.1. for patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 5 days or 100% of the minimum dose specified by the amended protocol

5.2. for patients in the cefaclor arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol

5.3. for patients in either the levofloxacin arm or the cefaclor designated a clinical failure at EOT, a minimum of 72 hours of study drug was to have been taken

5.4. for the levofloxacin arm, no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 5-7 doses of therapy, as specified by the amended protocol.

5.5. for patients in the cefaclor arm, no more than two missed doses requiring extension of the dosing interval to complete the full 7-10 days of therapy specified by the protocol

6. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

10. Investigators and study sites:

Protocol 90-070 was conducted by 27 investigators at a total of 31 separate sites (28 sites within the United States and 3 foreign sites in Costa Rica, Canada, and Mexico), as delineated below.

Lawrence K. Alwine, D.O.	- Downingtown Family Medicine, Downingtown, PA; USA
Kent E. Anthony, M.D.	- R/D Clinical Research, Inc., Nassau Bay, TX; USA
Edwin R. Brankston, M.D.	- The Oshawa Clinic, Oshawa, Ontario; Canada
Gregory V. Collins, M.D.a	- Charlotte, NC; USA
Mark O. Farber, M.D.	- Roudebush VA Medical Center, Indianapolis, IN; USA
Lee A. Fischer, M.D.a	- Palm Beach Center for Clinical Investigation, West Palm Beach, FL; USA
Charles Fogarty, M.D.	- Lung and Chest Medical Associates, Spartanburg, SC; USA
Layne O. Gentry, M.D.	- St. Luke's Episcopal Hospital, Houston, TX; USA;
	- Clinica Pavas, Hospital Mexico; Hospital San Juan de Dios
	- Cenare-National Rehabilitation Centre; Hospital Calderon Guardia, San Jose, Costa Rica
Larry I. Gilderman, D.O.	- University Clinical Research Associates, Inc., Pembroke Pines, FL; USA
Michael Habib, M.D.	- VA Medical Center, Tucson, AZ; USA
W.John Henry, M.D.b	- Internal Medicine of Greer, Greer, SC; USA
Fernando A. Keller, M.D.	- Pulmonary Associates, M.D., P.A., Miami, FL; USA
Richard B. Kohler, M.D.a	- Wishard Memorial Hospital, Indianapolis, IN; USA
Mark J. Kunkel, M.D.	- Danbury Hospital, Danbury, CT; USA
George Mestas, M.D.	- Clinical Study Center, Cape Coral, FL; USA
	- Clinical Study Center, Fort Myers, FL; USA
William Morowitz, M.D.	- The Delaware Valley Institute for Clinical Research, Cherry Hill, NJ; USA
Avi Nahum, M.D.a	- St. Paul Ramsey Medical Center, St. Paul, MN; USA
R. Dale Padgett, M.D.	- Bamberg, SC; USA
Richard H. Parker, M.D.a	- Providence Hospital, Washington, DC; USA
Alan R. Pollack, M.D.	- Rockville Internal Medical Group, Rockville, MD; USA
Philip J. Roos, M.D.a	- Jerry L. Pettis Memorial V.A. Hospital, Loma Linda, CA; USA
J. Daniel Scott, M.D.	- R/D Clinical Research, Inc., Lake Jackson, TX; USA
Judy Stone, M.D.	- Memorial Hospital and Medical Center of Cumberland, Inc., Cumberland, MD; USA
	- Hunt Club Medical Center, Ridgely, WV; USA
David W. Stryker, M.D.	- Albequerque, NM; Rio Rancho, NM; USA
James R. Taylor, M.D.	- Pulmonary Consultants, Tacoma, WA; USA
John Toney, M.D.	- James A. Haley VA Hospital, Tampa, FL; USA
James Wellman, M.D.	- Atlanta, GA; Deatur, GA; Tucker, GA; USA

[a] Did not enroll any subjects in the study. [b] Did not receive drug.

11. Study Population:

Approximately 380 subjects, men and women who were 18 years of age or older with a diagnosis of acute bacterial exacerbation of chronic bronchitis, were to be enrolled in this study to ensure 226 microbiologically evaluable subjects (113 per treatment group) for efficacy analysis. Subjects were enrolled according to the inclusion/exclusion criteria summarized below and described in detail in the protocol. Subjects with a diagnosis of acute bronchitis, pneumonia (as evidenced by acute infiltrates on the admission chest X-ray obtained within 12 hours prior to screening), or cystic fibrosis were not eligible for treatment under this protocol after the first amendment. Sixteen subjects with an admission diagnosis of pneumonia and approximately the same number of subjects without an admission diagnosis of chronic obstructive pulmonary disease (COPD) were enrolled prior to this amendment.

12. Efficacy as per sponsor:

12.1. Overview of Analysis Groups:

12.1.1. Demographics of Intent-to-treat Cohort:

Three hundred seventy-three subjects were enrolled in this study at 20 of the 27 centers (seven investigators did not enroll any subjects). The intent-to-treat group included 189 subjects who were randomized to the levofloxacin treatment group and 184 subjects who were randomized to the cefaclor treatment group. Two subjects randomized to receive levofloxacin actually received cefaclor; hence, the numbers of subjects who received levofloxacin and cefaclor were 187 and 186, respectively. Both subjects were clinically and microbiologically evaluable; thus, both are included in the analyses based on clinically evaluable subjects and those based on microbiologically evaluable subjects. The clinical response for these subjects was evaluated as "cured" and the microbiologic response as "eradicated". The demographic and baseline (admission) characteristics of the modified intent-to-treat group were comparable between the levofloxacin and cefaclor treatment groups. The mean age for all subjects was 60.5±14.7 years with a range of 19-89 years. Men accounted for 57.6% of all subjects enrolled and Caucasians for 94.1%. The majority (86.6%) of subjects had an initial diagnosis of COPD. There were no statistically significant differences (p=0.11) between the two treatment groups for any of the demographic features tested (i.e., age, sex, race) for any of the analysis groups.

Table 12.1.1.
Demographic and Baseline Characteristics:
Modified Intent-to-treat Cohort

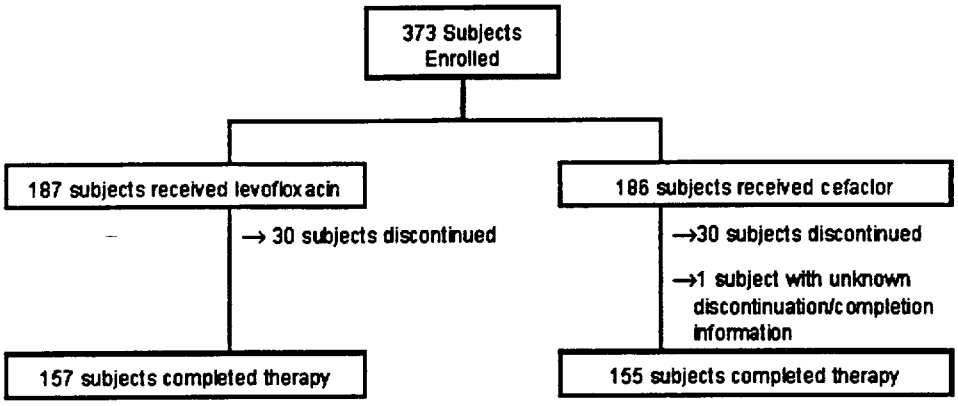
	Levofloxacin (N=187)		Cefaclor (N=186)		Total (N=373)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	107	(57.2)	108	(58.1)	215	(57.6)
Women	80	(42.8)	78	(41.9)	158	(42.4)
Race						
Caucasian	175	(93.6)	176	(94.6)	351	(94.1)
Black	7	(3.7)	5	(2.7)	12	(3.2)
Oriental	2	(1.1)	0	(0.0)	2	(0.5)
Hispanic	3	(1.6)	4	(2.2)	7	(1.9)
Other	0	(0.0)	1	(0.5)	1	(0.3)
Age (Years)						
≤45	38	(20.3)	34	(18.3)	72	(19.3)
46-64	65	(34.8)	63	(33.9)	128	(34.3)
≥65	84	(44.9)	89	(47.8)	173	(46.4)
Mean±SD	59.8±15.0		61.2±14.5		60.5±14.7	
Range	[redacted]		[redacted]		[redacted]	
Weight (lbs)						
N	184		183		367	
Mean±SD	167.7±42.3		165.0±42.1		166.4±42.2	
Range	[redacted]		[redacted]		[redacted]	
Missing	3		3		6	
COPD						
Yes	168	(89.8)	155	(83.3)	323	(86.6)
No	19	(10.2)	31	(16.7)	50	(13.4)

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.1.2. Discontinuation/Completion Information:

Of the 373 subjects enrolled in the study, 187 received levofloxacin and 186 received cefaclor (modified intent-to-treat group). As shown below, 30 (16.0%) subjects in the levofloxacin group discontinued therapy prematurely and 157 (84.0%) subjects completed therapy according to the regimen prescribed by the investigator. Of the 185 subjects in the cefaclor treatment group with known discontinuation/completion information, 30 (16.2%) discontinued therapy prematurely and 155 (83.8%) completed therapy. One subject in this group had unknown discontinuation/completion information.

Figure 12.1.2
Discontinuation/Completion Information: Modified Intent-to-treat Subjects



The most common reasons for therapy discontinuation were an adverse event and absence of an admission pathogen in the levofloxacin treatment group and clinical failure in the cefaclor treatment group. Absence of an admission pathogen was a reason for discontinuation of a subject from the study prior to the second protocol amendment that allowed subjects to continue in the study even if a pathogen was not isolated.

Table 12.1.2
Reasons for Premature Discontinuation: Modified Intent-to-Treat Subjects

	Levofloxacin (N=187)		Cefaclor (N=186)	
Reason	No.	(%)[a]	No.	(%)[a]
Adverse Event	12	(6.4)	6	(3.2)
No Admission Pathogen	12	(6.4)	9	(4.9)
Clinical Failure	5	(2.7)	12	(6.5)
Personal Reason	1	(0.5)	0	(0.0)
Resistant Pathogen	0	(0.0)	2	(1.1)
Other	0	(0.0)	1[b]	(0.5)
Total Discontinued	30	(16.0)	30	(16.2)
Total With Discontinuation/Completion Information	187	(100.0)	185	(100.0)
Total With Unknown Discontinuation/ Completion Information	0		1	

[a] Percentages based on total number with discontinuation/completion information.
[b] Subject received five doses of cefaclor and was dropped from the study after admission serum glucose results indicated that he should not have been enrolled in the study.

12.1.3. Demographics of Clinically and Microbiologically Evaluable Cohort(s):

One hundred fifty-four (82.4%) subjects in the levofloxacin treatment group and 155 (83.3%) subjects in the cefaclor treatment group were clinically evaluable. One hundred three (55.1%) subjects in the levofloxacin group and 89 (47.8%) subjects in the cefaclor 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 12.3.3.B, below. The main reasons that subjects were not clinically evaluable were insufficient course of therapy and inappropriate posttherapy clinical evaluation (levofloxacin group) and unconfirmed clinical diagnosis and insufficient course of therapy (cefaclor group), whereas the major reason that subjects were not microbiologically evaluable in the two treatment groups was absence of bacteriologically proven infection.

Table 12.1.3.A
Number of Subjects by Analysis Group and Study Center

	Levofloxacin			Cefaclor		
Investigator	Modified Intent-to-Treat	Clinical Efficacy	Microbiologic Efficacy	Modified Intent-to-Treat	Clinical Efficacy	Microbiologic Efficacy
Alwine	2	1 (50.0)	1 (50.0)	1	1 (100.0)	1 (100.0)
Anthony	1	1 (100.0)	1 (100.0)	1	1 (100.0)	0 (0.0)
Brankston	7	7 (100.0)	1 (14.3)	7	7 (100.0)	0 (0.0)
Farber	6	4 (66.7)	2 (33.3)	6	5 (83.3)	3 (50.0)
Fogarty	3	3 (100.0)	1 (33.3)	3	2 (66.7)	1 (33.3)
Gentry	29	28 (96.6)	18 (62.1)	31	31 (100.0)	19 (61.3)
Gilderman	7	3 (42.9)	3 (42.9)	7	5 (71.4)	4 (57.1)
Habib	33	31 (93.9)	22 (66.7)	34	29 (85.3)	17 (50.0)
Keller	2	2 (100.0)	2 (100.0)	0	0 –	0 –
Kunkel	2	0 (0.0)	0 (0.0)	3	0 (0.0)	0 (0.0)
Mestas	12	9 (75.0)	6 (50.0)	13	9 (69.2)	4 (30.8)
Morowitz	16	16 (100.0)	12 (75.0)	14	13 (92.9)	6 (42.9)
Padgett	12	6 (50.0)	2 (16.7)	12	7 (58.3)	2 (16.7)
Pollack	4	2 (50.0)	2 (50.0)	5	5 (100.0)	3 (60.0)
Scott	4	4 (100.0)	4 (100.0)	4	4 (100.0)	4 (100.0)
Stone	4	3 (75.0)	2 (50.0)	4	4 (100.0)	2 (50.0)
Stryker	9	7 (77.8)	6 (66.7)	10	8 (80.0)	6 (60.0)
Taylor	26	22 (84.6)	14 (53.8)	24	18 (75.0)	14 (58.3)
Toney	3	1 (33.3)	1 (33.3)	2	1 (50.0)	1 (50.0)
Wellman	5	4 (80.0)	3 (60.0)	5	5 (100.0)	2 (40.0)
Total	187	154 (82.4)	103 (55.1)	186	155 (83.3)	89 (47.8)

Numbers shown in parentheses are percentages for that category.

Table 12.1.3.B
Primary Reasons for Clinical or Microbiologic Nonevaluability: Sponsor's Modified Intent-to-Treat Cohort

Reasons	Levofloxacin (N=187)		Cefaclor (N=185)	
Clinical Efficacy				
Insufficient Course of Therapy	12		11	
Inappropriate Posttherapy Clinical Evaluation	11		6	
Clinical Diagnosis Unconfirmed	9		12	
Other Protocol Violation	1[a]		0	
Effective Concomitant Therapy	0		1	
Unevaluable for Safety	0		1	
Total Unevaluable For Clinical Efficacy	33	(17.6%)	31	(16.7%)
Microbiologic Efficacy				
Infection Not Bacteriological Proven	70		80	
Insufficient Course of Therapy	7		5	
Clinical Diagnosis Unconfirmed	4		6	
Inappropriate Bacteriologic Culture	2		4	
Other Protocol Violation	1[a]		0	
Effective Concomitant Therapy	0		1	
Unevaluable for Safety	0		1	
Total Unevaluable For Microbiologic Efficacy	84	(44.9%)	97	(52.2%)

[a] Subjects counted only once.
[b] Subject [redacted] took only one levofloxacin tablet (97.6 mg) per day.

The demographic and baseline characteristics of the subjects included in the clinically and microbiologically evaluable groups were comparable to the previously described modified intent-to-treat group with respect to age, sex, racial composition, and other baseline characteristics. The demographic and baseline characteristics of clinically evaluable and microbiologically evaluable subjects were comparable, with no statistically significant differences ($p^3 0.11$) between the two treatment groups.

Table 12.1.3.C
Demographic Characteristics: Sponsor's Clinically and Microbiologically Evaluable Patients

	Levofloxacin		Cefaclor	
	Clinically Evaluable (N=154)	Microbiologically Evaluable (N=103)	Clinically Evaluable (N=155)	Microbiologically Evaluable (N=89)
Sex				
Men	88	62	90	53
Women	66	41	65	36
Race				
Caucasian	144	96	151	86
Black	6	3	2	2
Oriental	2	2	0	0
Hispanic	2	2	1	0
Other	0	0	1	1
Age (Years)				
≤45	31	16	28	18
46-64	56	34	54	26
≥65	67	53	73	45
N	154	103	155	89
Mean±SD	59.7±14.8	62.1±14.0	61.1±14.0	60.8±14.5
Range	[redacted]	[redacted]	[redacted]	[redacted]
Weight (lbs)				
N	152	102	152	86
Mean±SD	166.4±41.8	162.6±39.9	164.5±41.2	163.1±45.8
Range	[redacted]	[redacted]	[redacted]	[redacted]
Missing	2	1	3	3
COPD				
Yes	142	96	136	79
No	12	7	19	10

NOTE: Values represent numbers of subjects unless otherwise indicated.
COPD = chronic obstructive pulmonary disease.

12.1.4. Extent of Exposure:

The mean duration of therapy was 6.6 days for levofloxacin-treated subjects and 8.7 days for cefaclor-treated subjects; the medians were 7 and 9, respectively. Six subjects reported dosing errors. Two subjects (3901 and 219) in the levofloxacin treatment group took only one levofloxacin tablet (97.6 mg) per day for four and seven days, respectively. The dosage was adjusted to five tablets per day for subject 3901. Prior to the first protocol amendment, one cefaclor-treated subject (405) took 250 mg cefaclor three times a day and after the first protocol amendment, three cefaclor-treated subjects (806, 918, and 4103) took 500 mg cefaclor three times a day.

Table 12.1.4
Extent of Exposure to Therapy: Sponsor's Intent-to-treat Subjects

Extent of Exposure	Levofloxacin (N=187)	Cefaclor (N=186)
Days on Therapy[a]		
Unknown	0	2
1	2	1
2	3	4
3	7	2
4	7	10
5	43	7
6	7	2
7	82	25
8	9	35
9	0	8
10	22	43
11	3	41
12	0	2
14	2	2
15	0	2
Mean±SD	6.6±2.1	8.7±2.5
Median	7	9
Number of Doses		
Total with Dosing Information	187	184
Total with Unknown Dosing Information	0	2
Mean±SD	6.5±2.1	24.1±7.6
Median	7	26
Range	1-14	1-42

NOTE: Levofloxacin had a q24h dosing schedule and cefaclor had a q8h dosing schedule.
[a] The original protocol specified the total planned duration of therapy for levofloxacin and cefaclor as seven to 14 days. The protocol was amended to specify 5 to 7 days of therapy for levofloxacin and 7 to 10 days for cefaclor. Days on therapy was defined as (last day - first day + 1).

12.1.5. Concomitant therapies:

With the exception of a larger percentage of cefaclor-treated subjects than levofloxacin-treated subjects taking CNS-acting drugs, comparable percentages of subjects in the levofloxacin and cefaclor treatment groups took these concurrent therapies.

Table 12.1.5
Summary of Concurrent Therapies: Modified Intent-to-Treat Subjects

	Levofloxacin (N=187)		Cefaclor (N=186)	
Therapy Classification	No.	(%)	No.	(%)
Total Who Took Concurrent Therapy	173	(92.5)	173	(93.0)
Central Nervous System*	74	(39.6)	96	(51.6)
Bronchodilators	56	(29.9)	67	(36.0)
Antacids	32	(17.1)	36	(19.4)
NSAID	21	(11.2)	19	(10.2)
Vitamins & Nutritional Supplements	10	(5.3)	12	(6.5)
Antimicrobials	5	(2.7)	8	(4.3)
Antidiabetic Therapy	4	(2.1)	6	(3.2)
Anticoagulants	1	(0.5)	8	(4.3)
Corticosteroids	0	(0.0)	1	(0.5)
Total with Concurrent Therapy Information	187		186	

* Besides the traditional central nervous system-acting drugs (antipsychotics, antidepressants, antiepileptics, hypnotics, sedatives, antiparkinson agents, opioid analgesics, and anesthetics), other drugs with secondary central nervous system effects were included.
See Appendices 10 and 11 for complete drug list.

12.2. Clinical Response

This section of the report focuses on results of the secondary efficacy, analyses of clinical response, based primarily on the group of subjects evaluable for clinical efficacy. The results from the other analysis groups were generally consistent with those from the clinically evaluable group.

12.2.1. Overall Clinical Response

Among clinically evaluable subjects in the levofloxacin treatment group, 72.1% were cured and 19.5% were improved, compared with 64.5% and 27.1% in the cefaclor treatment group. Thirteen (8.4%) subjects in each treatment group failed treatment. In the modified intent-to-treat group, levofloxacin treatment resulted in 62.6% cure, 26.2% improvement, and 9.6% failure; 1.6% of subjects could not be evaluated. Cefaclor treatment resulted in 59.1% cure, 29.0% improvement, and 10.2% failure; 1.6% of subjects could not be evaluated. Among modified intent-to-treat subjects with an admission pathogen, levofloxacin treatment resulted in 69.0% cure, 23.3% improvement, and 6.0% failure; 1.7% of subjects could not be evaluated. Cefaclor treatment resulted in 58.7% cure, 27.9% improvement, and 12.5% failure; 1.0% of subjects could not be evaluated. Similar results were found in the intent-to-treat group.

Table 12.2.1.A
Clinical Response Rate for Each Study Center:
Sponsor's Clinically Evaluable Subjects

	Levofloxacin				Cefaclor			
Investigator	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Alvine	1	1 (100.0)	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	0 (0.0)
Anthony	1	0 (0.0)	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	0 (0.0)
Brankston	7	2 (28.6)	5 (71.4)	0 (0.0)	7	1 (14.3)	6 (85.7)	0 (0.0)
Farber	4	3 (75.0)	1 (25.0)	0 (0.0)	5	2 (40.0)	3 (60.0)	0 (0.0)
Fogarty	3	3 (100.0)	0 (0.0)	0 (0.0)	2	1 (50.0)	0 (0.0)	1 (50.0)
Gentry	28	28 (100.0)	0 (0.0)	0 (0.0)	31	30 (96.8)	1 (3.2)	0 (0.0)
Gilderman	3	2 (66.7)	1 (33.3)	0 (0.0)	5	3 (60.0)	1 (20.0)	1 (20.0)
Habib	31	23 (74.2)	5 (16.1)	3 (9.7)	29	17 (58.6)	8 (27.6)	4 (13.8)
Keller	2	2 (100.0)	0 (0.0)	0 (0.0)	0	0 –	0 –	0 –
Mestas	9	9 (100.0)	0 (0.0)	0 (0.0)	9	8 (88.9)	1 (11.1)	0 (0.0)
Morowitz	16	11 (68.8)	1 (6.3)	4(25.0)	13	9 (69.2)	3 (23.1)	1 (7.7)
Padgett	6	6 (100.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	0 (0.0)
Pollack	2	1 (50.0)	1 (50.0)	0 (0.0)	5	0 (0.0)	4 (80.0)	1 (20.0)
Scott	4	3 (75.0)	1 (25.0)	0 (0.0)	4	3 (75.0)	1 (25.0)	0 (0.0)
Stone	3	2 (66.7)	1 (33.3)	0 (0.0)	4	3 (75.0)	1 (25.0)	0 (0.0)
Stryker	7	5 (71.4)	2 (28.6)	0 (0.0)	8	5 (62.5)	2 (25.0)	1 (12.5)
Taylor	22	9 (40.9)	8 (36.4)	5(22.7)	18	9 (50.0)	7 (38.9)	2 (11.1)
Toney	1	1 (100.0)	0 (0.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0 (0.0)
Wellman	4	0 (0.0)	3 (75.0)	1(25.0)	5	1 (20.0)	2 (40.0)	2 (40.0)
Combined*	57	40 (70.2)	16 (28.1)	1 (1.8)	64	35 (54.7)	23 (35.9)	6 (9.4)
Total	154	111 (72.1)	30 (19.5)	13 (8.4)	155	100 (64.5)	42 (27.1)	13 (8.4)

Numbers shown in parentheses are percentages for that category.
* Combined = centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Alvine, Anthony Brankston, Farber, Fogarty, Gilderman, Keller, Mestas, Padgett, Pollack, Scott, Stone, Stryker, Toney, and Wellman

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". Two-sided 95% confidence intervals around the difference in clinical success rates were calculated to evaluate therapeutic equivalence between treatments. Among clinically evaluable subjects, levofloxacin and cefaclor treatment each resulted in 91.6% clinical success, with a 95% confidence interval of [-6.5, 6.6] for the difference (cefaclor minus levofloxacin) in success rates. The upper limit of this confidence interval lies below the upper bound of 10% suggested by the FDA's Anti-Infective "Points to Consider" guideline for establishing clinical equivalence of treatments with success rates greater than 90%. The cure rates for the two treatment groups were also similar (72.1% for levofloxacin, 64.5% for cefaclor), with a 95% confidence interval on the difference in cure rates of [-18.2, 3.1]. In addition, the clinical success rates and cure rates were generally consistent regardless of sex or age. Given the small number of non-Caucasians in this study, no meaningful comparisons can be made based on race.

Table 12.2.1.B
Clinical Success/Failure Rates and Confidence Intervals by Study Center: Sponsor's Clinically Evaluable Subjects

	Levofloxacin			Cefaclor			
Investigator	N	Success[b]	Failure[b]	N	Success[b]	Failure[b]	95% Confidence Interval[a]
Alvine	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
Anthony	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
Brankston	7	7 (100.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	–
Farber	4	4 (100.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	–
Fogarty	3	3 (100.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	–
Gentry	28	28 (100.0)	0 (0.0)	31	31 (100.0)	0 (0.0)	(-1.8, 1.8)
Gilderman	3	3 (100.0)	0 (0.0)	5	4 (80.0)	1 (20.0)	–
Habib	31	28 (90.3)	3 (9.7)	29	25 (86.2)	4 (13.8)	(-22.1, 13.9)
Keller	2	2 (100.0)	0 (0.0)	0	0 –	0 –	–
Mestas	9	9 (100.0)	0 (0.0)	9	9 (100.0)	0 (0.0)	–
Morowitz	16	12 (75.0)	4 (25.0)	13	12 (92.3)	1 (7.7)	(-12.2, 46.8)
Padgett	6	6 (100.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	–
Pollack	2	2 (100.0)	0 (0.0)	5	4 (80.0)	1 (20.0)	–
Scott	4	4 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	–
Stone	3	3 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	–
Stryker	7	7 (100.0)	0 (0.0)	8	7 (87.5)	1 (12.5)	–
Taylor	22	17 (77.3)	5 (22.7)	18	16 (88.9)	2 (11.1)	(-13.9, 37.1)
Toney	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
Wellman	4	3 (75.0)	1 (25.0)	5	3 (60.0)	2 (40.0)	–
Combined[c]	57	56 (98.2)	1 (1.8)	64	58 (90.6)	6 (9.4)	(-16.4, 1.2)
Total	154	141 (91.6)	13 (8.4)	155	142 (91.6)	13 (8.4)	(-6.5, 6.6)

[a] Two-sided 95% confidence intervals around the difference (cefaclor 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: Alvine, Anthony, Brankston, Farber, Fogarty, Gilderman, Keller, Mestas, Padgett, Pollack, Scott, Stone, Stryker, Toney, and Wellman.

In the modified intent-to-treat group, the clinical success rate for treatment with levofloxacin was 88.8% and treatment with cefaclor was 88.2%. The corresponding rates for modified intent-to-treat subjects with an admission pathogen were 92.2% and 86.5%, respectively.

12.2.2. Clinical Response by Pathogen

Clinical response rates for clinically evaluable subjects infected with pathogens of interest alone or in combination with other pathogens are shown in Table 12. Among the pathogens of interest, H. influenzae, M. (Branhamella) catarrhalis, and H. parainfluenzae were the most prevalent pathogens across the two treatment groups. Clinical success rates (cured + improved) for the pathogens of interest listed in the table ranged from 84.2% (M. Branhamella catarrhalis) to 100% (H. parainfluenzae and S. aureus) for levofloxacin-treated subjects and from 66.7% (S. aureus) to 100% (M. catarrhalis and H. parainfluenzae) for cefaclor-treated subjects.

Table 12.2.2
Clinical Response Rates For Subjects with Pathogens of Primary Interest: Sponsor's Clinically Evaluable Subjects

	Levofloxacin				Cefaclor			
Pathogen	N*	Cured	Improved	Failed	N*	Cured	Improved	Failed
Haemophilus influenzae	21	12 (57.1)	8 (38.1)	1 (4.8)	24	13 (54.2)	8 (33.3)	3 (12.5)
Moraxella (Branhamella) catarrhalis	19	12 (63.2)	4 (21.1)	3 (15.8)	8	4 (50.0)	4 (50.0)	0 (0.0)
Haemophilus parainfluenzae	15	12 (80.0)	3 (20.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	0 (0.0)
Streptococcus pneumoniae	10	7 (70.0)	2 (20.0)	1 (10.0)	7	3 (42.9)	3 (42.9)	1 (14.3)
Staphylococcus aureus	9	6 (66.7)	3 (33.3)	0 (0.0)	3	2 (66.7)	0 (0.0)	1 (33.3)

Numbers shown in parentheses are percentages for that category.

* N=Number of subjects who had that pathogen alone or in combination with other pathogens.

12.2.3. Clinical Symptoms

The proportions of clinically evaluable subjects with resolution of clinical symptoms of bronchitis are presented in Table 13. In general, for both the levofloxacin and cefaclor treatment groups, there was clearing of individual symptoms from admission to posttherapy in approximately 60% or more subjects.

Table 12.2.3
Proportion of Subjects with Resolution of Clinically Symptoms of Bronchitis Based on Posttherapy Evaluation: Sponsor's Clinically Evaluable Subjects

	Levofloxacin		Cefaclor	
Symptom	Resolved*	(%)	Resolved*	(%)
Chills	57/ 60	(95.0)	66/ 72	(91.7)
Chest Pain	55/ 59	(93.2)	60/ 69	(87.0)
Shortness of Breath	80/127	(63.0)	78/133	(58.6)
Cough Increase	119/151	(78.8)	114/154	(74.0)
Sputum Increase	119/148	(80.4)	116/149	(77.9)
Purulent Sputum	117/136	(86.0)	116/136	(85.3)

* Symptom present at admission and absent at posttherapy evaluation.
* Denominator represents number of subjects with that symptom at admission.

12.3. Microbiologic Results

Microbiologic response was the primary efficacy variable in this study. The analyses of microbiologic response, based primarily on the group of subjects evaluable for microbiologic efficacy, are presented in detail in this section, with results of other analysis groups provided in the Supporting Data section at the end of the text and briefly described here. The results based on modified intent-to-treat and intent-to-treat subjects with an admission pathogen were generally consistent with those from the microbiologically evaluable group.

12.3.1. In Vitro Susceptibility

One hundred sixteen subjects in the levofloxacin treatment group and 104 subjects in the cefaclor treatment group had pathogens isolated at admission. The 116 levofloxacin-treated subjects had 157 pathogens with

known susceptibility and the 104 cefaclor-treated subjects had 117 pathogens with known susceptibility. As shown in Table 15, there were 154 (98.1%) pathogens isolated at admission from levofloxacin-treated subjects for moderately susceptible to levofloxacin and 89 (76.1%) pathogens isolated from cefaclor-treated subjects that were susceptible or moderately susceptible to cefaclor. The pathogens resistant to study drug received represented 1.9% and 23.9% of all isolates with known susceptibility from levofloxacin- and cefaclor-treated subjects.

Table 12.3.1.A
In vitro Susceptibility of All Pathogens isolated at Admission: Modified Intent-to-Treat Subjects with an Admission Pathogen

	No. (%)* of Pathogens			
Susceptibility of Pathogen	Levofloxacin		Cefaclor	
Susceptible	150	(95.5)	83	(70.9)
Moderately Susceptible	4	(2.5)	6	(5.1)
Resistant	3	(1.9)	28	(23.9)
Unknown	0		3	
Total No. Pathogens	157		120	

* Percentages were based on numbers of pathogens with known susceptibilities. Pathogens were isolated from 116 subjects in the levofloxacin group and 104 subjects in the cefaclor group.

One hundred eighty-six (67.9%) of 274 isolates with known susceptibility information for both levofloxacin and cefaclor were susceptible to both drugs; 270 (98.5%) isolates with known cross-susceptibilities were susceptible or moderately susceptible to levofloxacin and 207 (75.5%) isolates were susceptible or moderately susceptible to cefaclor. Resistance to both drugs was seen for one (0.4%) of the isolates. Three pathogens were levofloxacin-resistant and cefaclor-susceptible, while 66 pathogens were levofloxacin-susceptible or moderately susceptible and cefaclor-resistant. Cross-susceptibility to both drugs was unknown for three isolates.

Table 12.3.1.B
Cross-Susceptibility of Admission Isolated to Levofloxacin and Cefaclor: Modified Intent-to-Treat Subjects with an Admission Pathogen

		Cefaclor				
		S	M	R	U	
Levofloxacin	S	186	8	63	0	257
	M	8	2	3	0	13
	R	3	0	1	0	4
	U	0	0	0	3	3
		197	10	67	3	277

S = Susceptible, M = Moderate, R = Resistant, U = Unknown

One investigator (Gentry) enrolled subjects in Costa Rica. In vitro susceptibility to levofloxacin and cefaclor for pathogens isolated from Costa Rica was compared to those from the U.S. and Canada across all investigators. The distribution and susceptibility of key pathogens to both drugs were similar when comparing the data from Costa Rica and U.S./Canada.

12.3.2. Microbiologic Eradication Rates

12.3.2.1. Microbiologic Eradication Rates by Subject

Among microbiologically evaluable subjects in the levofloxacin treatment group the eradication rate was 94.2% (including 77.7% presumed eradication and 16.5% documented eradication) compared with 86.5% (including 76.4% presumed eradication and 10.1% documented eradication) in the cefaclor group, with a confidence interval of [-16.6, 1.3] for the difference (cefaclor minus levofloxacin) in eradication rates. The upper limit of this confidence interval lies below the upper bound of 10% suggested by the FDA's Anti-Infective "Points to Consider" guideline for establishing clinical equivalence of treatments with success rates greater than 90%. Six (5.8%) subjects in the levofloxacin treatment group and 12 (13.5%) subjects in the cefaclor group did not have their infection eradicated. Confidence intervals computed for each study center with 10 or more microbiologically evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers. The results observed for the microbiologically evaluable group that indicate equivalence between treatment groups were also generally observed across the various sex and age subgroups. Given the small number of non-Caucasians in this study, no meaningful comparisons can be made based on race. Among modified intent-to-treat subjects with an admission pathogen, levofloxacin treatment resulted in 89.7% eradication and 6.0% persistence; cefaclor treatment resulted in 82.7% eradication and 13.5% persistence. Confidence intervals were also computed to evaluate consistency across all analysis groups in microbiologic eradication rates. The individual confidence intervals for all other analysis groups are centered below zero and are consistent with equivalence of treatments in terms of microbiologic eradication rates.

Table 12.3.2.1
Microbiologic Eradication Rates and Confidence Intervals by Study Center: Sponsor's Microbiologically Evaluable Patients

	Levofloxacin			Cefador			
Investigator	N	Eradicated[a]	Persisted[a]	N	Eradicated[a]	Persisted[a]	95% Confidence Interval[b]
Alvine	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
Anthony	1	1 (100.0)	0 (0.0)	0	0 –	0 –	–
Brankston	1	1 (100.0)	0 (0.0)	0	0 –	0 –	–
Farber	2	2 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	–
Fogarty	1	1 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	–
Gentry	18	18 (100.0)	0 (0.0)	19	19 (100.0)	0 (0.0)	(-2.8, 2.8)
Gilderman	3	3 (100.0)	0 (0.0)	4	3 (75.0)	1 (25.0)	–
Habib	22	20 (90.9)	2 (9.1)	17	14 (82.4)	3 (17.6)	(-33.2, 16.1)
Keller	2	2 (100.0)	0 (0.0)	0	0 –	0 –	–
Mestas	6	6 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	–
Morowitz	12	10 (83.3)	2 (16.7)	6	5 (83.3)	1 (16.7)	–
Padgett	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	–
Pollack	2	2 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	–
Scott	4	4 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	–
Stone	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	–
Stryker	6	6 (100.0)	0 (0.0)	6	5 (83.3)	1 (16.7)	–
Taylor	14	12 (85.7)	2 (14.3)	14	9 (64.3)	5 (35.7)	(-56.1, 13.2)
Toney	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
Wellman	3	3 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	–
Combined[c]	49	47 (95.9)	2 (4.1)	39	35 (89.7)	4 (10.3)	(-18.5, 6.1)
Total	103	97 (94.2)	6 (5.8)	89	77 (86.5)	12 (13.5)	(-16.6, 1.3)

[a] Eradication of all pathogens isolated for a subject at admission.
[b] Two-sided 95% confidence interval around the difference (cefador minus levofloxacin) in microbiologic eradication rates were calculated for study centers enrolling 10 or more microbiologically evaluable subjects in each treatment group.
[c] Numbers shown in parentheses are percentages for that category.
[d] Combined = centers that enrolled fewer than 10 microbiologically evaluable subjects in either treatment group: Alvine, Anthony, Brankston, Farber, Fogarty, Gilderman, Keller, Mestas, Morowitz, Padgett, Pollack, Scott, Stone, Stryker, Toney, and Wellman.

12.3.2.2. Microbiologic Eradication Rates by Pathogen

The overall microbiologic eradication rates by pathogen in the levofloxacin and cefaclor were 95.0% and 86.5%, with a 95% confidence interval of [-16.4, -0.4], for the difference between treatments (cefaclor minus levofloxacin), assuming independence of multiple pathogens and multiple strains within a subject. This difference favors levofloxacin. The most prevalent pathogens for both levofloxacin and cefaclor treatment groups were gram-negative aerobes (84.2% and 86.5% of pathogens in the two treatment groups; the remaining pathogens were gram-positive aerobes 15.8% and 13.5% of pathogens in the two treatment groups). The microbiologic eradication rates for gram-negative and gram-positive aerobes in the levofloxacin treatment group were 95.7% and 90.9%, respectively. The corresponding eradication rates in the cefaclor treatment group were 86.7% and 85.7%. The most common pathogen, *H. influenzae*, was eradicated by levofloxacin in 100% of cases, compared with a 70.8% eradication rate with cefaclor treatment. There was 94.7% eradication of the second most common pathogen (*M. (Branhamella) catarrh allis*) and 93.3% eradication of the third most common pathogen (*H. parainfluenzae*) in the levofloxacin treatment group versus 100% for both pathogens in the cefaclor treatment group. There was 90.0% eradication of *S. pneumoniae* and 88.9% eradication of *S. aureus* in the levofloxacin treatment group versus 85.7% and 66.7% eradication of the second most common pathogen (*P. aeruginosa*) in the cefaclor treatment group versus 80.0% in the levofloxacin treatment group. No subject with susceptibility data available at posttherapy had microbiologic persistence of a pathogen that acquired resistance. In general, eradication rates were also comparable across the various sex and age subgroups.

Table 12.3.3.2

Microbiologic Evaluation Rates Summarized by Pathogen Category and Pathogen: Sponsor's Microbiologically Evaluable Patients

	Levofloxacin		Cefaclor		95% Confidence Interval[3]	
Pathogen Category/Pathogen	N	Eradicated[2]	N	Eradicated[2]		
Pathogen Category						
Gram positive aerobic pathogens	22	20 (90.9)	14	12 (85.7)	(-30.7,	20.3)
Gram negative aerobic pathogens	117	112 (95.7)	90	78 (86.7)	(-17.5,	-0.6)
Total by pathogen	139	132 (95.0)	104	90 (86.5)	(-16.4,	-0.4)
Total by subject	103	97 (94.2)	89	77 (86.5)	(-16.6,	1.3)
Pathogen[4]						
Haemophilus influenzae	21	21 (100.0)	24	17 (70.8)	(-49.7,	-8.6)
Moraxella (Branhamella) catarrhalis	19	18 (94.7)	8	8 (100.0)	-	-
Haemophilus parainfluenzae	15	14 (93.3)	7	7 (100.0)	-	-
Klebsiella pneumoniae	13	13 (100.0)	7	7 (100.0)	-	-
Pseudomonas aeruginosa	10	8 (80.0)	14	11 (78.6)	(-39.2,	36.4)
Streptococcus pneumoniae	10	9 (90.0)	7	6 (85.7)	-	-
Staphylococcus aureus	9	8 (88.9)	3	2 (66.7)	-	-
Klebsiella oxytoca	6	6 (100.0)	1	0 (0.0)	-	-
Escherichia coli	1	1 (100.0)	6	5 (83.3)	-	-

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

12.4. Pneumonia

Sixteen subjects (seven in the levofloxacin group and nine in the cefaclor group) had an admission diagnosis of pneumonia. The most common pathogens isolated were *C. pneumonia*, *S.* pneumoniae, and *H. influenzae*. One subject [redacted] had three pathogens isolated; the remainder had one or none. Five of six of the pathogens isolated in each of the treatment groups were eradicated. Six of seven levofloxacin-treated subjects and eight of nine cefaclor-treated subjects were cured or improved.

12.5. Superinfection

No subjects in the levofloxacin treatment group developed superinfections. Six subjects in the cefaclor treatment group developed superinfections and had the superinfecting organisms isolated during the posttherapy period. For these subjects, all of the isolates were susceptible or moderately susceptible to both levofloxacin and cefaclor.

Table 12.5
List of Subjects with Superinfections:
Sponsor's Modified Intent-to-Treat Cohort

Subject Number	Period	Pathogen	Type of Specimen	Susceptibility: Levofloxacin	Susceptibility: Cefaclor
Cefaclor					
	Posttherapy	*Haemophilus parainfluenzae*	Expectorate sputum	Susceptible	Susceptible
	Posttherapy	*Escherichia coli*	Expectorate sputum	Susceptible	Susceptible
	Posttherapy	*Moraxella (Branhamella) catarrhalis*	Expectorate sputum	Susceptible	Susceptible
	Posttherapy	*Haemophilus parainfluenzae*	Expectorate sputum	Susceptible	Susceptible
	Posttherapy	*Haemophilus influenzae*	Expectorate sputum	Moderate	Susceptible
	Posttherapy	*Haemophilus influenzae*	Expectorate sputum	Susceptible	Susceptible
	Posttherapy	*Streptococcus pneumoniae*	Expectorate sputum	Susceptible	Susceptible

Cross-reference: Appendix 16b; Tabulation 10a

12.6. Summary of Key Efficacy Results

Clinical success rates for the clinically evaluable group and two supportive modified intent-to-treat groups, and microbiologic eradication rates for microbiologically evaluable subjects and modified intent-to-treat subjects with an admission pathogen are summarized for the levofloxacin and cefaclor treatment groups in Table 12.6 on the following page. Within response category (microbiologic or clinical), the results are comparable among the analysis groups. Moreover, there is concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency and reliability of the clinical and microbiologic responses. The clinical and microbiologic results clearly demonstrate that levofloxacin is equivalent to cefaclor.

Table 12.6
Summary of Key Efficacy Results

Clinical and Microbiologic Response

Response/Group	Levofloxacin: Clinical Success or Microbiologic Eradication Rates[a]		Cefador: Clinical Success or Microbiologic Eradication Rates[a]		95% Confidence Interval[b]
Clinical Response					
Clinically Evaluable	141/154	(91.6)	142/155	(91.6)	(-6.5, 6.6)
Modified Intent-to-Treat	166/187	(88.8)	164/186	(88.2)	(-7.3, 6.2)
Modified Intent-to-Treat Subjects With an Admission Pathogen	107/116	(92.2)	90/104	(86.5)	(-14.4, 2.9)
Microbiologic Response					
Microbiologically Evaluable	97/103	(94.2)	77/89	(86.5)	(-16.6, 1.3)
Modified Intent-to-Treat Subjects With an Admission Pathogen	104/116	(89.7)	86/104	(82.7)	(-16.6, 2.7)

Microbiologic Response Versus Clinical Response[c]

	Clinical Response							
	Levofloxacin				Cefador			
Microbiologic Response	N	Cured[d]	Improved[d]	Failed[d]	N	Cured[d]	Improved[d]	Failed[d]
Eradicated	97	76 (78.4)	20 (20.6)	1 (1.0)	77	54 (70.1)	23 (29.9)	0 (0.0)
Persisted	6	1 (16.7)	2 (33.3)	3 (50.0)	12	1 (8.3)	3 (25.0)	8 (66.7)

[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 (cefador minus levofloxacin) in clinical success or microbiologic eradication rates.
[c] Based on microbiologically evaluable group.
[d] Cured, improved, or failed are clinical response outcomes.

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.

13. Efficacy as per Medical Officer:

13.1. Patient Population:

Of the sponsor's intent-to-treat cohort, the medical officer considered 85% (316/373) clinically evaluable according to the evaluability criteria outline under Section 11.2.1. Of the 316 clinically evaluable patients, the medical officer determined that 57% (179/316) of these were microbiologically evaluable. Of the clinically evaluable patients, 43% (137/316) were microbiologically unevaluable. The reasons for both clinical and microbiologic nonevaluability are summarized in a series of tables under section 13.1.2. The breakdown of the intent-to-treat cohort into evaluable subgroups is summarized in Table 13.1.A, below. These patients are further categorized by treatment group in Table 13.1.B.

Table 13.1.A
FDA Clinically and Microbiologically Evaluable Patients:
Breakdown as Subgroups of Sponsor's Intent-to-treat Cohort

FDA Clinically Evaluable		FDA Clinically Nonevaluable	
FDA Microbiologically Evaluable N (%)	FDA Microbiologically Nonevaluable N(%)	FDA Microbiologically Evaluable N(%)	FDA Microbiologically Nonevaluable N(%)
179 179/316 (57%) 179/373 (48%)	137 137/316 (43%) 137/373 (37%)	0	57 57/373 (15%)
316/373 (85%)		57/373 (15%)	
Intent-to-treat Cohort 373			

Table 13.1.B
FDA Clinically and Microbiologically Evaluable Patients:
Breakdown as Subgroups of Sponsor's Intent-to-treat Cohort

FDA Clinically Evaluable		FDA Clinically Nonevaluable	
FDA Microbiologically Evaluable N (%)	FDA Microbiologically Nonevaluable N(%)	FDA Microbiologically Evaluable N(%)	FDA Microbiologically Nonevaluable N(%)
179/316 (57%) Levofloxacin 98/179 (55%) Cefaclor 81/179 (45%)	137/316 (43%) Levofloxacin 60/137 (44%) Cefaclor 77/137 (66%)	0	57/57 (100%) Levofloxacin 29/57 (51%) Cefaclor 28/57 (49%)
FDA Clinically Evaluable 316/373 (85%) Levofloxacin 158/316 (50%) Cefaclor 158/316 (50%)		FDA Clinically Nonevaluable 57/373 (15%) Levofloxacin 29/57 (51%) Cefaclor 28/57 (49%)	
Intent-to-treat Cohort 373 Levofloxacin 187/373 (50%) Cefaclor 186/373 (50%)			

13.1.1. Demographics

13.1.1.1. Demographics of FDA Clinically and Microbiologically Evaluable Cohorts

Of the 316 patients in the FDA clinically evaluable patient cohort, 185 (59%) were female and 131 (42%) were male. This is similar to the distribution found in the intent-to-treat cohort, as summarized in Table 12.1.2. In the cohort of 179 patients who were both clinically and microbiologically evaluable, there were 109 (61%) males and 70 (42%) females. The distribution among racial groups was similar for both cohorts, and this was similar to the distribution in the intent-to-treat cohort. Likewise, the age distribution in the clinically and clinically/microbiologically evaluable cohorts was similar to that in the intent-to-treat cohort.

Table 13.1.1.A
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts

	FDA Clinically Evaluable Patients N (%)		FDA Clinically and Microbiologically Evaluable Patients N (%)	
TOTAL	316/373	(85%)	57/373	(15%)
Sex				
M	185/316	(59%)	109/179	(61%)
F	131/316	(42%)	70/179	(39%)
Race				
Caucasian	298/316	(94%)	169/179	(94%)
Black	11/316	(3.5%)	5/179	(2.8%)
Hispanic	4/316	(1.3%)	3/179	(1.7%)
Asian	2/316	(0.6%)	2/179	(1.1%)
Other	1/316	(0.3%)	0/179	(0%)
Age (yrs)				
≤45	64	(20%)	33	(18%)
46-64	110	(35%)	56	(31%)
≥65	142	(45%)	90	(50%)

13.1.1.2. Demographics of FDA Clinically and Microbiologically Evaluable Cohorts: Analysis by Treatment Groups

The demographics of the clinically evaluable and clinically and microbiologically evaluable patient groups are further subdivided by treatment group in Table 13.1.1.2, on the following page. The distribution of demographic variables for all subgroups remains comparable to that in the intent-to-treat cohort described under Section 12.1.2.

Table 13.1.1.2
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts:
Analysis by Treatment Group

	FDA Clinically Evaluable Patients N (%)			FDA Clinically and Microbiologically Evaluable Patients N (%)		
	ALL	LEVO	CEFACLOR	ALL	LEVO	CEFACLOR
TOTAL	316/373 (85%)	158/316 (50%)	158/316 (50%)	179/373 (15%)	98/179 (55%)	81/179 (45%)
Sex						
M	185 (59%)	92 (58%)	93 (59%)	109 (61%)	60 (61%)	49 (60%)
F	131 (42%)	66 (42%)	65 (41%)	70 (39%)	38 (39%)	32 (40%)
Race						
Caucasian	298 (94%)	147 (93%)	151 (96%)	169 (94%)	91 (93%)	78 (98%)
Black	11 (3.5%)	7 (4.4%)	4 (2.6%)	5 (2.8%)	3 (3%)	2 (2.5%)
Hispanic	4 (1.3%)	2 (1.3%)	2 (1.3%)	3 (1.7%)	2 (2%)	1 (1.7%)
Asian	2 (0.6%)	2 (1.3%)	0 (0%)	2 (1.1%)	2 (2%)	0 (0%)
Other	1 (0.3%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Age (yrs)						
≤45	64 (20%)	34 (22%)	30 (19%)	33 (18%)	16 (16%)	17 (20%)
46-64	110 (35%)	55 (35%)	55 (35%)	56 (31%)	32 (33%)	24 (21%)
≥65	142 (45%)	69 (44%)	73 (46%)	90 (50%)	50 (51%)	40 (49%)

13.1.2. Reasons for Nonevaluability

13.1.2.1. Reasons for Clinical Nonevaluability

Of the sponsor's intent-to-treat cohort, the medical officer considered 15% (57/373) clinically unevaluable according to the evaluability criteria outline under Section 11.2.1.. The reasons for nonevaluability in the remaining 16% are summarized in the tables below: Table 13.1.2.1.A contains an analysis for the entire cohort of FDA medical officer's clinically unevaluable patients, whereas Table 13.1.2.1.B contains only those patients in which the medical officer differed with the sponsor in the evaluability assessment.

Table 13.1.2.1.A
Reasons for Clinical Nonevaluability: ALL FDA Nonevaluable Patients

Reason for Nonevaluability	Total N	LEVO N	Cefaclor N	Subgroups of Reasons for Nonevaluability
Inappropriate clinical evaluation date	11	7	4	
Insufficient Course of therapy	24	12	12	
Clinical Diagnosis Unconfirmed	19	9	10	17 with infiltrates on chest X-ray consistent with pneumonia
Unevaluable for safety	2	2	--	
Protocol violation	1	--	1	H/O Seizure disorder
Clinical Nonevaluability **TOTAL Reasons** **TOTAL Patients**	 57 57	 30 30	 27 27	

Table 13.1.2.1.B.
Reasons for Clinical Nonevaluability:
Patients Evaluable by Sponsor but Nonevaluable by FDA

Reason for Nonevaluability	Total N	LEVO N	Cefaclor N	Subgroups of Reasons for Nonevaluability
Unevaluable for safety	1	1	--	No admission laboratories
Protocol violation	1	--	1	History of Seizure Disorder
Insufficient Course of therapy	2	--	2	
Clinical Diagnosis Unconfirmed	1	1	--	Pneumonia
TOTAL Reasons **TOTAL Patients**	5 5	2 2	3 3	

Preliminary statistical analysis revealed a substantially higher clinical success rate (combined group of clinically cured and improved) for patient receiving levofloxacin for 7-10 days (98.1%), as compared to 5-7 days (92.1%). Patients who received levofloxacin for 5 days had a clinical success rate of 83% and those who received levofloxacin for 6 days had a clinical cure rate of 75%. Thus, the final FDA evaluable patient cohort used in the statistical analysis contained only patients receiving levofloxacin for 7-10 days and cefaclor for 7-14 days. There were thus 94 patients made nonevaluable by these new criteria: 63 in the levofloxacin arm and 31 in the cefaclor arm. This final FDA evaluable patient group is described in Table 13.1.2.1.C below.

Table 13.1.2.1.C
Reasons for Clinical Nonevaluability: ALL FDA Nonevaluable Patients receiving Levofloxacin for 7-10 days and Cefaclor for 7-14 days

Reason for Nonevaluability	Total N	LEVO N	Cefaclor N	Subgroups of Reasons for Nonevaluability
Inappropriate clinical evaluation date				
Original Evaluability Criteria	11	7	4	
Final Evaluability Criteria				
<4 days post-therapy	42	19	23	
>8 days post-therapy	13	7	6	
Total removed from final cohort	66	33	33	
Insufficient course of therapy				
Original Evaluability Criteria	24	12	12	
Final Evaluability Criteria				
Levo <7 days or Cefaclor <7 days	61	49	12	
Levo >10 days or Cefaclor >14 days	3	2	1	
Total removed from final cohort	88	63	25	
Clinical Diagnosis Unconfirmed	19	9	10	**17 with infiltrates on chest X-ray consistent with pneumonia**
Unevaluable for safety	2	2	--	
Protocol violation	1	--	1	H/O Seizure disorder
Clinical Nonevaluability				
TOTAL Reasons	176	107	69	
TOTAL Patients	151	92	59	

13.1.2.2. Reasons for Microbiologic Nonevaluability

Of the 316 clinically evaluable patients, the medical officer determined that 57% (179/316) of these were microbiologically evaluable. Of the clinically evaluable patients, 63% (197/316) were microbiologically unevaluable. The reasons for microbiologic nonevaluability are listed by treatment group in Table 13.1.2.2 below. Please note that Table 13.1.2.2 summarizes the FDA microbiologically nonevaluable patient group PRIOR to the dosing duration restriction. The FDA statistician was unable to provide the medical officer with the number of patients that were removed from the microbiologically evaluable patient pool by each of the modifications in the evaluability criteria. **The final microbiologically evaluable cohort consisted of 126 patients: 61 levofloxacin-treated patients and 65 cefaclor-treated patients.**

Table 13.1.2.2
Reasons for Microbiologic Nonevaluability: All Admission Pathogens
FDA Original Evaluability Criteria

	Clinically Evaluable/ Microbiologically Unevaluable			Clinically and Microbiologically Unevaluable		
	ALL	LEVO	CEFACLOR	ALL	LEVO	CEFACLOR
No Admission Pathogen	123	55	68	28	15	13
Clinical Diagnosis Unconfirmed	--	--	--	11	4	7
Drug Therapy Insufficient duration of therapy	--	--	--	13	7	6
Protocol Violation Inappropriate Bacteriologic Culture Seizure Disorder	1 --	0 --	1 --	4 1	2 --	2 1
Residual Sputum at Posttherapy Visit not Cultured	13	5	8	--	--	--
Total: Microbiologically Nonevaluable Patients FDA Evaluable Patients: All Microorganisms	137	60	77	57	29	28
Total: Microbiologically Nonevaluable Patients FDA Evaluable Patients: All Microorganisms	137			57		
	194					

** Admission microorganism was not one of the four organisms accepted as pathogens in acute exacerbation of chronic bronchitis for purposes of this review. This review contains three analyses of efficacy data with (1) all pathogens, (2) only the subgroup of patients with the accepted four pathogens (*S. pneumo, S. aureus, H. flu, M. cat*) and (3) only the subgroup of patients with the accepted three pathogens (*S. pneumo, H. flu, M. cat*).
*** Total number of patients with *S. aureus* isolated on admission was 41, of these, 22 were microbiologically evaluable, 7 were microbiologically unevaluable, and 12 were isolated as part of polymicrobial infections and, therefore considered contaminants for the purposes of this analysis.

13.2. Clinical Efficacy:

Using the medical officer's clinical evaluability criteria delineated in Section 11.2.1 of this review, a total of 316 clinically evaluable patients were selected from the intent-to-treat cohort: 158 levofloxacin-treated patients and 158 cefaclor-treated patients. As specified by Protocol Amendment #1, dated June 1, 1992, the dosage duration for levofloxacin was shortened from the original 7-10 day to 5-7 days. As discussed above, on preliminary analysis by the FDA, there was found a substantially higher clinical success/clinical cure rate in the patients treated with levofloxacin for 7-10 days as compared to those treated from 5-7 days. Thus, under the direction of the supervisory medical officer, the evaluable patient cohort was limited to those who had received levofloxacin for 7-10 days and cefaclor for 7-14 days. The remainder of the efficacy analysis was conducted on this more narrowly defined patient cohort.

The overall cure rate at the posttherapy evaluation was 65% (62/95) for the levofloxacin-treated cohort and 58% (74/127) for the cefaclor-treated cohort. The 95% confidence interval around the difference in the overall clinical cure rates was $_{127,95}(-20.8,6.8)_{58\%,65\%}$ [3], indicating statistical equivalence of the cure rates of the two-treatments. Cure rates by investigator are summarized in Table 13.2.A, below.

Table 13.2.A
Posttherapy Clinical Cure Rates By Investigator:
FDA Clinically Evaluable Subjects

	Levofloxacin						Cefaclor					
Investigator	N[a]	Cure		Improve		Fail	N	Cure		Improve		Fail
Gentry	24	24	(100)	0	(0)	0 (0)	30	29	(97)	1	(3)	0 (0)
Taylor	15	3	(20)	10	(67)	2 (13)	15	5	(33)	9	(60)	1 (7)
Other	56	35	(63)	21	(38)	0 (0)	82	40	(49)	39	(48)	3 (4)
Total	95	62	(65)	31	(33)	2 (2)	127	74	(58)	49	(39)	4 (3)

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".
The difference in overall cure rates for all centers combined was not statistically significant in FDA's microbiologically evaluable patient group and the drugs are considered therapeutically equivalent; 95% confidence interval for cefaclor minus levofloxacin $_{127,95}(-20.8, 6.8)_{58\%,65\%}$.

[3] Dr. Nancy Silliman, Statistical Review of NDA 20-634 and 20-635.

If the clinically cured and clinically improved patients are grouped into one category of "clinical success", the levofloxacin-treated patients had an overall success rate of 98% (93/95) and the cefaclor-treated patients had an overall success rate of 97% (123/127). Overall success rates by investigator are summarized in Table 13.2.B, below. The 95% confidence intervals for (1) individual investigators and (2) the overall clinically evaluable cohort all overlapped zero.

Table 13.2.B
Posttherapy Clinical Success Rates By Investigator:
FDA Clinically Evaluable Subjects

Investigator	Levofloxacin		Cefaclor		95% Confidence Interval[c]
	N[a]	Success[b]	N	Success	
Gentry	24	24 (100)	30	30 (100)	N/A
Taylor	15	13 (87)	15	14 (93)	(-21.3, 34.7)
Other	56	56 (100)	82	79 (96)	(-9.2, 1.9)
Total	95	93 (98)	127	123 (97)	(-6.2, 4.1)

[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 (cefaclor minus levofloxacin) in clinical success rate.

13.2. Microbiologic Efficacy

Using the medical officer's clinical and microbiologic evaluability criteria delineated in Sections 11.2.1 and 11.2.2 of this review, a total of 179 patients were both clinically and microbiologically evaluable. With the addition of the dosing duration criteria to the evaluability criteria, this number was reduced to 126 subjects, 61 in the levofloxacin arm and 65 in the cefaclor arm. The FDA "Points-to-consider" recommendations for the development of antibiotics for the treatment of acute exacerbation of chronic bronchitis does not include recommendations of specific numbers of isolates for individual pathogens.

The clinical cure rates by pathogen for the *the pathogens requested by the sponsor in their proposed package insert* are listed in Table 13.2.A, below. The total number of pathogens in each category is limited, mainly as a result of the restricted evaluable patient pool defined by the dosing duration restriction applied after the preliminary analysis. The clinical success (cured and improved) rates are acceptable for all pathogens requested by the sponsor. However, the cure rates are suboptimal for *H. influenzae* and *Moraxella catarrhalis* and are borderline for *S. aureus*.

Table 13.2.A
Poststudy Clinical Cure Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects

	Levofloxacin				Cefaclor			
Pathogen	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Haemophilus influenzae	14	4 (29)	10 (71)	0 (0)	19	8 (42)	10 (53)	1 (5)
Haemophilus parainfluenzae	4	4 (100)	0 (0)	0 (0)	8	4 (50)	4 (50)	0 (0)
Moraxella catarrhalis	10	5 (50)	4 (40)	1 (10)	4	2 (50)	2 (50)	0 (0)
Staphylococcus aureus	4	3 (75)	1 (25)	0 (0)	2	1 (50)	1 (50)	0 (0)
Streptococcus pneumoniae	9	7 (78)	2 (22)	0 (0)	5	3 (60)	2 (40)	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.
As noted previously, there were no quantitative cultures included as part of this protocol. Therefore, it is unknown whether or not the cure rates and eradication rates for *S. aureus* represent isolates with a CFU count that were actually below the breakpoint for *S. aureus* as a pathogen.

The microbiologic eradication rates by pathogen for the major categories of respiratory pathogens and *the pathogens requested by the sponsor in their proposed package insert* are listed in Table 13.2.B, below. The microbiologic eradication rates are acceptable for all pathogens requested by the sponsor, although the 75% eradication rate for *S. aureus* is on the low end of the acceptable range.

Table 13.2.B
Overall Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects[a]

Pathogen Category/Pathogen	Levofloxacin		Cefaclor		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	14	12 (86)	9	9 (100)	-
Gram-negative aerobic pathogens	60	56 (93)	64	57 (89)	(-15.8, 7.3)
Total by pathogen	74	68 (92)	73	66 (90)	(-12.0, 9.1)
Total by subject	61	57 (93)	65	58 (89)	(-15.6, 7.1)
Pathogen					
Haemophilus influenzae	12	11 (92)	17	13 (76)	(-47.8, 17.4)
Haemophilus parainfluenzae	4	4 (100)	4	4 (100)	-
Moraxella catarrhalis	10	10 (100)	4	4 (100)	-
Staphylococcus aureus	4	3 (75)	2	2 (100)	-
Streptococcus pneumoniae	8	7 (88)	5	5 (100)	-

[a]Numbers shown in parentheses are percentages for that category.
[b]A two-sided confidence interval for the difference (cefaclor minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Table 13.2.B
Microbiologic Eradication Rates and Confidence Intervals By Investigator: FDA Microbiologically Evaluable Subjects

Investigator	Levofloxacin		Cefaclor		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Gentry	14	14 (100)	19	19 (100)	N/A
Taylor	10	8 (80)	12	8 (67)	(-58.9, 32.2)
Other	37	35 (95)	34	31 (91)	(-18.2, 11.4)
Total	61	57 (93)	65	58 (89)	(-15.6, 7.1)

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

13.4. Overall Success Rates:

The overall success (clinical cure or improvement plus microbiologic eradication) rates for the FDA microbiologically evaluable patient cohort are summarized by investigator in Table 13.3, below. The overall success rate was 92%, for the levofloxacin-treated arm and 91% for the cefaclor-treated arm. In all cases, the confidence interval around the difference between the overall success rate of each treatment groups overlaps zero, indicating statistical equivalence of the two treatments and no bias introduced into the overall outcome by an anomalous result at the major treatment centers.

Table 13.3
Overall Success Rates[a] and Confidence Intervals By Study Center:
FDA Microbiologically AND Clinically Evaluable Subjects

Investigator	Levofloxacin		Cefaclor		95% Confidence Interval[d]
	N[b]	Overall Success[c]	N	Overall Success	
Gentry	14	14 (100)	19	19 (100)	N/A
Taylor	10	7 (70)	12	8 (67)	(-51.5, 44.8)
Other	37	35 (95)	33	31 (94)	(-14.4, 13.1)
Total	61	56 (92)	64	58 (91)	(-12.7, 10.3)

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

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	N[b]	Overall Success[c]	N	Overall Success	
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Taylor	10	7 (70)	12	8 (67)	(-51.5, 44.8)
Other	37	35 (95)	33	31 (94)	(-14.4, 13.1)
Total	61	56 (92)	64	58 (91)	(-12.7, 10.3)

[a]Overall success is defined as clinical cure or improvement with microbiologic eradication.
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	N[b]	Overall Success[c]	N	Overall Success	
Gentry	14	14 (100)	19	19 (100)	N/A
Taylor	10	7 (70)	12	8 (67)	(-51.5, 44.8)
Other	37	35 (95)	33	31 (94)	(-14.4, 13.1)
Total	61	56 (92)	64	58 (91)	(-12.7, 10.3)

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

13.4. Overall Success Rates:

The overall success (clinical cure or improvement plus microbiologic eradication) rates for the FDA microbiologically evaluable patient cohort are summarized by investigator in Table 13.3, below. The overall success rate was 92%, for the levofloxacin-treated arm and 91% for the cefaclor-treated arm. In all cases, the confidence interval around the difference between the overall success rate of each treatment groups overlaps zero, indicating statistical equivalence of the two treatments and no bias introduced into the overall outcome by an anomalous result at the major treatment centers.

Table 13.3
Overall Success Rates[a] and Confidence Intervals By Study Center:
FDA Microbiologically AND Clinically Evaluable Subjects

Investigator	Levofloxacin			Cefaclor			95% Confidence Interval[d]
	N[b]	Overall Success[c]		N	Overall Success		
Gentry	14	14	(100)	19	19	(100)	N/A
Taylor	10	7	(70)	12	8	(67)	(-51.5, 44.8)
Other	37	35	(95)	33	31	(94)	(-14.4, 13.1)
Total	61	56	(92)	64	58	(91)	(-12.7, 10.3)

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

14. Safety Results as per Sponsor:

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any postadmission data were available. Subjects were classified according to the drug that was received. All but one of the 373 subjects enrolled were evaluated for safety. Of the 372 subjects, 187 received levofloxacin and 185 received cefaclor. One subject (1912) in the cefaclor treatment group was lost to follow-up with no postadmission data available and therefore excluded from the safety analysis.

14.2. Overview of Safety Data

The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal (GI) system, central and peripheral nervous system, and body as a whole, and consisted primarily of nausea, headache, insomnia, abdominal pain, and diarrhea. The nature and frequency of adverse events were generally comparable across the two treatment groups, except for a higher incidence of insomnia in the levofloxacin group (4.3%) than in the cefaclor group (1.1%) and small differences between treatments in some specific GI events. Although not a statistically significant difference, the incidence of central and peripheral nervous system adverse events was greater in the levofloxacin group (9.1%) than in the cefaclor group (5.4%); adverse events reported by levofloxacin-treated subjects in this body system consisted primarily of headache and dizziness. The body system with the highest reported incidence of adverse events for both treatment groups (17.1% for levofloxacin and 15.1% for cefaclor) was the gastrointestinal system.

Of the 16 subjects with adverse events considered marked in severity, seven subjects were in the levofloxacin treatment group and nine subjects were in the cefaclor treatment group. Thirteen (7.0%) levofloxacin-treated subjects and nine (4.9%) cefaclor-treated subjects had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug. Of the two subjects with marked drug-related adverse events, one was in the levofloxacin treatment group (abdominal pain) and one was in the cefaclor treatment group (diarrhea). Eighteen (4.8%) subjects discontinued study drug due to adverse events, 12 (6.4%) subjects in the levofloxacin treatment group and six (3.2%) subjects in the cefaclor treatment group. In the levofloxacin group, all of the adverse events leading to discontinuation emerged within the first five days of therapy; these adverse events included primarily gastrointestinal complaints or central and peripheral nervous system-related symptoms. Treatment-limiting adverse events in the cefaclor group most frequently consisted of gastrointestinal complaints. Two subjects in the levofloxacin treatment group and eight subjects in the cefaclor treatment group reported serious or potentially serious adverse events, all of which were unrelated or remotely related to the study drug and, in many cases, appeared to be related to the subject's underlying respiratory condition. One levofloxacin-treated subject and one cefaclor-treated subject died approximately three weeks after completing study therapy. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs occurred infrequently and were comparable across treatment groups.

14.3. Treatment-Emergent Adverse Events

Sixty-four (34.2%) of 187 safety-evaluable subjects in the levofloxacin treatment group and 62 (33.5%) of 185 safety-evaluable subjects in the cefaclor treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. The body system with the highest reported incidence of adverse events for both treatment groups (17.1% for levofloxacin and 15.1% for cefaclor) was the gastrointestinal system. The body system with the second highest reported incidence of adverse events for the levofloxacin treatment group was central and peripheral nervous system and for the cefaclor treatment group was body as a whole. The incidence of adverse events in these two body systems was approximately one-half that observed for the gastrointestinal system. The frequency of adverse events was comparable across the two treatment groups for all body systems with the exception of the central and peripheral nervous system and psychiatric disorders. Although not statistically significantly different, a higher percentage of levofloxacin-treated subjects compared with cefaclor-treated subjects reported psychiatric and central and peripheral nervous system adverse events. For the levofloxacin group, adverse events in these body systems consisted primarily of headache, dizziness, and insomnia. The overall proportions of subjects experiencing an adverse event were 34.2% and 33.5% for levofloxacin- and cefaclor-treated subjects, respectively, with a confidence interval of [-10.6, 9.2] for the difference between treatments. The 95% confidence interval included zero, indicating no statistically significant difference. All body systems had confidence intervals that included zero, indicating no statistically significant differences in frequency.

Table 14.3A
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol N93-006)

Body System	Levofloxacin (N=187) N	(%)	Cefaclor (N=185) N	(%)	95% Confidence Interval*
Gastrointestinal System Disorders	32	(17.1)	28	(15.1)	(-9.7, 5.8)
Central & Peripheral Nervous System Disorders	17	(9.1)	10	(5.4)	(-8.2, 1.8)
Body as a Whole–General Disorders	13	(7.0)	15	(8.1)	(-4.5, 6.8)
Psychiatric Disorders	11	(5.9)	7	(3.8)	(-6.7, 2.9)
Skin and Appendages Disorders	6	(3.2)	6	(3.2)	(-3.8, 3.9)
Musculo-Skeletal System Disorders	5	(2.7)	4	(2.2)	(-3.9, 2.9)
Respiratory System Disorders	5	(2.7)	8	(4.3)	(-2.4, 5.7)
Vision Disorders	3	(1.6)	1	(0.5)	(-3.4, 1.3)
Metabolic and Nutritional Disorders	3	(1.6)	2	(1.1)	(-3.1, 2.1)
Special Senses (Other), Disorders	2	(1.1)	0	(0.0)	(-2.8, 0.7)
Vascular (Extracardiac) Disorders	1	(0.5)	1	(0.5)	(-1.8, 1.8)
Resistance Mechanism Disorders	0	(0.0)	3	(1.6)	(-0.5, 3.7)
Urinary System Disorders	0	(0.0)	2	(1.1)	(-0.7, 2.8)
Reproductive Disorders, Female	0	(0.0)	2	(2.6)	(-1.6, 6.7)
Autonomic Nervous System Disorders	0	(0.0)	1	(0.5)	(-0.8, 1.9)
Platelet, Bleeding & Clotting Disorders	0	(0.0)	1	(0.5)	(-0.8, 1.9)
Total With Adverse Events (%)	64	(34.2)	62	(33.5)	(-10.6, 9.2)

* Two-sided 95% confidence interval around the difference (cefaclor minus levofloxacin) in incidence of adverse events.
* Percentages calculated from a total number of women in each treatment group. The total number of women who received levofloxacin was 80 and the total number of women who received cefaclor was 78.

Although similar percentages of levofloxacin-treated and cefaclor-treated subjects reported gastrointestinal adverse events overall, the incidence of specific gastrointestinal complaints showed small differences between treatments; some adverse events (e.g., nausea, flatulence, and dyspepsia) were more common in the levofloxacin group, while others (e.g., diarrhea and abdominal pain) had a higher incidence in the cefaclor group. In the other body systems, headache and insomnia were among the most common adverse events with levofloxacin-treated subjects showing a higher incidence of insomnia (4.3%) and headache (4.8%) compared with cefaclor-treated subjects (1.1% and 3.8%, respectively). The two treatment groups were generally comparable with respect to the type and incidence of other adverse events.

Table 14.3B
Incidence of Frequently Reported Adverse Events (≥2%)
Summarized by Primary Term: Subjects Evaluable for Safety

	Levofloxacin (N=167)		Cefaclor (N=165)	
Body System/Primary Term	N	(%)	N	(%)
All Body Systems	64	(34.2)	62	(33.5)
Gastrointestinal System Disorders				
Nausea	12	(6.4)	6	(3.2)
Diarrhea	6	(3.2)	12	(6.5)
Flatulence	5	(2.7)	2	(1.1)
Dyspepsia	4	(2.1)	1	(0.5)
Vomiting	3	(1.6)	4	(2.2)
Abdominal Pain	2	(1.1)	9	(4.9)
Central & Peripheral Nervous System Disorders				
Headache	9	(4.8)	7	(3.8)
Psychiatric Disorders				
Insomnia	8	(4.3)	2	(1.1)
Musculo-Skeletal System Disorders				
Myalgia	4	(2.1)	4	(2.2)
Body As A Whole–General Disorders				
Fever	0	(0.0)	4	(2.2)
Reproductive Disorders, Female[b]				
Vaginitis	0	(0.0)	2	(2.6)

[a] Primary term reported by ≥2% of subjects in either treatment group
[b] Percentages calculated from a total number of women in each treatment group. The total number of women who received levofloxacin was 80 and the total number of women who received cefaclor was 7[illegible]

The majority of adverse events were assessed as mild in severity. Seven subjects in the levofloxacin treatment group reported one or more adverse events of marked severity. Nine subjects in the cefaclor treatment group reported one or more marked adverse events, including respiratory disorders (exacerbation of COPD or respiratory insufficiency) in four subjects and diarrhea in two subjects. Most of the marked adverse events were considered by the investigator as unrelated or remotely related to the study drug. Of the two subjects with marked drug-related (probably or definitely related to study drug) adverse events, one was in the levofloxacin treatment group (abdominal pain) and one was in the cefaclor treatment group (diarrhea). Seven of the 16 subjects with marked adverse events discontinued study drug treatment (four subjects in the levofloxacin treatment group and three subjects in the cefaclor treatment group). Of these seven subjects, the adverse event was considered serious or potentially serious in one levofloxacin-treated subject and two cefaclor-treated subjects. Five additional subjects who did not discontinue the study (all in the cefaclor group) had marked adverse events that were considered serious or potentially serious. Thirteen (7.0%) subjects in the levofloxacin treatment group and nine (4.9%) subjects in

the cefaclor 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 nausea (2.1%), flatulence (1.6%), insomnia (1.1%), abdominal pain ≥1.0% of cefaclor-treated subjects were diarrhea (2.2%), vaginitis (1.3%), and abdominal pain (1.1%).

Table 14.3C
Subjects with Adverse Events of Marked Severity:
Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship to Drug[a]
Levofloxacin				
	79	F	Malaise	Possible
	59	F	Chest Pain	Remote
	70	F	Hypokalemia‡	None
			Vomiting‡	Remote
	69	M	Gastritis	Possible
	85	M	Arthralgia	None
	45	F	Leg Cramps	None
	70	M	Abdominal Pain	Probable
Cefaclor				
	67	F	Respiratory Disorder‡	Remote
	84	M	Respiratory Disorder‡	None
	79	M	Respiratory Disorder‡	None
	45	F	Abdominal Pain	Possible
			Diarrhea	Possible
			Headache	Possible
			Nausea	Possible
	69	M	Dyspnea	None
			Vascular Disorder‡	None
	49	M	Agitation‡	None
			Psychosis‡	None
	71	M	Vomiting‡	None
	52	F	Diarrhea	Probable
			Dizziness	Remote
			Parasthesia	Possible
	72	M	Respiratory Insufficiency‡	None

[a] Based on investigator's assessment.
[b] Exacerbation of COPD.
[c] Rupture of epigastric vessel.
[d] Respiratory failure.
[e] Subject discontinued due to this adverse event. (see Table 25)
‡ Serious or potentially serious adverse event. (see Table 26)

The profile of adverse events in the different sex and age subgroups was generally comparable to that observed in the study population as a whole. Given the small number of non-Caucasians in this study, no meaningful comparisons can be made based on race.

The majority of adverse events were assessed as mild or moderate in severity. Eight (2.4%) subjects reported one or more adverse events of marked severity; no marked adverse event of a specific type was reported by more than one subject. Pruritus and erythematous rash in one subject were considered by the investigator to be definitely related to study drug administration and genital moniliasis in another subject was considered probably related; none of the other markedly severe adverse events was considered drug-related. One of the eight subjects with marked adverse events discontinued study drug treatment due to adverse events. In general, the profile of adverse events in these different subgroups was comparable to that observed in the study population as a whole. The percentage of subjects 65 years of age or older who reported at least one adverse event was higher than in the overall study population (52.6% vs. 39.2%, respectively), but the significance of the finding is unclear given the small number (N=19) of subjects in this age subgroup.

14.4. Deaths and Discontinuations:

No deaths occurred during the study. However, one levofloxacin-treated subject [redacted] and one cefaclor-treated subject [redacted] died approximately three weeks after completing study therapy. The investigators considered the deaths of these subjects unrelated to study drug. Eighteen (4.8%) subjects discontinued the study drug due to adverse events, including 12 (6.4%) subjects in the levofloxacin treatment group and six (3.2%) in the cefaclor treatment group. In the levofloxacin group, all of the adverse events leading to discontinuation emerged within the first five days of therapy; these adverse events included primarily gastrointestinal complaints or central and peripheral nervous system-related symptoms. Treatment-limiting adverse events in the cefaclor group most frequently consisted of gastrointestinal complaints. The treatment-limiting adverse event was considered serious or potentially serious in one levofloxacin-treated subject (907-hypokalemia and vomiting) and two cefaclor-treated subjects.

Table 14.4.A
Subjects who Discontinued due to Adverse Events:
Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	78	F	Anorexia	2	Moderate	Probable	3
			Dizziness	2	Moderate	Probable	
			Gait Abnormal	2	Moderate	Probable	
			Diarrhea	3	Moderate	Probable	
	79	F	Malaise	1	Marked	Possible	5
	59	F	Headache	2	Moderate	Possible	3
			Insomnia	2	Mild	Probable	
			Nervousness	2	Moderate	Probable	
	70	F	Hypokalemia‡	3	Marked	None	2
			Vomiting‡	0	Marked	Remote	
	78	F	Dyspepsia	2	Mild	Possible	1
	62	M	Insomnia	1	Mild	Possible	2
			Nausea	1	Moderate	Probable	
			Taste Perversion (Funny taste and smell)	1	Moderate	Possible	
	70	M	Chest Pain[c]	5	Moderate	Remote	4
			Urticaria (Hives)	5	Moderate	Possible	
	68	M	Muscle Contractions Involuntary	3	Moderate	Possible	3
	69	M	Gastritis	3	Marked	Possible	3
	64	M	Flatulence	1	Mild	Probable	2
	60	F	Edema	2	Moderate	Probable	3
	70	M	Abdominal Pain	1	Marked	Probable	1
			Nausea	1	Moderate	Probable	
			Vomiting	1	Moderate	Probable	
Cefaclor							
	66	F	Rash	10	Moderate	Possible	9
	68	M	Dizziness	4	Moderate	Possible	5
			Nausea	4	Mild	Probable	
	79	M	Respiratory Disorder‡[d]	2	Marked	None	2
	45	F	Abdominal Pain	10	Marked	Possible	11
			Diarrhea	10	Marked	Possible	
			Fever	11	Mild	Possible	
			Headache	11	Marked	Possible	
			Nausea	11	Marked	Possible	
			Vomiting	11	Moderate	Possible	
	63	M	Abdominal Pain	1	Moderate	Possible	1
	71	M	Vomiting‡	6	Marked	None	6

[a] Relative to start of therapy (Day 1).
[b] Based on investigator's assessment.
[c] An IND safety report was filed with the FDA for this subject.
[d] Chest tightening.
[e] Exacerbation of COPD.
‡Serious or potentially serious adverse event. (see Table 26)
**Subject also had a markedly abnormal laboratory value. (see Table 30)

14.5. Serious or Potentially Serious Adverse Events

Two subjects in the levofloxacin treatment group and eight subjects in the cefaclor treatment group reported a serious or potentially serious adverse event during or up to approximately one week after completing study therapy. In all cases, the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug, and, in many cases, appeared to be related to the subject's underlying respiratory condition. Of these 10 subjects, one subject in each treatment group (levofloxacin subject [redacted] and cefaclor subject [redacted] subsequently died; both deaths occurred approximately three weeks after completion of study therapy and neither was considered by the investigator to be related to study drug. Of the 10 subjects with serious or potentially serious adverse events, three withdrew from the study because of the adverse events. In addition to these serious adverse events, one levofloxacin-treated subject [redacted] experienced a mild loss of consciousness (classified as "coma" in Attachments 13 and 14) on Day 3 of study therapy that lasted a few seconds before resolving spontaneously and was considered by the investigator to be unrelated to study therapy.

Table 14.4.B
Subjects with Serious Adverse Events:
Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day Of Onset[a]	Severity	Relationship To Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	76	M	Left-Sided Cardiac Failure[c]	16 (6PT)	–	None	10
	70	F	Hypokalemia	3	Marked	None	2
			Vomiting	0	Marked	Remote	
Cefaclor							
	67	F	Respiratory Disorder[d]	8	Marked	Remote	8
	84	M	Respiratory Disorder[d]	3	Marked	None	4
	79	M	Respiratory Disorder[d]	2	Marked	None	2
	69	M	Vascular Disorder[e]	2	Marked	None	2
	49	M	Agitation	12 (4PT)	Marked	None	8
			Psychosis	12 (4PT)	Marked	None	
	71	M	Vomiting	6	Marked	None	6
	77	M	Hyperglycemia[f]	**	–	None	2
	72	M	Respiratory Insufficiency[g]	2	Marked	None	2

[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] Subject subsequently died approximately three weeks after completing study therapy.
[d] An IND safety report was filed with the FDA for this subject.
[e] This serious adverse event was not captured at the scheduled posttherapy visit and therefore does not appear on the case report form or in the database for this individual study report. However, the event was collected as part of the RWJPRI serious adverse event reporting database and therefore is reflected in the pooled safety database for the NDA Integrated Safety Summary.
[f] Exacerbation of COPD.
[g] Rupture of epigastric vessel.
[h] Subject was hospitalized during the study for hyperglycemia due to uncontrolled diabetes present at admission. This event does not appear on the case report form or in the individual study report database. However, this event was captured as serious in the RWJPRI serious adverse event reporting database; it is therefore reflected as serious in the pooled safety database for the NDA Integrated Safety Summary.
[i] Respiratory failure.
[j] Subject discontinued due to this adverse event. (see Table VII)
[**] Onset of event was prior to admission.

14.5. Dosage Reductions and Concomitant Therapies

18 subjects had study drug therapy stopped due to adverse events, including three subjects in whom the event(s) were considered serious or potentially serious. An additional seven subjects reported serious or potentially serious adverse events. Several of these treatment-limiting adverse events and serious or potentially serious adverse events required treatment with concomitant therapies, as described in the individual narrative descriptions.

Table 14.5
Subjects who Required Concomitant Therapy for Adverse Events: Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day Of Onset[b]	Severity	Concomitant Therapy
Levofloxacin						
[redacted]	39	F	Rash	5	Mild	Desoximetasone
Cefaclor						
	73	M	Abdominal Pain	1	Moderate	Mylanta® (aluminum, magnesium, simethicone)
	68	F	Vaginitis	4	Mild	Clotrimazole
	52	F	Diarrhea	8	Marked	Loperamide, diphenoxylate

[a] Includes events considered by the investigator to be probably or definitely related to study drug except for those resulting in study drug discontinuation or considered serious or potentially serious as described in Sections IV.I.3.b. and IV.I.3.c.
[b] Relative to the start of therapy (Day 1).

14.6. Clinical Laboratory Tests

14.6.1. Overall Changes

There were no clinically significant mean changes from baseline for any laboratory analyte in the levofloxacin-treated or cefaclor-treated group, with comparable results in both groups. A Kolmogorov-Smirnov test was used to compare the two treatment groups with respect to the cumulative distribution of percentage change in laboratory test results from admission to posttherapy. No statistically significant differences between the two treatment groups were observed for any laboratory analyte.

14.6.2. Individual Subject Changes

The distribution of subjects with low, normal, or high values was comparable in the treatment groups at both pretherapy and posttherapy timepoints, and showed little change from pretherapy to posttherapy.

14.6.3. Marked Abnormalities

The laboratory values were classified as markedly abnormal according to standard criteria developed by RWJPRI, which take into account the posttherapy value of the analyte and the change or percentage change from admission. The incidence of markedly abnormal test results for individual analytes within a given treatment group for subjects who had admission data available was low (≤3.2% for all analytes except lymphocyte count) and comparable across the two treatment groups.

Table 14.6.A

Means and Mean Changes from Admission to Posttherapy for Laboratory Analytes: Subjects Evaluable for Safety with Data Available at Admission and Posttherapy

	Levofloxacin					Cefaclor				
Laboratory Test	N	Admission Mean (SD)		Posttherapy Mean (SD)		Change Mean (SD)	N	Admission Mean (SD)	Posttherapy Mean (SD)	Change Mean (SD)
Blood Chemistry										
Glucose (mg/dL)	160	110.5	(40.29)	111.2	(48.93)	0.7 (35.73)	155	109.1 (41.51)	106.1 (40.60)	-3.0 (46.32)
Calcium (mg/dL)	171	9.2	(0.50)	9.1	(0.48)	0.0 (0.48)	169	9.1 (0.49)	9.1 (0.45)	0.0 (0.52)
Sodium (mEq/L)	171	138.9	(2.68)	139.0	(2.54)	0.1 (2.47)	169	138.9 (3.33)	139.3 (2.78)	0.4 (3.37)
Potassium (mEq/L)	166	4.2	(0.47)	4.2	(0.46)	0.1 (0.46)	163	4.2 (0.44)	4.3 (0.47)	0.1 (0.45)
Chloride (mEq/L)	171	103.1	(4.04)	103.7	(3.90)	0.5 (3.58)	169	103.2 (4.55)	103.8 (4.16)	0.6 (4.18)
Phosphorus, Inorg. (mg/dL)	157	3.3	(0.62)	3.3	(0.59)	0.0 (0.65)	151	3.3 (0.62)	3.4 (0.58)	0.0 (0.56)
Blood Urea Nitrogen (mg/dL)	171	13.5	(5.46)	14.7	(5.53)	1.2 (4.38)	169	14.4 (5.49)	15.3 (5.80)	0.9 (4.30)
Lactic Dehydrogenase (U/L)	163	180.6	(42.13)	177.3	(48.55)	-3.2 (42.58)	162	183.9 (38.24)	179.8 (38.46)	-4.1 (31.61)
Total Protein (g/dL)	171	7.1	(0.52)	6.9	(0.48)	-0.2 (0.48)	169	7.1 (0.58)	7.0 (0.54)	-0.1 (0.47)
Albumin (g/dL)	161	3.9	(0.35)	3.9	(0.33)	0.0 (0.29)	157	3.9 (0.40)	3.9 (0.38)	-0.1 (0.35)
Uric Acid (mg/dL)	171	5.6	(1.56)	5.7	(1.57)	0.1 (0.84)	168	5.8 (1.80)	5.8 (1.90)	0.0 (1.01)
Creatinine (mg/dL)	171	1.2	(0.22)	1.1	(0.22)	0.0 (0.14)	169	1.2 (0.26)	1.1 (0.26)	0.0 (0.15)
Alkaline Phosphatase (U/L)	169	78.3	(24.14)	76.4	(31.41)	-1.9 (28.49)	165	82.8 (27.61)	80.9 (30.35)	-2.0 (14.37)
SGOT (U/L)	171	22.1	(11.31)	21.7	(11.45)	-0.4 (12.18)	169	22.3 (16.82)	22.0 (22.36)	-0.4 (20.76)
SGPT (U/L)	171	22.3	(17.52)	21.9	(15.89)	-0.4 (17.55)	169	20.4 (20.80)	21.6 (18.83)	1.2 (15.28)
Total Bilirubin (mg/dL)	161	0.5	(0.28)	0.5	(0.21)	0.0 (0.23)	157	0.6 (0.31)	0.5 (0.27)	0.0 (0.24)
Hematology										
Hemoglobin (g/dL)	157	14.7	(1.33)	14.7	(1.48)	0.0 (0.86)	153	14.4 (1.52)	14.3 (1.60)	-0.1 (0.74)
Hematocrit (%)	148	44.2	(4.08)	44.4	(4.62)	0.3 (2.77)	145	43.5 (4.68)	43.4 (4.97)	-0.1 (2.61)
WBC (x10³/μL)	157	9.4	(3.32)	8.5	(2.71)	-0.8 (2.95)	153	9.9 (4.02)	8.9 (3.03)	-1.0 (3.65)
RBC (x10⁶/μL)	157	4.8	(0.46)	4.9	(0.51)	0.0 (0.27)	153	4.7 (0.47)	4.7 (0.50)	0.0 (0.25)
Neutrophils (x10³/μL)	156	6.7	(3.19)	5.9	(2.65)	-0.8 (2.69)	153	7.2 (3.88)	6.2 (3.01)	-1.0 (3.69)
Lymphocytes (x10³/μL)	156	1.8	(0.78)	1.9	(0.86)	0.1 (0.76)	153	1.8 (0.89)	1.9 (0.84)	0.1 (0.89)
Eosinophils (x10³/μL)	156	0.2	(0.23)	0.2	(0.13)	0.0 (0.16)	153	0.2 (0.20)	0.2 (0.16)	0.0 (0.17)
Platelet Count (x10³/μL)	154	287.0	(70.35)	297.6	(71.44)	10.6 (65.76)	151	285.8 (89.44)	304.9 (103.30)	19.1 (79.11)

N=Number of subjects with admission and posttherapy results.

Note: Mean and mean change data for two levofloxacin-treated subjects [redacted] who had posttherapy laboratory data erroneously entered as repeat admission dat are not included in this analysis.

Table 14.6.B

Incidence of Treatment-emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

	Levofloxacin		Cefaclor	
Laboratory Test	Proportion*	%	Proportion*	%
Blood Chemistry				
Decreased Phosphorous	3/158	1.9	0/150	0.0
Elevated SGOT	1/172	0.6	1/168	0.6
Elevated SGPT	1/172	0.6	2/168	1.2
Elevated Alkaline Phosphatase	1/170	0.6	0/164	0.0
Elevated Glucose	1/161	0.6	2/154	1.3
Decreased Glucose	1/161	0.6	5/154	3.2
Elevated Bun	0/172	0.0	1/168	0.6
Hematology				
Decreased Lymphocytes	8/157	5.1	11/152	7.2
Decreased Hemoglobin	1/158	0.6	0/152	0.0

* Numerator = number of subjects with a treatment-emergent markedly abnormal test value and denominator = number of subjects evaluable for each test (i.e., admission and postadmission data available) for that analyte. Subjects with posttherapy laboratory results obtained more than 30 days PT ([redacted] levofloxacin, [redacted] cefaclor) are not included in this analysis.

Thirty-four subjects (14 in the levofloxacin group and 20 in the cefaclor group) had a total of 39 markedly abnormal test results after therapy start. Two subjects in each treatment group had markedly abnormal liver function tests (elevations in SGOT, SGPT, or alkaline phosphatase). Eight (5.1%) subjects in the levofloxacin group and 11 (7.2%) in the cefaclor group had lymphopenia, which was classified as mild (lymphocyte counts $^{3}0.59 \times 10^{3}$ /μL) for 14 of those subjects (five levofloxacin-treated subjects and nine cefaclor-treated subjects). Nine subjects had abnormal glucose levels: one levofloxacin-treated subject and two cefaclor-treated subjects had hyperglycemia. Of the three subjects with hyperglycemia, one [redacted] was considered mild (<250 mg/dL). One levofloxacin-treated subject and five cefaclor-treated subjects had hypoglycemia, including one levofloxacin-treated subject and two cefaclor-treated subjects whose hypoglycemia was classified as mild (serum glucose values of 60 mg/dL or higher). Three levofloxacin-treated subjects had hypophosphatemia (serum phosphorus level <2.0 mg/dL). Some abnormalities were related to the underlying disease state of the subject.

Table 14.6.C
Subjects with Treatment-emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

Subject Number	Age	Sex	Laboratory Test (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[2]	Follow-up Value (Therapy Day)	Duration of Therapy (Days)
Levofloxacin								
	56	M	Lymphocytes (<1.0 x 10⁹/μL)	1.51	0.69	16 (5PT)	–	7
	67	M	SGOT (>75 IU/L)	30.0	122.0	14 (7PT)	–	7
			SGPT (>75 IU/L)	29.0	158.0	14 (7PT)	–	
	61	M	Lymphocytes (<1.0 x 10⁹/μL)	2.92	0.54	14 (8PT)	–	6
	76	M	Lymphocytes (<1.0 x 10⁹/μL)	2.61	0.65	11 (6PT)	–	5
	64	M	Glucose (<70 or >200 mg/dL)	190.0	375.0	12 (5PT)	–	7
			Lymphocytes (<1.0 x 10⁹/μL)	1.75	0.95	12 (5PT)	–	
	54	F	Hemoglobin (<12.0 g/dL)	13.30	8.50	14 (7PT)	–	7
	62	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	2.60	1.80	3 (1PT)	–	2
	74	M	Lymphocytes (<1.0 x 10⁹/μL)	1.27	0.76	14 (5PT)	–	5
	52	M	Lymphocytes (<1.0 x 10⁹/μL)	1.16	0.69	13 (6PT)	1.87 20 (13PT)	7
			Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.60	1.70	13 (6PT)	4.00 20 (13PT)	
	33	F	Alkaline Phosphatase (>250 IU/L)	75.0	343.0	14 (7PT)	–	7
	54	M	Lymphocytes (<1.0 x 10⁹/μL)	0.39	0.16	12 (5PT)	–	7
	48	M	Glucose (<70 or >200 mg/dL)	144.0	62.0	14 (7PT)	–	7
	64	M	Lymphocytes (<1.0 x 10⁹/μL)	2.52	0.36	6 (4PT)	–	2
	61	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	2.60	1.70	10 (5PT)	–	5
Cefaclor								
	61	M	Lymphocytes (<1.0 x 10⁹/μL)	1.57	0.77	15 (5PT)	–	10
	67	M	SGPT (>75 IU/L)	13.0	120.0	22 (11PT)	–	11
	58	F	Lymphocytes (<1.0 x 10⁹/μL)	1.96	0.79	14 (8PT)	–	8
	79	M	BUN (>40 mg/dL)	25.0	47.0	16 (11PT)	–	5
	77	M	Lymphocytes (<1.0 x 10⁹/μL)	1.59	0.57	9 (4PT)	–	5
	72	F	Lymphocytes (<1.0 x 10⁹/μL)	1.71	0.75	15 (5PT)	–	10
	36	F	Lymphocytes (<1.0 x 10⁹/μL)	1.08	0.59	6	–	6
	75	M	Glucose (<70 or >200 mg/dL)	120.0	231.0	17 (6PT)	–	11
			Lymphocytes (<1.0 x 10⁹/μL)	1.12	0.71	17 (6PT)	–	
	52	M	Glucose (<70 or >200 mg/dL)	121.0	59.0	14 (4PT)	–	10
	35	M	SGOT (>75 IU/L)	31.0	270.0	15 (7PT)	–	8
			SGPT (>75 IU/L)	24.0	129.0	15 (7PT)	–	
	56	M	Lymphocytes (<1.0 x 10⁹/μL)	3.97	0.84	12 (4PT)	–	8
	63	M	Lymphocytes (<1.0 x 10⁹/μL)	1.28	0.67	20 (19PT)	–	1
	71	M	Glucose (<70 or >200 mg/dL)	70.0	360.0	15 (6PT)	–	9
	69	M	Lymphocytes (<1.0 x 10⁹/μL)	2.04	0.20	12 (5PT)	–	7
	63	M	Glucose (<70 or >200 mg/dL)	102.0	66.0	20 (10PT)	–	10
	55	M	Glucose (<70 or >200 mg/dL)	86.0	56.0	17 (7PT)	–	10
	74	F	Glucose (<70 or >200 mg/dL)	144.0	63.0	14 (7PT)	–	7
	67	M	Lymphocytes (<1.0 x 10⁹/μL)	1.51	0.34	17 (7PT)	–	10
	58	F	Glucose (<70 or >200 mg/dL)	358.0	56.0	12 (5PT)	–	7
	69	M	Lymphocytes (<1.0 x 10⁹/μL)	1.15	0.60	10 (2PT)	–	8

[1] Only range given in table. For complete criteria see Attachment 24a.
[2] Relative to start of therapy (Day 1). NOTE: PT refers to the numbers of days posttherapy, relative to the last day of study drug administration.
[3] Subject discontinued due to adverse event. (see Table 25)

15. Medical Officer's Conclusions from Study K90-070:

15.1. Protocol design and implementation issues:

15.1.1 Protocol K90-070 has significant flaws in the protocol design including:

15.1.1.1. The protocol was a completely unblinded study. This is particularly significant in light of the fact that all of the endpoints are clinical and, thus, subjective and subject to bias by both (1) **observer/expectation bias** from the investigator and (2) **reporting/recall bias** in the patient reporting the symptoms[4].

15.1.1.2. The windows for clinical evaluation at both the End-of-therapy

[4] Sackett DL. Bias in Clinical Research. J Chronic Dis 32:51-63, 1979.

and End-of-study evaluations were inappropriate to allow for a definitive test-of-cure evaluation from which could be derived a stable point estimate for the clinical cure rate. In this protocol, the EOT evaluation was conducted too early to assess a stable cure rate and there were no later EOS evaluations, as recommended by the IDSA Guidelines, to assess (1) clinical failures (early relapses) resulting from partial response to study drug or superinfection and (2) late relapses from reinfection with the same organism or infection with another organism.

15.1.1.3. Original windows for follow-up culture were too close to the end of therapy to preclude suppression of regrowth by residual antibiotic levels or post-antibiotic effect

15.1.1.4. Inadequate documentation of the patients baseline (clinical symptoms of chronic bronchitis in the absence of acute exacerbation) clinical status to allow for accurate assessment of the clinical categories of "cured" and "improved" at the posttherapy follow-up. Since patient with chronic bronchitis are symptomatic in their "healthy" baseline status, the accurate assessment of response to therapy is dependent on comparison of posttherapy symptoms with the patient's baseline symptoms of chronic bronchitis in the absence of an acute exacerbation.

15.1.2. Protocol K90-070 has significant flaws in the protocol implementation including:

15.1.2.1. Omission of culture of persistent sinus secretions at the follow-up visits (both EOT and EOS), with overuse of the designation of "presumed eradication" in cases where documentation of microbiologic outcome was possible.

15.1.2.2. Changes in drug dosage and duration were made during the course of the study

15.1.2.3. Changes in the days of the post-therapy follow-up evaluation were made during the course of the study

15.1.2.4. The end-of-study evaluation was dropped from the protocol during the course of the study

15.2. Efficacy results

15.2.1. Clinical Efficacy Results

The **clinical cure rate** of levofloxacin was statistically equivalent to cefaclor in Protocol K90-070. The clinical cure rate for the levofloxacin arm was 65% (62/95), and that for the cefaclor arm was 58% (74/127), with the 95% confidence interval around the difference being $_{127,95}$(-20.8 to 6.8)$_{58\%,65\%}$. Thus, levofloxacin meets regulatory criteria for approval for the treatment of acute exacerbation of chronic bronchitis based on the demonstration of statistical equivalence to an approved competitor. The clinical cure rate in the levofloxacin arm in Protocol M92-024 was 68% (134/196), and, thus, was comparable to the 68% clinical cure rate in the levofloxacin arm of Protocol K90-070.

The **clinical *success* rate** (clinically cured plus improved) of levofloxacin was statistically equivalent to cefaclor in Protocol K90-070. The clinical success rate for the levofloxacin arm was 98% (93/95), and that for the cefaclor arm was 97% (123/127), with the 95% confidence interval around the difference being $_{127,95}$(-6.2 to 4.1)$_{97\%,98\%}$. Thus, levofloxacin meets regulatory criteria for approval for the treatment of acute exacerbation of chronic bronchitis based on the demonstration of statistical equivalence to an approved competitor. The clinical success rate in the levofloxacin arm in Protocol M92-024 was 98% (93/95), and, thus, was comparable to the 68% clinical cure rate in the levofloxacin arm of Protocol K90-070.

The **overall success rate** (clinically cured or improved plus microbiologically eradicated) of levofloxacin was statistically equivalent to cefaclor in Protocol K90-070. The overall success rate for the levofloxacin arm was 92% (56/61), and that for the cefaclor arm was 91% (58/64), with the 95% confidence interval around the difference being $_{64,61}$(12.7 to 10.3)$_{91,92\%}$. Thus, levofloxacin meets regulatory criteria for approval for the treatment of acute exacerbation of chronic bronchitis based on the demonstration of statistical equivalence to an approved competitor. The overall success rate in the levofloxacin arm in Protocol M92-024 was 91% (106/116), and, thus, was comparable to the 68% clinical cure rate in the levofloxacin arm of Protocol K90-070.

15.2.2. Microbiologic Efficacy Results

Microbiologic eradication rates for **levofloxacin** for the pathogens requested by the sponsor in the proposed package labeling (*S. pneumoniae, H. influenzae, H. parainfluenzae, M. catarrhalis* and *S. aureus)* are above 75% in Protocol K90-070. In fact, the microbiologic rates for the pathogens other than *S. aureus (S. pneumoniae, H. influenzae, H. parainfluenzae, M. catarrhalis)* are all above 88%. *S. aureus*, on the other hand, had an eradication rate of 75% in this protocol. The 95% confidence interval around the difference between the **overall eradication rates** of levofloxacin and cefaclor overlapped zero, indicating that the two treatments were statistically equivalent in this regard. The 95% confidence interval around that difference in eradication rates for *H. influenzae* overlapped zero, indicating statistical equivalence for the eradication of this organism. However, because of the low numbers of

individual isolates, the calculation of confidence intervals around the difference in eradication rates was not possible for *S. aureus, S. pneumoniae, H. parainfluenzae, M. catarrhalis* in Protocol K90-070. Therefore, because of the small number of individual isolates in this study, the eradication rates by individual pathogen are discussed in conjunction with the microbiologic results from Protocol M92-024 under the Recommendations Section that follow the review of Protocol M92-024.

15.3. Issues involving microbial resistance to the quinolone antibiotics:
The use of levofloxacin for the treatment of acute exacerbation of chronic bronchitis in the community will, in general, be empiric, thus, its coverage for organisms in which there could be pre-existing or rapid development of resistance may be suboptimal and may not be known with great accuracy.

15.3.1. Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*.

Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*, with methicillin-resistant *S. aureus* (MRSA) developing resistance at a more rapid rate than methicillin-sensitive *S. aureus* (MSSA). Ciprofloxacin-resistance in *S. aureus* is well documented, with reports resistance developing during therapy with these agents[5]. One study surveyed the development of ciprofloxacin-resistance in methicillin-resistant *S. aureus* (MRSA) in patients treated with the antibiotic for nonstaphylococcal infections in a VA Medical Center. These authors reported that 79% of MRSA isolates were resistant to ciprofloxacin one year after introduction of the drug, and 91% of MRSA isolates were resistant to ciprofloxacin two years after introduction of the drug[6]. Piercy et.al. reported development of resistance in 16% (6/37) of patients who were being treated with ciprofloxacin for MRSA colonization and Mulligan et.al. reported 32% (7/22) of treatment episodes were associated with the development of ciprofloxacin-resistant MRSA during the course of antibiotic therapy[7]. Resistance among methicillin-susceptible *S. aureus* (MSSA) has been less widespread than with MRSA, but has still been

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[5] Daum TE, Schaberg DR. Increasing resistance of *S. aureus* to ciprofloxacin. Antimicrob Agents Chemother 34:1862-3, 1990; Blumberg HM, Rimland D, et.al. Rapid development of ciprofloxacin resistance in Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. J Infect Dis 163:1279-85, 1991; Mulligan ME, Ruane PJ, et.al. Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization. Am J Med 82 (Suppl.4A):215-9, 1987; Piercy EA, Barbaro D, et.al. Ciprofloxacin for methicillin-resistant Staphylococcus aureus infections. Antimicrob Agents Chemother 33:128-30, 1989; Scaefler S. Methicillin-resistant strains of Staphylococcus aureus resistant to the quinolones. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Widespread quinolone resistance among methicillin resistant S. aureus. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Ciprofloxacin resistance in epidemic methicillin-resistant *S. aureus*. Lancet 2:843, 1988.

[6] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[7] Piercy EA. Antimicrob Agents Chemother 33:128-30, 1989; Mulligan ME, Ruane PJ, et.al. Am J Med 82 (Suppl.4A):215-9, 1987.

reported[8].

While the mechanism of resistance of *S. aureus* to quinolones is not completely understood, there are authors who suggest that the rapid emergence of ciprofloxacin resistance in *S. aureus* may be due to the fact that a single-step point mutation alone can lead to high-level resistance[9]. For *S. aureus*, the frequency of alterations in DNA gyrase caused by single-step mutations increases from 1 in 10^2 to 1 in 10^5 when bacteria are exposed to concentrations close to the minimal inhibitory concentration. The frequency of single-step mutation to fluoroquinolone resistance in *S. aureus* ranges from 1.5 x10-5 at twice the MIC to ≤3.6 x 10 -12 at eight times the MIC; and high level resistance occurs with serial exposure of bacteria to increasing concentrations of fluoroquinolones[10].

15.3.2. Quinolone-resistance has been documented to occur in *Streptococcus pneumoniae*.

The mechanism for pneumococcal resistance to the quinolones is also a one-step point mutation (single amino acid substitution) in the DNA gyrase leading to high level resistance[11]. Quinolone resistance to ciprofloxacin is more prevalent than resistance to ofloxacin, with one paper in 1992 reporting 95% of pneumococcal isolates susceptible to ofloxacin and only 68% of isolates susceptible to ciprofloxacin[12]. However, it should be noted that development of resistance to antimicrobial agents is a time-dependent phenomenon, and that ciprofloxacin has been in use longer than ofloxacin. Data presented by the Center for Disease Control[13] at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy showed that there could be significant development of resistance to ofloxacin in the period of one year, such that the point prevalence for pneumococcal

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[8] Scaefler S. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Lancet 2:843, 1988; Daum TE, Schaberg DR. Antimicrob Agents Chemother 34:1862-3, 1990.

[9] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991; Oshita Y, Hiramatsu K. A point mutation in *norA* gene is responsible for quinolone resistance in *Staphylococcus aureus*. Biochem Biophys Res Commun 172:1028-34, 1990; Yoshida H, Bogaki M, et.al. Nucleotide sequence and characterization of the Staphylococcus *norA* gene, which confers resistance to the quinolones. J Bacteriol 172:6942-9, 1990; Neu HC. Bacterial resistance to the fluoroquinolones. Rev Infect Dis 10(suppl.1):57-63, 1988; Sreedharan S, Oram M. DNA gyrase *gyrA* mutations in ciprofloxacin-resistant strains of *S. aureus*: close similarity with quinolone resistant mutations in *E. coli*. J Bacteriol 172:7260-2, 1990.

[10] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[11] Piddock LJV, Wise R. The selection and frequency of streptococci with decreased susceptibility to ofloxacin and the other quinolones. J Antimicrobial Chemo 22(suppl C):45-51, 1988.

[12] Jones RN, Reller LB, Rosati LA. Ofloxacin, a new Broad Spectrum Fluoroquinolone: Results from a Multicenter, National Comparative Activity Surveillance Study. Diag. Microbial Infect Dives 15:425-34, 1992.

[13] Butler JC, Hofman J, Elliot JA, et.al. Late breaking abstract. 35th ICAAC, San Francisco, CA, September 17-20, 1995.

intermediate resistance to ofloxacin was 1% in 1993 and 9.5% in 1994. However, it should be noted that there was no absolute resistance detected in this study.

Pharmacokinetic/pharmacodynamic data have been used to attempt to predict the clinical efficacy of antimicrobial agents against specific microorganisms. In the case of the quinolone antimicrobials, the inhibitory quotient, defined as the AUC/MIC ratio (the ratio of the Area Under the Concentration-time Curve (AUC) of the antibiotic to the minimum inhibitory concentration (MIC) of the *S. pneumoniae* isolate) has been shown to be predictive of clinical efficacy, with an AUC/MIC value of 40 being the breakpoint for *S. pneumonaie*[14]. Levofloxacin, being the active isomer of ofloxacin, achieves higher blood level of the active isomer, and thus has a better inhibitory quotient for *S. pneumonaie*, as described in the table below. However, it should be noted that the MIC90 of some strains of *S. pneumonaie* is now ≥4 mcg/mL for both ciprofloxacin and ofloxacin. At this higher MIC, the inhibitory quotient for levofloxacin falls below the breakpoint of 40. Thus, the margin for coverage of organisms with even a marginal drift in *MIC* afforded even by the higher blood levels of levofloxacin is borderline.

It should be noted that all these calculations are theoretical based on the pharmacokinetic/pharmacodynamic data of these compounds. For ofloxacin, there remains a discrepancy between the theoretically inadequate inhibitory quotient and the clinical efficacy, with the clinical efficacy being better than would be predicted by the marginal inhibitory quotient against *S. pneumonaie*.

Table 15.3.A

Inhibitory quotients against *Streptococcus pneumonaie* for several of the Fluoroquinolone Antibiotics: Calculated for MICs of 2 mcg/mL and 4 mcg/mL

Quinolone Antimicrobial →	Inhibitory Quotient (AUC/MIC) for MIC 2 mcg/mL		Inhibitory Quotient (AUC/MIC) for MIC 4 mcg/mL	
	MIC	AUC/MIC	MIC	AUC/MIC
Ciprofloxacin	2 mcg/mL	11.6	4 mcg/mL	5.8
Ofloxacin	2 mcg/mL	43.5	4 mcg/mL	21.8
Levofloxacin	2 mcg/mL	60.7	4 mcg/mL	30.4

[14] Dr. David C. Hooper . Presented at the 35th ICAAC, San Francisco, CA, September, 1995.

Recommendations for the use of levofloxacin in the treatment of acute exacerbation of chronic bronchitis:

The recommendations derived from the review of Protocol K90-070 are discussed in conjunction with the recommendations derived from review of Protocol M92-024. This discussion follows Section 15. Conclusions. of the Medical Officer's Review of Protocol M92-024.

Medical Officer's Review of NDA 20-634
Elequin ® (levofloxacin tablets) Tablets

Indication: Acute Exacerbation of Chronic Bronchitis

Protocol: K92-024

Study Title: A multicenter, randomized, open-label study to compare the safety and efficacy of oral levofloxacin (500mg PO QD for 5-7 days) with cefuroxime (250mg PO BID for 7-10 days) in the treatment of acute exacerbation of chronic bronchitis in adults

Study dates: DATE STUDY INITIATED: August 31, 1993
DATE STUDY COMPLETED: May 16, 1994

1. Study Objective:

The objective of this study was to compare the safety and efficacy of 500 mg levofloxacin administered orally once daily for five to seven days with that of 250 mg cefuroxime axetil administered orally twice daily for 10 days in the treatment of acute bacterial exacerbation of chronic bronchitis due to susceptible organisms in adult outpatients.

2. Protocol design:

This was a randomized, open-label, active-control, multicenter study designed to evaluate levofloxacin in the treatment of acute bacterial exacerbation of chronic bronchitis. This study was conducted in the United States. Approximately 400 adult subjects were to be enrolled to ensure clinically evaluable data from a minimum of 294 subjects (147 subjects per treatment group). Enrollment continued until sufficient numbers of evaluable subjects with infections due to important pathogens were entered.

Subjects were assigned randomly to receive either 500 mg levofloxacin orally once daily for five to seven days or 250 mg cefuroxime axetil orally twice daily for 10 days. A computer-generated schedule was prepared by the R. W. Johnson Pharmaceutical Research Institute (RWJPRI) and supplied to each investigator. The schedule was generated using random permuted blocks of four and stratified by study center to assign subjects in equal numbers to receive either levofloxacin or cefuroxime axetil on an open-label basis. Subjects received an identification number in consecutive order of study entry.

For subjects meeting the entry criteria, admission (baseline) evaluations included a pertinent medical history (including chest X-ray) and physical examination (including vital sign measurements and chest examination); respiratory specimen for culture, gram stain, and susceptibility testing; blood cultures (two per subject if bacteremia suspected); samples for hematology, blood chemistry, urinalysis, and, if indicated, theophylline levels; and pregnancy test for women of childbearing potential. Between Days 3 and 5 of study drug

Medical Officer's Review of NDA 20-634
Elequin ® (levofloxacin tablets) Tablets

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Subjects were assigned randomly to receive either 500 mg levofloxacin orally once daily for five to seven days or 250 mg cefuroxime axetil orally twice daily for 10 days. A computer-generated schedule was prepared by the R. W. Johnson Pharmaceutical Research Institute (RWJPRI) and supplied to each investigator. The schedule was generated using random permuted blocks of four and stratified by study center to assign subjects in equal numbers to receive either levofloxacin or cefuroxime axetil on an open-label basis. Subjects received an identification number in consecutive order of study entry.

For subjects meeting the entry criteria, admission (baseline) evaluations included a pertinent medical history (including chest X-ray) and physical examination (including vital sign measurements and chest examination); respiratory specimen for culture, gram stain, and susceptibility testing; blood cultures (two per subject if bacteremia suspected); samples for hematology, blood chemistry, urinalysis, and, if indicated, theophylline levels; and pregnancy test for women of childbearing potential. Between Days 3 and 5 of study drug

administration, subjects returned for a scheduled on-study visit and were examined for overall clinical progress. Subjects were allowed to remain in the study in the absence of recovery of an admission pathogen, or if the pathogen(s) isolated at admission were resistant to either study drug, as long as in the opinion of the investigator, there had been no deterioration in clinical status. Subjects were examined for overall clinical progress. Two blood cultures were obtained for subjects who were bacteremic at admission. Efficacy evaluations included assessments of clinical signs and symptoms, clinical response (assessed as cured, improved, failed, or unable to evaluate) and microbiologic eradication rates (assessed as eradicated, persisted, or unknown). Clinical symptoms were recorded as present or absent after completion of therapy (five to seven days posttherapy). Clinical signs of bronchitis obtained from a chest examination were graded by the investigator as none, mild, moderate, or severe after completion of therapy (five to seven days posttherapy). Clinical response was assessed by the investigator at the final visit, five to seven days after the end of therapy. Microbiological response was assessed by RWJPRI by evaluating the culture results from the final visit, five to seven days after the end of therapy. Safety evaluations included the incidence of treatment-emergent adverse events; laboratory tests of hematology, blood chemistry, and urinalysis; and physical examinations including vital sign measurements. Theophylline levels were monitored during the study, if indicated. Criteria were added to clarify the provisions for enrollment of subjects failing previous antimicrobial therapy and the exclusion criteria regarding subjects with seizure disorders or unstable psychiatric conditions. In addition, the definition of clinical response of "improved" was modified to clarify that subjects who required additional nonstudy antimicrobial therapy at the posttherapy visit could not be considered clinically improved; the definition of "unable to evaluate" was also clarified. The MIC and inhibition zone criteria for susceptibility of *H. influenzae* were also specified. Several changes in evaluability criteria for the efficacy analysis were also made: (I) deletion of resistance to study drug as a criterion for classifying a subject as clinically or microbiologically unevaluable; (ii) specification that subjects with clinical failure receiving greater than 48 hours but less than five days of therapy could be considered evaluable; (iii) requirement that bacteriologic cultures be obtained between 1-10 days posttherapy (PT) rather than 2-10 days PT for subjects to be evaluable; (iv) omission of plans for efficacy summaries by severity of infection; and (v) omission of the provisions that subjects who had taken study drug for more than 20 days or who failed to meet specific entrance criteria would be excluded from the efficacy analysis. The second amendment to the protocol on July 14, 1994 clarified the minimum duration of therapy for levofloxacin as four days and cefuroxime axetil as five days for analysis of microbiologic response.

3. Diagnostic criteria:

The primary diagnosis of acute exacerbation of chronic bronchitis was defined by clinical and radiographic signs and symptoms of acute bacterial exacerbation of chronic bronchitis:

3.1. **Clinical: Subjects with a diagnosis of acute bacterial exacerbation of chronic bronchitis, as evidenced by all of the following:**

- history of chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema)
- recent increase in cough

- change in character and/or increase in production of sputum
- physical findings consistent with a diagnosis of acute bacterial exacerbation of chronic bronchitis.

3.2. Radiographic: Absence of acute infiltrates on the admission chest x-ray obtained within 12 hours prior to study entry.

4. Inclusion and exclusion criteria:

Inclusion/exclusion criteria were as elaborated below. There was no microbiologic evaluation incorporated into the study, thus only clinical and radiologic criteria were incorporated into the inclusion/exclusion criteria.

4.1. Inclusion criteria:

4.1.1. Inclusion criteria as per original study protocol:

Subjects may be included in the study if they satisfy the following:

1. Age: 18 or older
2. Sex: male or female
3. All subjects will be appropriate candidates for oral therapy. Patients in nursing homes may be enrolled if they are ambulatory and are able to carry out the activities of daily life.
4. Subjects with a diagnosis of acute bacterial exacerbation of chronic bronchitis, as evidenced by all of the following:
   - history of chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema)
   - recent increase in cough
   - change in character and/or increase in production of sputum • physical findings consistent with a diagnosis of acute bacterial exacerbation of chronic bronchitis.

An appropriate sputum specimen must be available for entry into the study.

5. If female, the subject must
   - be post-menopausal for at least one year, or
   - have had a hysterectomy, or
   - have had a tubal ligation, or
   - have taken oral contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods during the study, or
   - use another acceptable method of contraception and agree to continue with the same method during the study.

   If female and of childbearing potential, the subject must have
   - had a normal menstrual flow within one month prior to study entry, and
   - a negative pregnancy test (serum b-subunit hCG) immediately prior to entry.

If obtaining the serum pregnancy test result would cause a delay in treatment, a subject may be entered on the basis of a negative urine pregnancy test sensitive to at least 50 mIU/mL, pending results of the serum pregnancy test. Subsequently, if the result of the serum test is positive, the subject must be discontinued from the study and followed as indicated.

6. Completion of the confidential follow-up form
7. Reading and signing of the informed consent (and California Bill of Rights, if applicable) after the nature of the study has been fully explained.

4.1.2. Inclusion criteria as per amended study protocol dated March 9, 1994:

1. Age: 18 or older
2. Sex: male or female
3. All subjects will be appropriate candidates for oral therapy. Patients in nursing homes may be enrolled if they are ambulatory and are able to carry out the activities of daily life.
4. Subjects with a diagnosis of acute bacterial exacerbation of chronic bronchitis, as evidenced by all of the following:

- history of chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema)
- recent increase in cough
- change in character and/or increase in production of sputum
- physical findings consistent with a diagnosis of acute bacterial exacerbation of chronic bronchitis.

An appropriate sputum specimen must be available for entry into the study.

5. Subjects who have received previous antimicrobial therapy may be enrolled if:
   - previous therapy duration is 24 hours or less
   - previous therapy duration is greater than 24 hours, but subject did not improve or stabilize on that therapy
6. If female, the subject must
   - be post-menopausal for at least one year, or
   - have had a hysterectomy, or
   - have had a tubal ligation, or
   - have taken oral contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods during the study, or
   - use another acceptable method of contraception and agree to continue with the same method during the study.

If female and of childbearing potential, the subject must have
- had a normal menstrual flow within one month prior to study entry, and
- a negative pregnancy test (serum b-subunit hCG) immediately prior to entry.

If obtaining the serum pregnancy test result would cause a delay in treatment, a subject may be entered on the basis of a negative urine pregnancy test sensitive to at least 50 mIU/mL, pending results of the serum pregnancy test. Subsequently, if the result of the serum test is positive, the subject must be discontinued from the study and followed as indicated.

7. Completion of the confidential follow-up form
8. Reading and signing of the informed consent (and California Bill of Rights, if applicable) after the nature of the study has been fully explained.

4.1.3. Inclusion criteria as per amended study protocol dated July 14, 1994:

Inclusion criteria were unchanged from March 9, 1994 protocol amendment reviewed under Section 4.1.2, above.

4.2. Exclusion criteria:

4.2.1. Exclusion criteria as per original study protocol:

Subjects with any of the following criteria will not be eligible for admission into the study:

1. Severity of illness requiring parenteral antimicrobial therapy
2. Subjects with an infection due to organisms known to be resistant to the study drug prior to study entry
3. Previous allergic or serious adverse reaction to levofloxacin or any other members of the quinolone or beta-lactam classes of antimicrobials
4. Calculated creatinine clearance less than or equal to 50 mL/min
5. Diagnosis of acute bronchitis, pneumonia (as evidenced by acute infiltrates on the admission chest x-ray obtained within 12 hours prior to study entry), or cystic fibrosis
6. Requirement of a second systemic antimicrobial agent
7. Effective systemic antimicrobial therapy within 48 hours prior to admission
8. Use of an investigational agent within 30 days prior to admission
9. Pregnancy or a nursing mother
10. Previous treatment under this protocol
11. Any disorder or disease that may interfere with the evaluation of the study drugs
12. History of seizure disorder or condition requiring the administration of major tranquilizers.

Reasons why any subjects were not enrolled must be documented on the Potential Subject Roster.

4.2.2. Exclusion criteria as per amended study protocol dated March 9, 1994:

Subjects with any of the following criteria will not be eligible for admission into the study:

1. Severity of illness requiring parenteral antimicrobial therapy
2. Subjects with an infection due to organisms known to be resistant to the study drug prior to study entry
3. Previous allergic or serious adverse reaction to levofloxacin or any other members of the quinolone or beta-lactam classes of antimicrobials
4. Calculated creatinine clearance less than or equal to 50 mL/min
5. Diagnosis of acute bronchitis, pneumonia (as evidenced by acute infiltrates on the admission chest x-ray obtained within 12 hours prior to study entry), or cystic fibrosis
6. Requirement of a second systemic antimicrobial agent
[7. Effective systemic antimicrobial therapy within 48 hours prior to admission]
7. Use of an investigational agent within 30 days prior to admission
8. Pregnancy or a nursing mother
9. Previous treatment under this protocol
10. Any disorder or disease that may interfere with the evaluation of the study drugs
11. History Presence of seizure disorder or condition requiring the administration of major tranquilizers.
12. Unstable psychiatric conditions.

4.2.3. Exclusion criteria as per amended study protocol dated July 14, 1994:

Subjects with any of the following criteria will not be eligible for admission into the study:

1. Severity of illness requiring parenteral antimicrobial therapy
2. Subjects with an infection due to organisms known to be resistant to the study drug prior to study entry
3. Previous allergic or serious adverse reaction to levofloxacin or any other members of the quinolone or beta-lactam classes of antimicrobials
4. Calculated creatinine clearance less than or equal to 50 mL/min
5. Diagnosis of acute bronchitis, pneumonia (as evidenced by acute infiltrates on the admission chest x-ray obtained within 12 hours prior to study entry), or cystic fibrosis
6. Requirement of a second systemic antimicrobial agent
[7. Effective systemic antimicrobial therapy within 48 hours prior to admission]
7. Use of an investigational agent within 30 days prior to admission
8. Pregnancy or a nursing mother
9. Previous treatment under this protocol
10. Any disorder or disease that may interfere with the evaluation of the study drugs
11. *[History]* Presence of seizure disorder *[or condition requiring the administration of major tranquilizers.]*
12. Unstable psychiatric conditions.

5. Concomitant use of medications and other antimicrobial agents:

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 might decrease the bioavailability of levofloxacin. However, if administration of an antacid was necessary, it was to be administered at least two hours before or after levofloxacin administration. If the administration of any other medication was required, it was reported on the subject's CRF.

6. Efficacy Criteria per Sponsor:

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, 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. Safety evaluations included the incidence of treatment-emergent adverse events; laboratory tests of hematology, blood chemistry, and urinalysis; and physical examinations including vital signs.

6.1. Clinical Efficacy Evaluations:

6.1.1. Clinical Signs and Symptoms:

Clinical symptoms of acute bacterial exacerbation of chronic bronchitis, including chills, chest pain, shortness of breath, increased cough, sputum increase, and purulent sputum, were indicated by the investigator as present or absent at admission and at the posttherapy visit five to seven days after the end of therapy. Clinical signs of bronchitis obtained from a chest examination (diminished breath sounds, rales, rhonchi, and wheezes) were graded by the investigator as none, mild, moderate, or severe at admission and at the posttherapy visit five to seven days after the end of therapy.

6.1.2. Clinical Response Rating:

At the posttherapy visit five 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:

Cure: Resolution of signs and symptoms associated with active infection.
Improved: Incomplete resolution of signs and symptoms and no additional antimicrobial therapy required.
Failure: No response to therapy.
Unable to evaluate: Not able to evaluate because subject lost to follow-up.

6.2. Microbiologic Efficacy Evaluations:

6.2.1. Specimen Collection:

6.2.1.1. Respiratory Secretions:

Specimens were obtained from respiratory secretions including deep expectorated or suctioned sputum, transtracheal aspirates, bronchial brushings, biopsies, or washings. Respiratory specimens were collected within 48 hours prior to admission for culture, Gram stain, and susceptibility tests. If the subject could produce sputum, specimens were obtained at the posttherapy visit (five to seven days posttherapy) for culture, susceptibility testing, or Gram stain.

6.2.1.2. Blood Culture

Blood cultures were obtained at admission if associated bacteremia was suspected. Cultures were repeated at later time points if bacteremia was found at admission.

6.2.1.3.Serology

Prior to the first amendment, serology studies for *Mycoplasma pneumoniae, Legionella pneumophila,* and *Chlamydia pneumoniae* were performed at admission for all subjects. A four-fold rise or fall in titer of antibodies from admission to posttherapy or a single diagnostic titer was considered evidence of an infection.

6.2.2. Susceptibility Testing:

Susceptibility to levofloxacin and cefuroxime axetil was determined for all pathogens at admission and, if indicated, at five to seven days posttherapy. The MIC susceptibility was the primary susceptibility criterion. If the MIC values were not available, discs were used to determine susceptibility. Disc susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) methods using 5 μg levofloxacin discs provided by RWJPRI for levofloxacin susceptibility and cefuroxime axetil discs provided by the study center for cefuroxime axetil susceptibility.

6.3. Primary and Secondary Efficacy variables:

6.3.1. Clinical Response:

The primary efficacy variable was clinical response, assessed by the investigator as cured, improved, failed, or unable to evaluate at the final visit five to seven days after the end of therapy. The clinical cure rate was evaluated by determining the percentage of clinically

evaluable subjects who were cured and the clinical success rate was based on the percentage of clinically evaluable subjects who were cured or improved.

6.3.2 Microbiologic Response:

Microbiologic response to treatment was evaluated by RWJPRI in terms of pathogen and infection eradication rates. The microbiologic response for pathogens isolated at admission was determined by evaluating the posttherapy/withdrawal culture results. A culture or evaluation was considered valid if the subject was not receiving any effective concomitant treatment.The microbiologic response for the subject's infection was based on eradication of all the pathogens isolated at admission 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 occurs such that no sputum is produced and invasive procedures for culture are contraindicated, then the pathogen is considered eradicated.

Persisted: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/early termination culture. If a subject was discontinued due to 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 termination culture with documented acquisition of resistance.

Unknown: No posttherapy/early termination culture results available due to lost-to-follow-up, lost culture, or culture not done when specimen was available. If culture was performed on last day of therapy and subject was not a clinical failure or culture done while subject was receiving effective antimicrobial agent for reasons other than clinical failure, the response was unknown.

6.4. Clinical Laboratory Tests

The following standard clinical laboratory evaluations were performed before dosing (admission) and at the posttherapy visit. A central laboratory was used.

Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, red blood cell (RBC) count, and platelet count.

Blood Chemistry: glucose, blood urea nitrogen (BUN), total bilirubin, total protein, albumin, uric acid, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), creatinine, calcium, inorganic phosphorus, sodium, potassium, chloride, and bicarbonate.

Urinalysis: pH, specific gravity, and microscopic examination for red blood cells, white blood cells, and nonamorphous crystals.

7. Schedule and procedures for evaluation of efficacy criteria:

7.1. Clinical Response Rating at Posttherapy (End-of-Therapy/EOT) Evaluation (Five to Seven Days After Completion of Therapy):

7.1.1. The clinical response at posttherapy was assessed as cured, improved, relapse, or unable to evaluate. The definitions for these assessments are as follows:

Cured - Disappearance of signs and symptoms with radiographic evidence of stabilization/improvement at the posttherapy visit with no further therapy required.
Improved - Incomplete resolution of signs and symptoms or incomplete resolution of radiographic signs of acute bacterial exacerbation of chronic bronchitis and no further therapy required.
Failed - No clinical response to therapy or worsening of the radiographic evidence of infection.
Unable to Evaluate - Subject did not return for follow-up evaluation.

7.1.2. Radiographic examinations were to be repeated at the posttherapy evaluation for subjects with suspected relapse. The main findings from the radiographic tests were also described.

7.1.3. Microbiologic evaluations were performed on patients with suspected failure or relapse only as felt to be indicated by the investigator.

7.2. Clinical Response Rating at Post-study (End-of-Study/EOS) Evaluation (28 to 32 Days After Completion of Therapy):

7.2.1. The **clinical response at poststudy** was assessed as cured, improved, relapse, or unable to evaluate. The definitions for these assessments are as follows:

Cured - Complete resolution of signs and symptoms.
Improved - Continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period and no further therapy required.
Relapse - Resolution or improvement of signs and symptoms at posttherapy visit but reappearance or deterioration of signs and symptoms of the infection at Poststudy visit.
Unable to Evaluate - No Poststudy evaluations.

7.2.2. Radiographic examinations were to be repeated at the poststudy evaluation for subjects with suspected relapse. The main findings from the radiographic tests were also described.

7.2.3. Microbiologic evaluations were performed on patients with suspected failure or relapse only as felt to be indicated by the investigator.

8. Safety Evaluation:

Adverse events were defined as treatment-emergent signs and symptoms, i.e., events that were not present at admission or events that represented an increase in severity or frequency of a sign or symptom already present at admission. Subjects were instructed to record on diary cards how they were feeling on each day of the study. These diary cards were reviewed by the investigator during study visits with the subject and any treatment-emergent adverse vents noted on the diary cards were transcribed onto the case report forms RWJPRI study and medical monitors also reviewed these diary cards for treatment-emergent adverse events. Each subject was also assessed at each visit for possible adverse events that might have occurred throughout the study period. The investigator recorded all adverse events on the CRFs and graded their severity as mild, moderate, or

marked. The investigator also assessed the relationship of the adverse event to trial treatment using the following ratings: none, remote, possible, probable, or definite. Other information recorded on the subject's CRF included the date of onset of the event, control measures taken (i.e., discontinuation of study drug, or administration of remedial therapy), the outcome (resolved, persisted, or unknown), and the date of resolution of the event. Serious adverse events were defined as those events that presented a significant threat to the well-being of the subject. Serious adverse events included any event that was fatal, life-threatening, permanently or significantly disabling, required hospitalization or prolonged hospitalization, resulted in long-term outpatient treatment (greater than six months), or was a congenital anomaly, cancer, or overdose. Investigators were instructed to report all serious adverse events immediately to RWJPRI. A 5 cc venous blood sample for determination of plasma levofloxacin concentration was to be obtained at the time of a serious adverse event. However, due to practical limitations, these blood samples were not consistently obtained as planned.

9. Evaluability Criteria:

9.1. Evaluability criteria as per Sponsor:

9.1.1. Evaluability criteria as outlined in Original Protocol dated February 19, 1993:

1. Safety Analysis

To be evaluable for the safety analysis, a subject must take the study medication and must relay safety information.

2. Efficacy Analysis

A subject will be evaluable for microbiological efficacy unless categorized into one of the following groups:

a. Unevaluable for safety
b. Infection not bacteriologically proven. No pathogen identified in the admission respiratory or blood cultures.
c. Resistant to study drug. Admission pathogen is resistant to the assigned drug
d. Insufficient course of therapy. Subject does not take the study drug for at least five days. Subjects who take study drug for less than five days because they are judged a clinical failure by the investigator are evaluable.
e. Effective concomitant therapy. Subject takes an effective systemic antimicrobial agent between time of admission culture (within 48 hours prior to start of therapy) through test-of cure culture (post-therapy). If the subject takes an effective systemic antimicrobial because they have been judged a clinical failure by the investigator, they are evaluable.
f. Inappropriate bacteriologic cultures
    1) Admission culture is greater than 48 hours prior to the start of therapy
    2) Post-therapy culture is not between 2-10 days post-therapy. If the subject is discontinued due to a persistent pathogen or clinical failure and the post-therapy culture is obtained on the last day of therapy, the subject is considered evaluable.
    3) Adequate microbiological data is not available
g. Lost to follow-up but relays safety information
h. Other protocol violation, e.g.,
    1) Subject fails specific entrance criteria
    2) Subject re-enters study
    3) Subject does not take at least 70% of assigned study drug
    4) Subject takes study drug for more than 20 days (unless due to a persistent pathogen)

Additionally, a subject will be evaluable for clinical efficacy, unless the clinical diagnosis was unconfirmed or the subject was classified by categories a, d, e, g, and/or h, above.

9.1.2. Evaluability criteria as outlined in Protocol Amendment #1 dated March 9, 1994:

The evaluability criteria were changed from those in the original protocol by the following deletions (shown in brackets) and additions (shown in bold font):

1. Safety Analysis
To be evaluable for the safety analysis, a subject must take the study medication and must relay safety information.
2. Efficacy Analysis
A subject will be evaluable for microbiological efficacy unless categorized into one of the following groups:
a. Unevaluable for safety
b. Infection not bacteriologically proven.No pathogen identified in the admission respiratory or blood cultures.
[Deletion: c. Resistant to study drug. Admission pathogen is resistant to the assigned drug]
c. Insufficient course of therapy. Subject does not take the study drug for at least five days. Subjects who take study drug for *[Deletion: less than five days because they are judged a clinical failure by the investigator are evaluable]* **greater than 48 hours but for less than 5 days because they are judged a clinical failure by the investigator are evaluable. The pathogen(s) is(are) presumed to persist in these situations.**
d. Effective concomitant therapy. Subject takes an effective systemic antimicrobial agent between time of admission culture (within 48 hours prior to start of therapy) through test-of-cure culture (post-therapy). If the subject takes an effective systemic antimicrobial because they have been judged a clinical failure by the investigator, they are evaluable.
e. Inappropriate bacteriologic cultures
1) Admission culture is greater than 48 hours prior to the start of therapy
2) Post-therapy culture/evaluation is not between 21-10 days post-therapy. If the subject is discontinued due to a persistent pathogen or clinical failure and the post-therapy culture is obtained on the last day of therapy, the subject is considered evaluable.
3) Adequate microbiological data is not available
f. Lost to follow-up but relays safety information
g. Other protocol violation, e.g.,
[Deletion: 1) Subject fails specific entrance criteria]
1) Subject re-enters study
2) Subject does not take at least 70% of assigned study drug
[4) Subject takes study drug for more than 20 days (unless due to a persistent pathogen)]

Medical Officer's Comment: Note that the inclusion criteria and exclusion criteria were removed form the evaluability criteria by this protocol amendment.

9.1.3. Evaluability criteria as outlined in Protocol Amendment #2 dated July 14, 1994:

The evaluability criteria were changed from those in Protocol Amendment #1 by the following deletions (shown in brackets) and additions (shown in bold font):

1. Safety Analysis
To be evaluable for the safety analysis, a subject must take the study medication and must relay safety information.
2. Efficacy Analysis
A subject will be evaluable for microbiological efficacy unless categorized into one of the following groups:
a. Unevaluable for safety
b. Infection not bacteriologically proven. No pathogen identified in the admission respiratory or blood cultures.
[Deletion: c. Resistant to study drug. Admission pathogen is resistant to the assigned drug]

c. Insufficient course of therapy. Subject does not take the study drug levofloxacin for at least four days or the cefuroxime axetil for at least five days. Subjects who take study drug for [less than five days because they are judged a clinical failure by the investigator are evaluable] greater than 48 hours but for less than 5 days because they are judged a clinical failure by the investigator are evaluable. The pathogen(s) is(are) presumed to persist in these situations.

d. Effective concomitant therapy. Subject takes an effective systemic antimicrobial agent between time of admission culture (within 48 hours prior to start of therapy) through test-of-cure culture (post-therapy). If the subject takes an effective systemic antimicrobial because they have been judged a clinical failure by the investigator, they are evaluable.

e. Inappropriate bacteriologic cultures
   1) Admission culture is greater than 48 hours prior to the start of therapy
   2) Post-therapy culture/evaluation is not between 21-10 days post-therapy. If the subject is discontinued due to a persistent pathogen or clinical failure and the post-therapy culture is obtained on the last day of therapy, the subject is considered evaluable.
   3) Adequate microbiological data is not available

f. Lost to follow-up but relays safety information

g. Other protocol violation, e.g.,
   [Deletion: 1) Subject fails specific entrance criteria]
   2) 1) Subject re-enters study
   3) 2) Subject does not take at least 70% of assigned study drug
   [Deletion: 4) Subject takes study drug for more than 20 days (unless due to a persistent pathogen)]

9.1.4. Evaluability criteria as outlined in CANDA submission:

Clinical response to treatment was the primary efficacy variable. Microbiologic response was assessed as a secondary efficacy variable, with eradication rates by pathogen and by infection evaluated separately. Subject evaluability was categorized according to a specified hierarchy. The first category of the hierarchy into which a subject was classified was designated as the primary reason for nonevaluability.

9.1.1.1. Clinical Evaluability Criteria:

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

1. Not evaluable for safety (did not take at least one dose of study drug or had no postadmission data available)
2. Unconfirmed clinical diagnosis
3. Insufficient course of therapy (minimum of four days of levofloxacin therapy and five days of cefuroxime axetil therapy)
4. Effective concomitant therapy.
5. Posttherapy clinical evaluation not done during Posttherapy Day 1-10 interval (window).
6. Lost to follow-up but provided safety information
7. Protocol violation (e.g., subject reentered study or did not take at least 70% of study medication corresponding to reported number of days on therapy).

9.1.2. Microbiologic Evaluability Criteria:

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

1. Not evaluable for safety (did not take at least one dose of study drug or had no postadmission data available).
2. Absence of bacteriologically proven infection.
3. Unconfirmed clinical diagnosis
4. Insufficient course of therapy

5. Effective concomitant therapy
6. Inappropriate timing of bacteriologic cultures (>48 hours prior to admission or outside of acceptable window of one to 10 days posttherapy)
7. Lost to follow-up but provided safety information,
8. Other protocol violation (e.g., subject reenters study or does not take at least 70% of study medication corresponding to reported number of days on therapy).

10.2. Evaluability criteria as per Medical Officer:

10.2.1. Clinical Evaluability Criteria as per Medical Officer:

1. The subject met the inclusion criteria
2. The subject did **NOT** meet any of the exclusion criteria at the time of enrollment
3. A **posttherapy/end-of therapy/EOT** clinical evaluation was performed. The exception was for patients who were declared clinical failures prior to the posttherapy visit, but did not have a posttherapy follow-up visit, here the failure declared on-therapy was carried forward.
4. A symptomatic response could be evaluated at the **posttherapy** time point.
5. With regard to establishing time point for follow-up after treatment of acute bacterial exacerbation of chronic bronchitis, both (1) the **natural history of the disease** and (2) the **half-life of the antimicrobial agent** under investigation need to be taken into account. The windows for follow-up after an episode of acute bacterial exacerbation of chronic bronchitis will be the same for patients treated with any **antimicrobial agent with a relatively short half-life**. It is only in the case of a prolonged half-life that the window for follow-up needs to be extended because blood levels and tissue levels persist far beyond the last dose of the antimicrobial drug. For levofloxacin, whose serum half-life is 6.34-6.310 hours in the clinical tablet, the window of follow-up can be the same as for other antibiotics with relatively short half-lives.

   5.1. The **IDSA Guidelines** recommend standard follow-up after an episode of acute bacterial exacerbation of chronic bronchitis as follows:

   > "Assessment after completion of therapy and follow-up: Patients should undergo clinical and microbiologic assessment within 48 hours, 7-14 days, and 21-28 days after completion of therapy. Clinical assessment should include assessment of cough, dyspnea, sputum volume and sputum purulence."[1]

   5.2. Recent **regulatory precedent** for the appropriate time point for test of cure has been established in other reviews of antimicrobial agents with short half-lives for the indication of acute bacterial exacerbation of chronic bronchitis, and these confirm the need for

[1] Guidelines for the Evaluation of Anti-infective Drug Products. Clin Infect Dis 15(suppl 1):s78, 1992.

late post-therapy follow-up to determine a stable point-estimate for clinical cure at the test-of-cure evaluation[2].

The original protocol 100-070 specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but with an End-of-Study evaluation at 3-6 weeks post-therapy to provide a late follow-up assessment and stable estimate for the test-of-cure. Protocol Amendment #1 also specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but the late follow-up at 3-6 weeks was deleted from the protocol under this. **Therefore, acknowledging that the 5-7 day posttherapy visit is suboptimal for establishing a stable point estimate of the test-of-cure, the medical officer had no choice but to use the only existing endpoint for the follow-up clinical evaluation as the time point for the primary clinical endpoint for the purposes of this evaluation.**

6. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

   6.1. A patient was **fully clinically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

   - Within 48 hours prior to enrollment in the protocol
   - During the treatment period
   - From the end of the treatment period to the poststudy evaluation
   - At the evaluation for clinical relapse

   6.2. If the patient received an antimicrobial agent prior to enrollment in the study, but there was **a pathogenic organism isolated on admission culture**, the patient was considered **clinically evaluable**

   6.3. If the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **clinically unevaluable.**

   6.4. If the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **clinically evaluable (only) as a treatment failure.**

7. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

   7.1. For patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 5 days or 100% of the minimum dose specified by the amended protocol

[2] Dr. Rosemary Roberts, Merepenam NDA Review. NDA Number 50706, Division HFD-520.

7.2. For patients in the cefuroxime arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol

7.3. For patients in either the levofloxacin arm or the cefuroxime designated a clinical failure at EOT, a minimum of 72 hours of study drug was to have been taken

7.4. For the levofloxacin arm, no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 5-7 doses of therapy, as specified by the amended protocol.

7.5. For patients in the cefuroxime arm, no more than two missed doses requiring extension of the dosing interval to complete the full 7-10 days of therapy specified by the protocol

8. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

10.2.2. Microbiologic evaluability criteria as per Medical Officer:

1. A subject met criteria for clinical evaluability at all time points during the study
2. Pretherapy sputum culture was positive for a microorganism known to be pathogenic in acute exacerbation of chronic bronchitis
3. Any residual secretions present at the EOT visit were sent for culture. The medical officer would not accept the category of "presumed eradication" in cases in which there were persistent secretions that were not cultured. The medical officer felt that it was incumbent upon the sponsor and investigators to document eradication when and where possible.

   3.1. Only in cases where there were no residual secretions would the designation "clinical cure/presumed eradication" be accepted.

   3.2. If there residual **purulent** secretions that were not cultured, the medical officer defaulted to "presumed persistence".

   3.3. If there residual **nonpurulent** secretions that were not cultured, the medical officer defaulted to "microbiologically unevaluable".

   3.4. In cases of clinical failure, a microbiologic assessment of "presumed persistence" was universally applied.

4. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

   4.1. a patient was **fully microbiologically evaluable** only if

the patient did **NOT** receive concomitant antibiotic therapy:

- **For the 48 hour period prior to enrollment (see exception under item (ii) below)**
- **During the treatment period**
- **From the end of the treatment period to the posttherapy evaluation and culture**
- **At the evaluation for clinical relapse**

4.2. if the patient received **pretherapy** antimicrobial treatment with another antibiotic, the patient was microbiologically evaluable if there was a pathogen isolated on admission culture. If **no** pathogen was isolated on admission culture, the patient was both clinically and microbiologically unevaluable.

4.3. if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **microbiologically unevaluable.**

4.4. if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **microbiologically evaluable (only) as a persistent pathogen.**

5. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

5.1. for patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 5 days or 100% of the minimum dose specified by the amended protocol

5.2. for patients in the cefuroxime arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol

5.3. for patients in either the levofloxacin arm or the cefuroxime designated a clinical failure at EOT, a minimum of 72 hours of study drug was to have been taken

5.4. for the levofloxacin arm, no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 5-7 doses of therapy, as specified by the amended protocol.

5.5. for patients in the cefuroxime arm, no more than two missed doses requiring extension of the dosing interval to complete the full 7-10 days of therapy specified by the protocol

6. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

10. Investigators and study sites:

Study M 92-024 was conducted by 28 investigators at a total of 33 separate sites, as delineated below:

B. Steven Burke, M.D.a	West Chester, PA; USA
Holly Carveth, M.D.	Veterans Affairs Medical Center, Salt Lake City, UT; USA
Richard Clover, M.D.a	The Univ. of Texas Medical Branch at Galveston, Galveston, TX; USA
C. Andrew DeAbate, M.D.	Metairie, LA; New Orleans, LA; USA
	Waldon's Health Care, Kenner, LA; USA
Henry M. Faris, Jr., M.D.	Woodward Medical Center, Greenville, SC; USA
Robert A. Fiddes, M.D., J.D.,	FCLM - Southern California Research Institute, Whittier, CA; USA
Joseph V. Follett, M.D.	Internal Medicine Group, P.C., Cheyenne, WY; USA
Stuart M. Garay, M.D.	New York Pulmonary Associates, PC, New York, NY; USA
David Ginsberg, D.O.	Harleysville Medical Associates, Harleysville, PA; USA
Glenn Gomes, M.D.	Ochsner Clinic of Baton Rouge, Baton Rouge, LA; USA
Jay Grossman, M.D.	Allergy Care Consultants, Ltd., Tucson, AZ; USA
Robert N. Hunt, M.D.	South Bend, IN; USA
Alan R. Rosenthal, Pharm.D.	Heartland Research Center, South Bend, IN; USA
	Mishawaka, IN; USA
	Osceola, IN; USA
	Health Family Center, Mishawaka, IN; USA
	South Bend Clinic, South Bend, IN; New Carlisle, IN; USA
	South Bend Community Health Center, South Bend, IN; USA
	McKinley Medical Clinic, Mishawaka, IN; USA
	Michiana Family Clinic, South Bend, IN; USA
	Michiana Internal Medicine Ass., South Bend, IN; USA
	Osceola Clinic, Inc., Osceola, IN; USA
	Nappanee, IN; The Medical Group, Michigan City, IN; USA
	The Elkhart Clinic, Elkhart, IN; USA
	Family Practice Associates, Elkhart, IN; USA
William M. Hunter, M.D.	Lovelace Scientific Resources, Albuquerque, NM; USA
Benjamin Interiano, M.D.	The Asthma Institute of Houston, Baylor College of Medicine/The Methodist Hospital, Houston, TX; USA
Mitchell G. Kaye, M.D.	Minnesota Lung Center, Minneapolis, MN; USA
Wm. B. Klaustermeyer, M.D.	Wadsworth VA Medical Center/West Los Angeles, Los Angeles, CA; USA
Phillip E. Korenblat, M.D.	Associated Specialists in Medicine, St. Louis, MO: USA
	Barnes West County Hospital, St. Louis, MO; USA
Peter Kussin, M.D.	Duke University Medical Center, Durham, NC; USA
Thom. W. Littlejohn, III, M.D.	Piedmont Research Associates, Winston-Salem, NC; USA
	Salem Family Practice, Winston-Salem, NC; USA
	Maplewood Family Practice, Winston-Salem, NC; USA
	Salem Chest Specialists, Winston-Salem, NC; USA
Thomas C. Marbury, M.D.	Orlando Clinical Research Center, Orlando, FL; USA
J. Tyler Martin, M.D.	Norfolk, NE; USA
Donald John Matthees, M.D.	Dakota Clinic, Ltd., Fargo, NC; USA
Michael McAdoo, M.D.	Milan, TN; USA
Phillip McElvaine, M.D.	El Paso, TX; USA
Nazir A. Memon, M.D.	Atlantic Pulmonary and Critical Care Associates, Absecon, NJ; USA
Richard R. Moyer, M.D.	Mesaba Clinic, Hibbling, MN; USA
S. Vijayachandran Nair, M.D.	Carl T. Hayden VAMC, Phoenix, AZ; USA
Ronald Lee Nichols, M.D.	Tulane Medical School, New Orleans, LA; USA
	Tulane University Hospital, New Orleans, LA; USA
	Medical Center of Louisiana (Charity Hospital of Louisiana), New Orleans, LA; USA
	Physician's Center, Marrero, LA; USA
Gregory Scott Pape, M.D.	Hanover Medical Specialists, P.A., Wilmington, NC; USA
Anthony D. Puopolo, M.D.	Milford Emergency Associates, Milford, MA; USA
	High St. Medical Center, Clinton, MA; USA
Kathryn Rice, M.D.	Minneapolis VAMC, Minneapolis, MN; USA
Robert D. Rosen, M.D.	Salem Research Group, Inc., Winston-Salem, NC; USA
Melvin Russell, M.D.	Community Medical Arts Center, Tallassee, AL; USA

Jerome J. Schnapp, M.D.	Silver Spring, MD; USA
Robert D. Schreiner, M.D.	St. Joseph's Hospital of Atlanta, Atlanta, GA; USA
William B. Smith, M.D.	Louisiana Cardiovascular Research Center, New Orleans, LA; USA James
Gregory Sullivan, M.D.	Birmingham, AL; USA
Warren R. Summer, M.D.	LSUMC Lions Clinic, New Orleans, LA; USA
Allen Thomas, M.D.	Maricopa Medical Center, Phoenix, AZ; USA
John J. Upchurch, M.D.	St. Vincent's Family Medical Center, Birmingham, AL; USA
William Brent Young, M.D.	Florida Pharmaceutical Research Corp., Spring Hill, FL; USA
Marcus Zervos, M.D.	William Beaumont Hospital, Royal Oak, MI; USA
Steven K. Zorn, M.D.	Pulmonary Medicine P.C., West Des Moines, IA; USA

11. Study Population:

Approximately 400 subjects, men and women who were 18 years of age or older with a diagnosis of acute bacterial exacerbation of chronic bronchitis, were to be enrolled in this study to attain a sample size of 147 clinically evaluable subjects per treatment group for efficacy analysis. Enrollment continued until sufficient numbers of evaluable subjects with infections due to important pathogens were entered. Subjects were enrolled according to the inclusion/exclusion criteria summarized below and described in detail in the protocol. Subjects with a diagnosis of acute bronchitis or pneumonia (as evidenced by acute infiltrates on the admission chest X-ray obtained within 12 hours prior to screening) or cystic fibrosis were not eligible for treatment under this protocol.

12. Efficacy as per Sponsor:

12.1. Demographics of Analysis Groups:

12.1.1. Demographics of Randomized Cohort:

Four hundred ninety-two subjects were enrolled in this study at 34 of the 43 centers (nine investigators did not enroll any subjects). The intent-to-treat group included 246 subjects who were randomized to the levofloxacin treatment group and 246 subjects who were randomized to the cefuroxime axetil treatment group. Two subjects randomized to receive cefuroxime axetil actually received levofloxacin; hence, the numbers of subjects who received levofloxacin and cefuroxime axetil were 248 and 244, respectively. Subject was clinically and microbiologically evaluable while subject was clinically and microbiologically unevaluable. Thus, only one misdosed subject who received levofloxacin instead of cefuroxime axetil is included in the analyses based on clinically evaluable subjects and those based on microbiologically evaluable subjects. The clinical response for this subject was evaluated as "cured" and the microbiologic response as "eradicated". The demographic and baseline (admission) characteristics for the modified intent-to-treat group were comparable between the levofloxacin and cefuroxime axetil treatment groups. The mean age for all subjects was 52.4±17.8 years with a range of 18-97 years. Men accounted for 53.7% of all subjects enrolled and Caucasians for 72.8%. The majority (89.4%) of subjects had an admission diagnosis of COPD. There were no statistically significant differences ($p \geq 0.08$) found between the treatment groups for the variables tested (i.e., age, sex, race). The demographic and baseline characteristics of the sponsor's modified intent-to-treat cohort are summarized in Table 12.2.1 on the following page.

Table 12.1.1.
Demographic and Baseline Characteristics:
Modified Intent-to-treat Cohort (Study M92-024)

	Levofloxacin (N=248)		Cefuroxime axetil (N=244)		Total (N=492)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	124	(50.0)	140	(57.4)	264	(53.7)
Women	124	(50.0)	104	(42.6)	228	(46.3)
Race						
Caucasian	181	(73.0)	177	(72.5)	358	(72.8)
Black	40	(16.1)	45	(18.4)	85	(17.3)
Oriental	1	(0.4)	0	(0.0)	1	(0.2)
Hispanic	26	(10.5)	20	(8.2)	46	(9.3)
Other	0	(0.0)	2	(0.8)	2	(0.4)
Age (Years)						
≤45	100	(40.3)	96	(39.3)	196	(39.8)
46-64	75	(30.2)	63	(25.8)	138	(28.0)
≥65	73	(29.4)	85	(34.8)	158	(32.1)
Mean±SD	51.7±18.0		53.1±17.5		52.4±17.8	
Range	[redacted]		[redacted]		[redacted]	
Weight (lb)						
N	246		243		489	
Mean±SD	172.0±47.4		177.4±43.7		174.6±45.6	
Range	[redacted]		[redacted]		[redacted]	
Missing	2		1		3	
Height (in)						
N	246		243		489	
Mean±SD	66.7±4.43		67.0±4.18		66.8±4.30	
Range	[redacted]		[redacted]		[redacted]	
Missing	2		1		3	
COPD						
Yes	221	(89.1)	219	(89.8)	440	(89.4)
No	27	(10.9)	25	(10.2)	52	(10.6)

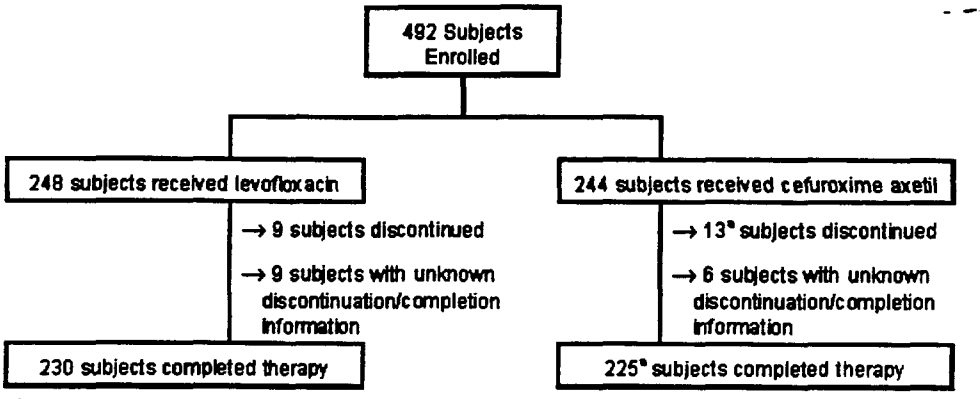
NOTE: Values represent numbers of subjects except as otherwise indicated.

COPD = Chronic obstructive pulmonary disease.

12.1.2. Discontinuation/Completion Information:

Of the 492 subjects enrolled in the study, 248 received levofloxacin and 244 received cefuroxime axetil (modified intent-to-treat group). Of the 239 subjects in the levofloxacin group with known discontinuation/ completion information, nine (3.8%) discontinued therapy prematurely and 230 (96.2%) completed therapy according to the regimen prescribed by the investigator. Discontinuation/completion information is unknown for an additional nine subjects who did not return for the final visit. Of the 238 subjects in the cefuroxime axetil treatment group with known discontinuation/completion information, 13 (5.5%) discontinued therapy prematurely and 225 (94.5%) completed therapy. There were an additional six subjects in this group with unknown discontinuation/completion information. The most common reason for discontinuation in both treatment groups was an adverse event. The subjects discontinuing treatment prematurely and the reasons for their discontinuation are summarized in Figure 12.2.2.A and Table 12.2.2.B on the following page.

Figure 12.1.2.A
Discontinuation/Completion Information:
Modified Intent-to-treat Subjects (Study M92-024)



[a] NOTE: See Section VIII for relevant erratum.

Table 12.1.2.B
Reasons for Premature Discontinuation:
Modified Intent-to-Treat Subjects (Study M92-024)

Reasons	Levofloxacin (N=248)		Cefuroxime axetil (N=244)	
Clinical Efficacy				
Inappropriate Posttherapy Evaluation Date	10		3	
Insufficient Course of Therapy	5		4	
Unevaluable for Safety	5		3	
No Posttherapy Evaluation	4		3	
Effective Concomitant Therapy	1		2	
Other Protocol Violation	1[b]		0	
Total Unevaluable For Clinical Efficacy	26	(10.5%)	15	(6.1%)
Microbiologic Efficacy				
Infection Not Bacteriologically Proven	101		88	
Unevaluable for Safety	5		3	
Inappropriate Timing of Culture Evaluation	4		2	
Insufficient Course of Therapy	3		3	
No Posttherapy Evaluation	1		1	
Total Unevaluable For Microbiologic Efficacy	114	(46.0%)	97	(39.8%)

[a] Subjects counted only once.
[b] This subject ([redacted]) was hospitalized for a serious adverse event and did not return for the posttherapy evaluation and test-of-cure assessment yet had a clinical evaluation of "improved".

12.1.3. Data Set Analyzed

Two hundred twenty-two (89.5%) subjects in the levofloxacin treatment group and 229 (93.9%) subjects in the cefuroxime axetil treatment group were clinically evaluable. One hundred thirty-four (54.0%) subjects in the levofloxacin-treated group and 147 (60.2%) subjects in the cefuroxime axetil-treated group were microbiologically evaluable.

Table 12.1.3
Number of Subjects by Analysis Group and Study Center
(Study M92-024)

	Levofloxacin			Cefuroxime axetil		
Investigator[a]	Modified Intent-to Treat	Clinically Evaluable	Microbiologically Evaluable	Modified Intent-to Treat	Clinically Evaluable	Microbiologically Evaluable
Carveth	5	4 (80.0)	2 (40.0)	6	6 (100.0)	2 (33.3)
DeAbate	51	50 (98.0)	43 (84.3)	49	48 (98.0)	43 (87.8)
Faris	18	16 (88.9)	11 (61.1)	18	18 (100.0)	10 (55.6)
Fiddes	8	8 (100.0)	5 (62.5)	7	5 (71.4)	5 (71.4)
Follett	1	0 (0.0)	0 (0.0)	2	2 (100.0)	0 (0.0)
Garay	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Ginsberg	7	6 (85.7)	5 (71.4)	7	7 (100.0)	6 (85.7)
Gomes	8	7 (87.5)	1 (12.5)	7	5 (71.4)	1 (14.3)
Grossman	3	3 (100.0)	1 (33.3)	2	2 (100.0)	0 (0.0)
Hunt	4	4 (100.0)	2 (50.0)	4	4 (100.0)	2 (50.0)
Hunter	1	0 (0.0)	0 (0.0)	0	0 –	0 –
Interiano	5	4 (80.0)	2 (40.0)	5	5 (100.0)	3 (60.0)
Kaye	0	0 –	0 –	2	2 (100.0)	0 (0.0)
Klaustermeyer	1	1 (100.0)	1 (100.0)	2	2 (100.0)	1 (50.0)
Korenblat	2	2 (100.0)	0 (0.0)	1	1 (100.0)	1 (100.0)
Littlejohn	1	1 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)
Marbury	0	0 –	0 –	1	1 (100.0)	1 (100.0)
McAdoo	4	4 (100.0)	2 (50.0)	5	5 (100.0)	2 (40.0)
McElvaine	22	18 (81.8)	12 (54.5)	22	18 (81.8)	9 (40.9)
Memon	7	7 (100.0)	2 (28.6)	7	6 (85.7)	4 (57.1)
Moyer	10	7 (70.0)	2 (20.0)	10	9 (90.0)	3 (30.0)
Nair	2	2 (100.0)	2 (100.0)	2	1 (50.0)	1 (50.0)
Nichols	0	0 –	0 –	1	1 (100.0)	1 (100.0)
Puopolo	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)
Rice	10	9 (90.0)	5 (50.0)	10	10 (100.0)	7 (70.0)
Rosen	6	6 (100.0)	6 (100.0)	6	5 (83.3)	4 (66.7)
Russell	33	30 (90.9)	15 (45.5)	32	31 (96.9)	22 (68.8)
Smith	4	3 (75.0)	1 (25.0)	2	1 (50.0)	0 (0.0)
Sullivan	1	1 (100.0)	0 (0.0)	2	2 (100.0)	2 (100.0)
Summer	2	1 (50.0)	0 (0.0)	2	2 (100.0)	1 (50.0)
Thomas	5	5 (100.0)	1 (20.0)	3	3 (100.0)	3 (100.0)
Upchurch	13	10 (76.9)	5 (38.5)	11	11 (100.0)	5 (45.5)
Zervos	5	4 (80.0)	2 (40.0)	5	5 (100.0)	3 (60.0)
Zorn	6	6 (100.0)	6 (100.0)	6	6 (100.0)	5 (83.3)
Total	248	222 (89.5)	134 (54.0)	244	229 (93.9)	147 (60.2)

Numbers shown in parentheses are percentages for that category.

[a] Nine investigators (Burke, Clover, Kussin, Martin, Mathews, Pape, Schnapp, Schreiner, and Young) did not enroll any subjects.

12.1.4. Demographics of Clinically and Microbiologically Evaluable Patients:

Two hundred twenty-two (89.5%) subjects in the levofloxacin treatment group and 229 (93.9%) subjects in the cefuroxime axetil treatment group were clinically evaluable. One hundred thirty-four (54.0%) subjects in the levofloxacin-treated group and 147 (60.2%) subjects in the cefuroxime axetil-treated group were microbiologically evaluable. The main reasons that subjects were not clinically evaluable were inappropriate posttherapy evaluation date (levofloxacin group) and insufficient course of therapy (cefuroxime axetil group), whereas the major reason that subjects were not microbiologically evaluable was absence of bacteriologically proven infection (both groups). The demographic and baseline characteristics of the subjects included in the clinically and microbiologically evaluable groups were comparable to the modified intent-to-treat group with respect to age, sex, racial composition, and other baseline characteristics. There were no statistically significant differences ($p \geq 0.08$) found between the treatment groups for the variables tested (i.e., age, sex, race).

Table 12.1.4
Demographic and Baseline Characteristics: Sponsor's Clinically and Microbiologically Evaluable Cohort (Study M92-024)

	Levofloxacin		Cefuroxime Axetil	
	Clinically Evaluable (N=222)	Microbiologically Evaluable (N=134)	Clinically Evaluable (N=229)	Microbiologically Evaluable (N=147)
Sex				
Men	112	66	130	82
Women	110	68	99	65
Race				
Caucasian	161	93	167	100
Black	38	27	44	35
Oriental	1	1	0	0
Hispanic	22	13	16	11
Other	0	0	2	1
Age (Years)				
≤45	89	57	88	63
46-64	68	42	60	40
≥65	65	35	81	44
N	222	134	229	147
Mean±SD	51.8±17.5	49.7±17.4	53.4±17.3	52.0±17.0
Range	[redacted]	[redacted]	[redacted]	[redacted]
Weight (lb)				
N	220	133	228	146
Mean±SD	170.6±44.2	166.7±41.4	177.9±44.4	178.1±47.0
Range	[redacted]	[redacted]	[redacted]	[redacted]
Missing	2	1	1	1
Height (in)				
N	220	133	228	146
Mean±SD	66.6±4.45	66.6±4.04	67.1±4.20	67.1±4.23
Range	[redacted]	[redacted]	[redacted]	[redacted]
Missing	2	1	1	1
COPD				
Yes	202	124	208	137
No	20	10	21	10

NOTE: Values represent numbers of subjects unless otherwise indicated.
COPD = Chronic obstructive pulmonary disease.

12.2. Compliance/Protocol variations::

Subjects were to receive either one 500-mg levofloxacin tablet once daily or two 250-mg cefuroxime axetil tablets every 12 hours for a total daily dose of 500 mg cefuroxime axetil. The total planned duration of therapy for the levofloxacin group was five to seven days and for the cefuroxime axetil treatment group 10 days but either therapy could be extended at the discretion of the investigator if indicated. A minimum of four days of levofloxacin therapy and five days of cefuroxime axetil therapy was required for analysis of clinical response; subjects who had failed clinically (in the judgment of the investigator) and had taken more than 48 hours of study drug were not classified as unevaluable due to insufficient course of therapy. There were no significant protocol variations reported except for the drug dispensing and dosing errors previously described and the enrollment of one subject [redacted] with renal insufficiency, an exclusion criterion for study admission.

12.3. Medications:

12.3.1. Concurrent Therapies:

Concurrent therapies administered during the study that were considered to possibly have a clinically relevant interaction with quinolones are summarized in Table 6 along with the total number of subjects who received any concurrent therapy. Comparable percentages of subjects in the levofloxacin and cefuroxime axetil treatment groups took these concomitant medications. One subject each in the levofloxacin and cefuroxime axetil groups had unknown concomitant medication information. Percentages are based on the number of subjects with known concomitant medication information. Besides the traditional central nervous system-acting drugs (antipsychotics, antidepressants, antiepileptics, hypnotics, sedatives, antiparkinson agents, opioid analgesics, and anesthetics), other drugs with secondary central nervous system effects were included.

Table 12.3.1
Summary of Concurrent Therapies:
Modified Intent-to-Treat Subjects (Study M92-024)

	Levofloxacin (N=248)		Cefuroxime axetil (N=244)	
Therapy Classification	No.	(%)[a]	No.	(%)[a]
Total Who Took Concurrent Therapy	210	(85.0)	208	(85.6)
Central Nervous System[b]	120	(48.6)	123	(50.6)
Bronchodilators	41	(16.6)	39	(16.0)
Antacids	31	(12.6)	38	(15.6)
NSAID	23	(9.3)	32	(13.2)
Vitamins & Nutritional Supplements	12	(4.9)	13	(5.3)
Antimicrobials	12	(4.9)	20	(8.2)
Antidiabetic Therapy	8	(3.2)	7	(2.9)
Anticoagulants	2	(0.8)	8	(3.3)
Total with Concurrent Therapy Info.	247	(100.0)	243	(100.0)
Unknown	1		1	

[a] One subject each in the levofloxacin and cefuroxime axetil groups had unknown concomitant medication information. Percentages are based on the number of subjects with known concomitant medication information.

[b] Besides the traditional central nervous system-acting drugs (antipsychotics, antidepressants, antiepileptics, hypnotics, sedatives, antiparkinson agents, opioid analgesics, and anesthetics), other drugs with secondary central nervous system effects were included. See Appendices 10 and 11 for complete drug list.

12.3.2. Extent of exposure

The extent of exposure to therapy is shown by treatment group in Table 12.3.2 for the modified intent-to-treat group. The mean duration of therapy was seven days for levofloxacin-treated subjects and 10 days for cefuroxime axetil-treated subjects; the medians were also 7 and 10, respectively. Four subjects required dosage adjustments due to subject dosing errors. Two subjects in the levofloxacin treatment group took levofloxacin b.i.d. before the dosage was adjusted to once a day. Two subjects took cefuroxime axetil b.i.d. and then reduced the dosage to once a day.

Table 12.3.2
Extent of Exposure to Therapy:
Sponsor's Intent-to-treat Subjects (Study M92-024)

Extent of Exposure	Levofloxacin (N=248)	Cefuroxime axetil (N=244)
Days on Therapy*		
Unknown	8	4
1	1	0
2	1	1
3	3	1
4	2	1
5	1	2
6	3	3
7	219	2
8	3	3
9	1	2
10	1	177
11	1	42
12	2	3
14	2	1
15	0	2
Mean±SD	7.0±1.1	10.0±1.3
Median	7	10
Number of Doses		
Total with Dosing Information	240	240
Total Unknown Dosing Information	8	4
Mean±SD	7.0±1.2	19.5±2.4
Median	7	20
Range	1-14	2-28

NOTE: Levofloxacin had a q24h dosing schedule and cefuroxime axetil had a q12h dosing schedule. The total planned duration of therapy was five to seven days for levofloxacin and 10 days for cefuroxime axetil.

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

12.4. Clinical Results as per Sponsor:

This section of the report focuses on results of the primary efficacy analyses of clinical response, based on the group of subjects evaluable for clinical efficacy. The results from the modified intent-to-treat and intent-to-treat groups were generally consistent with those from the clinically evaluable group.

12.4.1. Overall Clinical Response

Among clinically evaluable subjects in the levofloxacin treatment group, 80.6% were cured and 14.0% were improved, compared with 75.5% and 17.0% in the cefuroxime axetil treatment group. Twelve (5.4%) subjects in the levofloxacin treatment group and 17 (7.4%) subjects in the cefuroxime axetil treatment group failed treatment. In the modified intent-to-treat group, levofloxacin treatment resulted in 75.0% cure, 15.3% improvement, and 6.0% failure; 3.6% of subjects could not be evaluated. Cefuroxime axetil treatment resulted in 72.5% cure, 17.6% improvement, and 7.4% failure; 2.5% of subjects could not be evaluated. Similar results were found in the intent-to-treat group. Furthermore, 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". Two-sided 95% confidence intervals around the difference in clinical success rates were calculated to evaluate therapeutic equivalence between treatments. Among clinically evaluable subjects, levofloxacin treatment resulted in 94.6% clinical success while cefuroxime axetil treatment resulted in 92.6% clinical success, with a 95% confidence interval of [-6.8, 2.7] for the difference (cefuroxime axetil minus levofloxacin) in success rates. All of the treatment differences in this confidence interval lie below the upper bound of 10% for establishing clinical equivalence of treatments with success rates greater than 90%. Confidence intervals computed for each study center with 10 or more clinically evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers. The cure rates for the two treatment groups for all centers combined were similar (80.6% for levofloxacin, 75.5% for cefuroxime axetil), with a 95% confidence interval on the difference in cure rates of [-12.9, 2.8]. Similar cure rates were observed in the two treatment groups across the study centers and across the analysis groups. The results observed for the evaluable subject roup that indicate equivalence between treatment groups were also observed across various sex, age, and race subgroups. In the modified intent-to-treat group, the clinical success rates for treatment with levofloxacin and cefuroxime axetil were 90.3% and 90.2%, respectively. To evaluate consistency across all analysis groups in clinical success rates, 95% confidence intervals for the difference in success rates are provided and presented graphically. The individual confidence intervals for all of the analysis groups are centered below

Table 12.2.1.A
Clinical Response Rate for Each Study Center: Sponsor's Clinically Evaluable Subjects (Study M92-024)

	Levofloxacin				Cefuroxime axetil			
Investigator	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Carveth	4	3 (75.0)	1 (25.0)	0 (0.0)	6	5 (83.3)	0 (0.0)	1 (16.7)
DeAbate	50	49 (98.0)	1 (2.0)	0 (0.0)	48	46 (95.8)	0 (0.0)	2 (4.2)
Faris	16	13 (81.3)	3 (18.8)	0 (0.0)	18	12 (66.7)	6 (33.3)	0 (0.0)
Fiddes	8	6 (75.0)	2 (25.0)	0 (0.0)	5	1 (20.0)	4 (80.0)	0 (0.0)
Follett	0	0 —	0 —	0 —	2	2 (100.0)	0 (0.0)	0 (0.0)
Garay	1	1 (100.0)	0 (0.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0 (0.0)
Ginsberg	6	6 (100.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)
Gomes	7	7 (100.0)	0 (0.0)	0 (0.0)	5	4 (80.0)	1 (20.0)	0 (0.0)
Grossman	3	2 (66.7)	1 (33.3)	0 (0.0)	2	2 (100.0)	0 (0.0)	0 (0.0)
Hunt	4	4 (100.0)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)
Interiano	4	2 (50.0)	2 (50.0)	0 (0.0)	5	2 (40.0)	3 (60.0)	0 (0.0)
Kaye	0	0 —	0 —	0 —	2	0 (0.0)	1 (50.0)	1 (50.0)
Klaustermeyer	1	1 (100.0)	0 (0.0)	0 (0.0)	2	0 (0.0)	2 (100.0)	0 (0.0)
Korenblat	2	2 (100.0)	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	0 (0.0)
Littlejohn	1	1 (100.0)	0 (0.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	0 (0.0)
Marbury	0	0 —	0 —	0 —	1	1 (100.0)	0 (0.0)	0 (0.0)
McAdoo	4	4 (100.0)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)
McElvaine	18	14 (77.8)	4 (22.2)	0 (0.0)	18	15 (83.3)	2 (11.1)	1 (5.6)
Memon	7	6 (85.7)	1 (14.3)	0 (0.0)	6	5 (83.3)	1 (16.7)	0 (0.0)
Moyer	7	5 (71.4)	0 (0.0)	2 (28.6)	9	7 (77.8)	1 (11.1)	1 (11.1)
Nair	2	1 (50.0)	0 (0.0)	1 (50.0)	1	1 (100.0)	0 (0.0)	0 (0.0)
Nichols	0	0 —	0 —	0 —	1	0 (0.0)	1 (100.0)	0 (0.0)
Puopolo	2	2 (100.0)	0 (0.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	0 (0.0)
Rice	9	4 (44.4)	3 (33.3)	2 (22.2)	10	2 (20.0)	5 (50.0)	3 (30.0)
Rosen	6	4 (66.7)	2 (33.3)	0 (0.0)	5	3 (60.0)	2 (40.0)	0 (0.0)
Russell	30	22 (73.3)	6 (20.0)	2 (6.7)	31	27 (87.1)	2 (6.5)	2 (6.5)
Smith	3	3 (100.0)	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	0 (0.0)
Sullivan	1	1 (100.0)	0 (0.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	0 (0.0)
Summer	1	0 (0.0)	1 (100.0)	0 (0.0)	2	0 (0.0)	1 (50.0)	1 (50.0)
Thomas	5	1 (20.0)	2 (40.0)	2 (40.0)	3	2 (66.7)	0 (0.0)	1 (33.3)
Upchurch	10	6 (60.0)	1 (10.0)	3 (30.0)	11	8 (72.7)	2 (18.2)	1 (9.1)
Zervos	4	4 (100.0)	0 (0.0)	0 (0.0)	5	4 (80.0)	1 (20.0)	0 (0.0)
Zorn	6	5 (83.3)	1 (16.7)	0 (0.0)	6	3 (50.0)	1 (16.7)	2 (33.3)
Combined*	98	75 (76.5)	16 (16.3)	7 (7.1)	103	65 (63.1)	27 (26.2)	11 (10.7)
Total	222	173 (80.6)	31 (14.0)	12 (5.4)	229	173 (75.5)	39 (17.0)	17 (7.4)

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: Carth, Fiddes, Follett, Garay, Ginsberg, Gomes, Grossman, Hunt, Interiano, Kaye, Klaustermeyer, Korenblat, Littlejohn, Marbury, McAdoo, Memon, Moyer, Nair, Nichols, Puopolo, Rice, Rosen, Smith, Sullivan, Summer, Thomas, Zervos, and Zorn.

Table 12.4.1.B
Clinical Success/Failure Rates and Confidence Intervals by Study Center: Sponsor's Clinically Evaluable Subjects (Study M92-024)

	Levofloxacin					Cefuroxime axetil					
Investigator	N	Success[a]		Failure[a]		N	Success[a]		Failure[a]		95% Confidence Interval[a]
Carveth	4	4	(100.0)	0	(0.0)	6	5	(83.3)	1	(16.7)	–
DeAbate	50	50	(100.0)	0	(0.0)	48	46	(95.8)	2	(4.2)	(-10.9, 2.5)
Faris	16	16	(100.0)	0	(0.0)	18	18	(100.0)	0	(0.0)	(-3.1, 3.1)
Fiddes	8	8	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)	–
Follett	0	0	–	0	–	2	2	(100.0)	0	(0.0)	–
Garay	1	1	(100.0)	0	(0.0)	1	1	(100.0)	0	(0.0)	–
Ginsberg	6	6	(100.0)	0	(0.0)	7	6	(85.7)	1	(14.3)	–
Gomes	7	7	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)	–
Grossman	3	3	(100.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	–
Hunt	4	4	(100.0)	0	(0.0)	4	4	(100.0)	0	(0.0)	–
Interiano	4	4	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)	–
Kaye	0	0	–	0	–	2	1	(50.0)	1	(50.0)	–
Klaustermeyer	1	1	(100.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	–
Korenblat	2	2	(100.0)	0	(0.0)	1	1	(100.0)	0	(0.0)	–
Littlejohn	1	1	(100.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	–
Marbury	0	0	–	0	–	1	1	(100.0)	0	(0.0)	–
McAdoo	4	4	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)	–
McElvaine	18	18	(100.0)	0	(0.0)	18	17	(94.4)	1	(5.6)	(-18.9, 7.6)
Memon	7	7	(100.0)	0	(0.0)	6	6	(100.0)	0	(0.0)	–
Moyer	7	5	(71.4)	2	(28.6)	9	8	(88.9)	1	(11.1)	–
Nair	2	1	(50.0)	1	(50.0)	1	1	(100.0)	0	(0.0)	–
Nichols	0	0	–	0	–	1	1	(100.0)	0	(0.0)	–
Puopolo	2	2	(100.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	–
Rice	9	7	(77.8)	2	(22.2)	10	7	(70.0)	3	(30.0)	–
Rosen	6	6	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)	–
Russell	30	28	(93.3)	2	(6.7)	31	29	(93.5)	2	(6.5)	(-13.9, 14.3)
Smith	3	3	(100.0)	0	(0.0)	1	1	(100.0)	0	(0.0)	–
Sullivan	1	1	(100.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	–
Summer	1	1	(100.0)	0	(0.0)	2	1	(50.0)	1	(50.0)	–
Thomas	5	3	(60.0)	2	(40.0)	3	2	(66.7)	1	(33.3)	–
Upchurch	10	7	(70.0)	3	(30.0)	11	10	(90.9)	1	(9.1)	(-17.9, 59.0)
Zervos	4	4	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)	–
Zorn	6	6	(100.0)	0	(0.0)	6	4	(66.7)	2	(33.3)	–
Combined[c]	98	91	(92.9)	7	(7.1)	103	92	(89.3)	11	(10.7)	(-11.9, 4.6)
Total	**222**	**210**	**(94.6)**	**12**	**(5.4)**	**229**	**212**	**(92.6)**	**17**	**(7.4)**	**(-6.8, 2.7)**

[a] Two-sided 95% confidence interval around the difference (cefuroxime axetil minus levofloxacin) in clinical success rate (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: Carveth, Fiddes, Follett, Garay, Ginsberg, Gomes, Grossman, Hunt, Interiano, Kaye, Klaustermeyer, Korenblat, Littlejohn, Marbury, McAdoo, Memon Moyer, Nair, Nichols, Puopolo, Rice, Rosen, Smith, Sullivan, Summer, Thomas, Zervos, and Zorn.

12.4.2 Clinical Response by Pathogen

Clinical response rates for clinically evaluable subjects infected with key pathogens alone or in combination with other pathogens are shown in Table 12. *H. influenzae*, *H. parainfluenzae*, and *M. (Branhamella) catarrhalis* were the most prevalent pathogens in the levofloxacin treatment group. *S. aureus*, *H. parainfluenzae*, and *M. (Branhamella) catarrhalis* were the most prevalent pathogens in the cefuroxime axetil treatment group. Clinical success rates (cured + improved) for the key pathogens ranged from 87.5% (*S. pneumoniae*) to 96.3% (*H. parainfluenzae*) for levofloxacin-treated subjects and from 87.5% (*M. catarrhalis*) to 100% (*H. influenzae* and *S. pneumoniae*) for cefuroxime-treated subjects.

Table 12.4.2
Clinical Response Rates For Subjects with Pathogens of Primary Interest: Sponsor's Clinically and Microbiologically Evaluable Subjects (Study M92-024)

	Levofloxacin				Cefuroxime axetil			
Pathogen	N*	Cured	Improved	Failed	N*	Cured	Improved	Failed
Haemophilus influenzae	44	37 (84.1)	5 (11.4)	2 (4.5)	31	23 (74.2)	8 (25.8)	0 (0.0)
Haemophilus parainfluenzae	27	24 (88.8)	2 (7.4)	1 (3.7)	32	24 (75.0)	5 (15.6)	3 (9.4)
Moraxella (Branhamella) catarrhalis	25	20 (80.0)	4 (16.0)	1 (4.0)	32	23 (71.9)	5 (15.6)	4 (12.5)
Streptococcus pneumoniae	16	12 (75.0)	2 (12.5)	2 (12.5)	10	10 (100.0)	0 (0.0)	0 (0.0)
Staphylococcus aureus	10	9 (90.0)	0 (0.0)	1 (10.0)	35	31 (88.6)	2 (5.7)	2 (5.7)

Numbers shown in parentheses are percentages for that category.

12.4.3. Clinical Symptoms/radiographic signs:

In general, for both the levofloxacin and cefuroxime axetil treatment groups, there was clearing of individual symptoms from admission to posttherapy in approximately 70% or more subjects. The proportions of clinically evaluable subjects with resolution or improvement of signs of bronchitis based on the chest examination revealed that a trend toward resolution or improvement was evident in both the levofloxacin and cefuroxime axetil treatment groups.

Table 12.4.3
Proportion of Subjects with Resolution of Clinically Symptoms of Bronchitis Based on Posttherapy Evaluation: Sponsor's Clinically Evaluable Subjects (Study M92-024)

	Levofloxacin		Cefuroxime axetil	
Symptom	Resolved*	(%)	Resolved*	(%)
Chills	77/79	(97.5)	72/75	(96.0)
Chest Pain	95/104	(91.3)	99/111	(89.2)
Shortness of Breath	129/185	(69.7)	134/185	(72.4)
Cough Increase	197/220	(89.5)	195/226	(86.3)
Sputum Increase	203/219	(92.7)	204/223	(91.5)
Purulent Sputum	194/218	(89.0)	195/225	(86.7)

* Symptom present at admission and absent at posttherapy evaluation.
* Denominator represents number of subjects with that symptom at admission.

12.5. Microbiologic Results:

Microbiologic response was a secondary efficacy variable in this study.

12.5.1. *In Vitro* Susceptibility:

One hundred forty-five subjects in the levofloxacin treatment group and 156 subjects in the cefuroxime axetil treatment group had pathogens isolated at admission. The 145 subjects in the levofloxacin group had 202 pathogens with known susceptibility isolated at admission and the 156 subjects in the cefuroxime axetil group had 227 pathogens isolated at admission with known susceptibility. There were 198 (98.0%) pathogens isolated at admission from levofloxacin-treated subjects that were susceptible or moderately susceptible to levofloxacin and 206 (90.7%) pathogens isolated from cefuroxime axetil-treated subjects that were susceptible or moderately susceptible to cefuroxime axetil. The resistant pathogens represented 2.0% and 9.3% of all isolates with known susceptibility from levofloxacin- and cefuroxime axetil-treated subjects. Percentages were based on numbers of pathogens with known susceptibilities.

Table 12.5.1.A
In vitro Susceptibility of All Pathogens isolated at Admission: Modified Intent-to-Treat Subjects with an Admission Pathogen (Study M92-024)

	No. (%)* of Pathogens			
Susceptibility of Pathogen	Levofloxacin		Cefuroxime axetil	
Susceptible	192	(95.0)	191	(84.1)
Moderately Susceptible	6	(3.0)	15	(6.6)
Resistant	4	(2.0)	21	(9.3)
Unknown	4		4	
Total No. Pathogens	206		231	

* Percentages were based on numbers of pathogens with known susceptibilities. Pathogens were isolated from 145 subjects in the levofloxacin group and 156 subjects in the cefuroxime axetil group.

Pathogens were isolated from 145 subjects in the levofloxacin group and 156 subjects in the cefuroxime axetil group. In regards to cross susceptibilities, three hundred fifty-three (82.7%) of 427 isolates with known susceptibilities to both levofloxacin and cefuroxime axetil were susceptible to both drugs; 422 (98.8%) isolates with known cross-susceptibilities were susceptible or moderately susceptible to levofloxacin and 394 (92.3%) isolates were susceptible or moderately susceptible to cefuroxime axetil. Resistance to both drugs was seen for 4 (0.9%) of the isolates. Four pathogens were levofloxacin-resistant and cefuroxime axetil-susceptible or moderately susceptible, while 29 pathogens were levofloxacin-susceptible or moderately susceptible and cefuroxime axetil-resistant. Cross-susceptibility to both drugs was unknown for seven isolates.

Table 12.5.1.B
Cross-Susceptibility of Admission Isolated to Levofloxacin and Cefuroxime: Modified Intent-to-Treat Subjects with an Admission Pathogen (Study M92-024)

		Cefuroxime axetil				
		S	M	R	U	
Levofloxacin	S	353	27	27	3	410
	M	8	2	2	0	12
	R	2	2	4	0	8
	U	0	0	0	7	7
		363	31	33	10	437

S = Susceptible, M = Moderate, R = Resistant, U = Unknown

12.5.2. Microbiologic Eradication Rates:

12.5.2.1. Microbiologic Eradication Rates by Subject:

Among microbiologically evaluable subjects in the levofloxacin treatment group the eradication rate was 96.3% (including 87.3% presumed eradication and 9.0% documented eradication) compared with 93.2% (including 89.1% presumed eradication and 4.1% documented eradication) in the cefuroxime axetil group. Five (3.7%) subjects in the levofloxacin treatment group and 10 (6.8%) subjects in the cefuroxime axetil group had microbiologic persistence. Eradication rates were consistent regardless of sex, age, or race. In the modified intent-to-treat group, levofloxacin treatment resulted in 92.4% eradication and 3.4% persistence; cefuroxime axetil treatment resulted in 89.7% eradication and 7.1% persistence.

Table 12.5.2.1
Microbiologic Eradication Rates and Confidence Intervals by Study Center: Sponsor's Microbiologically Evaluable Patients (Study M92-024)

	Levofloxacin					Cefuroxime axetil						
Investigator	N	Eradicated[a]		Persisted[a]		N	Eradicated[a]		Persisted[a]		95% Confidence Interval[b]	
Carveth	2	2	(100.0)	0	(0.0)	2	1	(50.0)	1	(50.0)	–	
DeAbate	43	43	(100.0)	0	(0.0)	43	42	(97.7)	1	(2.3)	(-8.0,	3.3)
Faris	11	11	(100.0)	0	(0.0)	10	10	(100.0)	0	(0.0)	(-5.0,	5.0)
Fiddes	5	5	(100.0)	0	(0.0)	5	5	(100.0)	0	(0.0)	–	
Ginsberg	5	5	(100.0)	0	(0.0)	6	6	(100.0)	0	(0.0)	–	
Gomes	1	1	(100.0)	0	(0.0)	1	1	(100.0)	0	(0.0)	–	
Grossman	1	1	(100.0)	0	(0.0)	0	0	–	0	–	–	
Hunt	2	2	(100.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	–	
Interiano	2	1	(50.0)	1	(50.0)	3	3	(100.0)	0	(0.0)	–	
Klaustermeyer	1	1	(100.0)	0	(0.0)	1	1	(100.0)	0	(0.0)	–	
Korenblat	0	0	–	0	–	1	1	(100.0)	0	(0.0)	–	
Marbury	0	0	–	0	–	1	1	(100.0)	0	(0.0)	–	
McAdoo	2	2	(100.0)	0	(0.0)	2	2	(100.0)	0	(0.0)	–	
McElvaine	12	12	(100.0)	0	(0.0)	9	8	(88.9)	1	(11.1)	–	
Memon	2	2	(100.0)	0	(0.0)	4	4	(100.0)	0	(0.0)	–	
Moyer	2	0	(0.0)	2	(100.0)	3	3	(100.0)	0	(0.0)	–	
Nair	2	1	(50.0)	1	(50.0)	1	1	(100.0)	0	(0.0)	–	
Nichols	0	0	–	0	–	1	1	(100.0)	0	(0.0)	–	
Rice	5	5	(100.0)	0	(0.0)	7	6	(85.7)	1	(14.3)	–	
Rosen	6	6	(100.0)	0	(0.0)	4	4	(100.0)	0	(0.0)	–	
Russell	15	15	(100.0)	0	(0.0)	22	22	(100.0)	0	(0.0)	(-3.3,	3.3)
Smith	1	1	(100.0)	0	(0.0)	0	0	–	0	–	–	
Sullivan	0	0	–	0	–	2	2	(100.0)	0	(0.0)	–	
Summer	0	0	–	0	–	1	1	(100.0)	0	(0.0)	–	
Thomas	1	0	(0.0)	1	(100.0)	3	2	(66.7)	1	(33.3)	–	
Upchurch	5	5	(100.0)	0	(0.0)	5	4	(80.0)	1	(20.0)	–	
Zervos	2	2	(100.0)	0	(0.0)	3	1	(33.3)	2	(66.7)	–	
Zorn	6	6	(100.0)	0	(0.0)	5	3	(60.0)	2	(40.0)	–	
Combined[d]	65	60	(92.3)	5	(7.7)	72	63	(87.5)	9	(12.5)	(-15.6,	6.0)
Total	134	129	(96.3)	5	(3.7)	147	137	(93.2)	10	(6.8)	(-8.6,	2.5)

[a] Eradication of all pathogens isolated for a subject at admission.
[b] Two-sided 95% confidence interval around the difference (cefuroxime axetil minus levofloxacin) in microbiologic eradication rates were calculated for study centers enrolling 10 or more microbiologically evaluable subjects in each treatment group.
[c] Numbers shown in parentheses are percentages for that category.
[d] Combined centers that enrolled fewer than 10 microbiologically evaluable subjects in either treatment group: Carveth, Fiddes, Ginsberg, Gomes, Grossman, Hunt, Interiano, Klaustermeyer, Korenblat, Marbury, McAdoo, McElvaine, Memon, Moyer, Nair, Nichols, Rice, Rosen, Smith, Sullivan, Summer, Thomas, Upchurch, Zervos, and Zorn.

12.5.2.2. Microbiologic Eradication Rates by Pathogen:

The overall microbiologic eradication rates by pathogen in the levofloxacin and cefuroxime axetil treatment groups were 97.4% and 94.6%, with a 95% confidence interval of [-6.8, 1.2] for the difference between treatments (cefuroxime axetil minus levofloxacin), assuming independence of multiple pathogens and multiple strains within a subject. The eradication rates in the levofloxacin and cefuroxime axetil treatment groups by subject were 96.3% and 93.2%, with a 95% confidence interval of [-8.6, 2.5] for the difference between treatments. Using a confidence interval upper bound of 10% for eradication rates greater than 90%, this interval supports therapeutic equivalence between the two treatments. The most prevalent pathogens for both levofloxacin and cefuroxime axetil treatment groups were gram-negative aerobes (77.4% and 72.1% of pathogens for the two treatment groups); the remaining pathogens were gram-positive aerobes (22.6% and 27.9% of pathogens in the two treatment groups). The

microbiologic eradication rates for gram-negative and gram-positive aerobes in the levofloxacin treatment group were 98.0% and 95.3%. The eradication rates for the same types of organisms in the cefuroxime axetil treatment group were 93.8% and 96.8%. There was 95.5% eradication of the most common pathogen (*H. influenzae*) and 100.0% eradication of the second and third most common pathogens (*H. parainfluenzae* and *M. (Branhamella) catarrhallis*) in the levofloxacin treatment group versus 90.6% to 93.8% eradication in the cefuroxime axetil treatment group. There was a 100% eradication of *S. aureus* and 87.5% eradication of *S. pneumoniae* in the levofloxacin treatment group versus 97.1% and 100.0% eradication, respectively, in the cefuroxime axetil group.

Table 12.5.2.2
Microbiologic Eradication Rates Summarized by Pathogen Category and Pathogen: Sponsor's Microbiologically Evaluable Patients (Study M92-024)

	Levofloxacin		Cefuroxime axetil		
Pathogen Category/Pathogen	N	Eradicated[a]	N	Eradicated[a]	95% Confidence Interval[b]
Pathogen Category					
Gram positive aerobic pathogens	43	41 (95.3)	62	60 (96.8)	(-7.4, 10.3)
Gram negative aerobic pathogens	147	144 (98.0)	160	150 (93.8)	(-8.9, 0.5)
Total by pathogen	190	185 (97.4)	222	210 (94.6)	(-6.8, 1.2)
Total by subject	134	129 (96.3)	147	137 (93.2)	(-8.6, 2.5)
Pathogen[c]					
Haemophilus influenzae	44	42 (95.5)	31	29 (93.5)	(-14.1, 10.3)
Haemophilus parainfluenzae	27	27 (100.0)	32	30 (93.8)	(-16.5, 4.0)
Moraxella (Branhamella) catarrhalis	25	25 (100.0)	32	29 (90.6)	(-21.5, 2.7)
Streptococcus pneumoniae	16	14 (87.5)	10	10 (100.0)	(-8.7, 33.7)
Staphylococcus aureus	10	10 (100.0)	35	34 (97.1)	(-13.4, 7.7)
Pseudomonas aeruginosa	10	9 (90.0)	9	8 (88.9)	- -
Escherichia coli	8	8 (100.0)	6	6 (100.0)	- -
Streptococcus Group C	5	5 (100.0)	5	4 (80.0)	- -
Streptococcus milleri	4	4 (100.0)	5	5 (100.0)	- -
Klebsiella pneumoniae	3	3 (100.0)	11	10 (90.9)	- -
Haemophilus parahaemolyticus	2	2 (100.0)	5	4 (80.0)	- -
Serratia marcescens	1	1 (100.0)	5	5 (100.0)	- -
Neisseria meningitidis	0	0 -	5	5 (100.0)	- -

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

12.6. Superinfection:

Three subjects in the levofloxacin treatment group and four subjects in the cefuroxime axetil treatment group developed superinfections and had the superinfecting organisms isolated during the posttherapy period. For these subjects, all of the isolates with known susceptibility information were susceptible to both levofloxacin and cefuroxime axetil.

Table 12.6
List of Subjects with Superinfections:
Sponsor's Modified Intent-to-Treat Cohort (Study M92-024)

Subject Number	Period	Pathogen	Type of Specimen	Susceptibility: Levofloxacin	Susceptibility: Cefuroxime axetil
Levofloxacin					
	Posttherapy	*Neisseria meningitidis*	Expectorate Sputum	Susceptible	Susceptible
	Posttherapy	*Streptococcus viridans*	Expectorate Sputum	Susceptible	Susceptible
	Posttherapy	*Streptococcus pneumoniae*	Expectorate Sputum	Unknown	Unknown
Cefuroxime axetil					
	Posttherapy	*Haemophilus parahaemolyticus*	Expectorate Sputum	Susceptible	Susceptible
	Posttherapy	*Streptococcus* Group C	Expectorate Sputum	Susceptible	Susceptible
	Posttherapy	*Streptococcus* Group G	Expectorate Sputum	Susceptible	Susceptible
	Posttherapy	*Klebsiella pneumoniae*	Expectorate Sputum	Susceptible	Moderate
	Posttherapy	*Pseudomonas aeruginosa*	Expectorate Sputum	Unknown	Unknown

12.7. Summary of Key Efficacy Results

The clinical responses rates for the clinically evaluable and modified intent-to-treat groups and the microbiologic response rates for the microbiologically evaluable and modified intent-to-treat groups are summarized for the levofloxacin and cefuroxime axetil treatment groups in the table below. Within response category (clinical or microbiologic), the results are comparable between the analysis groups. Moreover, there is concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency and reliability of the clinical and microbiologic responses. The clinical and microbiologic results clearly demonstrate that levofloxacin is equivalent to cefuroxime axetil.

Table 12.7
Summary of Key Efficacy Results:
Sponsor's Clinically and Microbiologically Evaluable Subjects
(Study M92-024)

Clinical and Microbiologic Response			
	Levofloxacin	Cefuroxime Axetil	
Response/Group	Clinical Success or Microbiologic Eradication Rate[a]	Clinical Success or Microbiologic Eradication Rate[a]	95% Confidence Interval[b]
Clinical Response			
Modified Intent-to-Treat	224/248 (90.3)	220/244 (90.2)	(-5.6, 5.3)
Clinically Evaluable	210/222 (94.6)	212/229 (92.6)	(-6.8, 2.7)
Microbiologic Response			
Modified Intent-to-Treat[c]	134/145 (92.4)	140/156 (89.7)	(-9.4, 4.1)
Microbiologically Evaluable[d]	129/134 (96.3)	137/147 (93.2)	(-8.6, 2.5)

Microbiologic Response Versus Clinical Response[e]								
	Clinical Response							
	Levofloxacin				Cefuroxime Axetil			
Microbiologic Response	N	Cured[f]	Improved[f]	Failed[f]	N	Cured[f]	Improved[f]	Failed[f]
Eradicated	129	109(84.5)	17 (13.2)	3 (2.3)	137	109(79.6)	26(19.0)	2 (1.5)
Persisted	5	0 (0.0)	1 (20.0)	4(80.0)	10	2(20.0)	0 (0.0)	8(80.0)

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

13.2. Demographics of FDA Clinically and Microbiologically Evaluable Patient Groups:

13.2.1. Overall Demographics

The FDA medical officer's clinically evaluable patient cohort, selected prior to the modification of the evaluability criteria for the dosage duration and the follow-up clinical evaluation, contained 458 patients. Of these 458 patients, 245 (53%) were female and 213 (47%) were male. This is similar to the distribution found in the intent-to-treat cohort, as summarized in Table 12.1.2. In the cohort of 105 patients who were both clinically and microbiologically evaluable, there were 150 (53%) males and 133 (47%) females. The distribution among racial groups was similar for both cohorts, and this was similar to the distribution in the intent-to-treat cohort. Likewise, the age distribution in the clinically and clinically/microbiologically evaluable cohorts was similar to that in the intent-to-treat cohort.

Table 13.2.1
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts (Study M92-024)

	FDA Clinically Evaluable Patients N (%)	FDA Clinically and Microbiologically Evaluable Patients N (%)
TOTAL	458	283/458 (62%)
Sex		
M	245/458 (53%)	150/283 (53%)
F	213/458 (47%)	133/283 (47%)
Race		
Caucasian	335/458 (73%)	195/283 (69%)
Black	82/458 (18%)	62/283 (22%)
Hispanic	38/458 (8.3%)	24/283 (8.5%)
Asian	1/458 (0.2%)	1/283 (0.3%)
Other	2/458 (0.4%)	1/283 (0.3%)
Age (yrs)		
≤45	178/458 (39%)	119/283 (42%)
46-64	131/458 (29%)	83/283 (29%)
≥65	149/458 (32%)	81/283 (29%)

13. Efficacy as per Medical Officer:

13.1. Patient Population:

Of the sponsor's intent-to-treat cohort, the medical officer considered 93% (458/492) clinically evaluable according to the medical officer's clinical evaluability criteria delineated in Section 11.2.1 of this review. Of the 458 clinically evaluable patients, the medical officer determined that 62% (283/458) of these were microbiologically evaluable according to the medical officer's microbiologic evaluability criteria delineated in Section 11.2.2 of this review. The breakdown of the intent-to-treat cohort by evaluable subgroups and treatment groups is summarized in Table 13.1, below. The reasons for both clinical and microbiologic nonevaluability are summarized in a series of tables under section 13.1.2.

Table 13.1
FDA Clinically and Microbiologically Evaluable Patients:
Breakdown as Subgroups of Sponsor's Intent-to-treat Cohort

<table>
<tr><th colspan="2">FDA Clinically Evaluable</th><th colspan="2">FDA Clinically Nonevaluable</th></tr>
<tr><th>FDA Microbiologically Evaluable N (%)</th><th>FDA Microbiologically Nonevaluable N(%)</th><th>FDA Microbiologically Evaluable N(%)</th><th>FDA Microbiologically Nonevaluable N(%)</th></tr>
<tr><td>283/458 (62%)
Levofloxacin 136/283 (48%)
Cefuroxime 147/283 (52%)</td><td>175/458 (38%)
Levofloxacin 91/175 (52%)
Cefuroxime 84/175 (48%)</td><td>0</td><td>34/492 (7%)
Levofloxacin 21/34 (62%)
Cefuroxime 13/34 (38%)</td></tr>
<tr><td colspan="2">FDA Clinically Evaluable
458/492 (93%)
Levofloxacin 227/458 (50%)
Cefuroxime 231/458 (50%)</td><td colspan="2">FDA Clinically Nonevaluable
34/492 (7%)
Levofloxacin 21/34 (62%)
Cefuroxime 13/34 (38%)</td></tr>
<tr><td colspan="4">Intent-to-treat Cohort
492
Levofloxacin 248/492 (50%)
Cefuroxime 244/492 (50%)</td></tr>
</table>

As discussed in the review of protocol K90-070, a preliminary analysis of the clinical cure rates for 7-10 days of levofloxacin therapy were substantially greater than for 5-7 days of levofloxacin, thus the dosage range for the evaluable patient group was restricted 7-10 days of therapy with levofloxacin in the final statistical analysis of protocol K90-070. In order to maintain comparability of the evaluable patient groups for protocol K90-070 and M92-024, the dosage duration was also restricted in the evaluable patient group for protocol M92-024: 7-10 days duration for levofloxacin therapy and 10-11 days for cefuroxime axetil therapy. Of the 227 FDA clinically evaluable patients, 93% (212/227) received levofloxacin for 7 days were, therefore, considered clinically evaluable in the statistical analysis of protocol M92-024.

In addition to the restriction on dosing duration added after the medical officer's evaluability criteria had been applied, the window for follow-up evaluation was changed to 4-8 days posttherapy. Therefore, after the application of these two further restrictions, the clinically evaluable patient pool used for the final statistical analysis was restricted to 399 patients: 196 levofloxacin-treated patients and 203 cefuroxime-treated patients.

13.2.2. Demographics of FDA Clinically and Microbiologically Evaluable Cohorts: Analysis by Treatment Groups

The demographics of the 458 patients in the FDA clinically evaluable patient cohort are analyzed by treatment group in Table 13.2.2, below. The distribution of all demographic variables is comparable to the distribution found in the intent-to-treat cohort, as summarized in Table 12.1.2.

Table 13.2.2
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts:
Analysis by Treatment Group (Study M92-024)

	FDA Clinically Evaluable Patients N (%)			FDA Clinically and Microbiologically Evaluable Patients N (%)		
	ALL	LEVO	Cefuroxime	ALL	LEVO	Cefuroxime
TOTAL	458 458/492 (93%)	227 227/458 (50%)	231 231/458 (50%)	283 283/458 (62%)	136 136/283 (48%)	147 147/283 (52%)
Sex						
M	245/458 (53%)	114/227 (50%)	131/231 (57%)	150/283 (53%)	67/136 (49%)	83/147 (56%)
F	213/458 (47%)	113/227 (50%)	100/231 (63%)	133/283 (47%)	69/136 (51%)	64/147 (44%)
Race						
Caucasian	335/458 (73%)	166/227 (73%)	169/231 (73%)	195/283 (69%)	95/136 (70%)	100/147 (68%)
Black	82/458 (18%)	38/227 (17%)	44/231 (19%)	62/283 (22%)	27/136 (20%)	35/147 (24%)
Hispanic	38/458 (8%)	22/227 (9.6%)	16/231 (7%)	24/283 (8.5%)	13/136 (9.6%)	11/147 (7.5%)
Asian	1/458 (0.2%)	1/227 (0.4%)	0	1/283 (0.3%)	1/136 (0.4%)	0
Other	2/458 (0.4%)	0	2/231 (1%)	1/283 (0.3%)	0	1/147 (0.5%)
Age (yrs)						
≤45	178/458 (39%)	90/227 (40%)	88/231 (38%)	119/283 (42%)	57/136 (42%)	62/147 (42%)
46-64	131/458 (29%)	70/227 (31%)	61/231 (26%)	83/283 (29%)	42/136 (31%)	41/147 (28%)
≥65	149/458 (32%)	67/227 (30%)	82/231 (35%)	81/283 (29%)	37/136 (27%)	44/147 (30%)

13.3. Reasons for Nonevaluability

13.3.1. Reasons for Clinical Nonevaluability

Of the sponsor's intent-to-treat cohort, the medical officer considered 7% (34/492) clinically unevaluable according to the clinical evaluability criteria delineated under Section 11.2.1 of this review. The addition of the more restrictive evaluability criteria for dosing duration and dates of follow-up clinical assessment, which were added in order to make the analysis of Protocol M92-024 analogous to the analysis of Protocol K90-070, reduced the clinically evaluable patient group to 399 patients. Table 13.3.1 summarizes the reasons for nonevaluability in the entire cohort of clinically nonevaluable patients. The two evaluability criteria which underwent late modification, appropriate clinical evaluation date and insufficient course of therapy, are subdivided to show the effect of the late modification of the evaluability criteria on the FDA clinically evaluable patient cohort.

Table 13.3.1
Reasons for Clinical Nonevaluability:
ALL FDA Nonevaluable Patients (Study M92-024)

Reason for Nonevaluability	Total N	LEVO N	Cefuroxime N
Inappropriate Clinical Evaluation Date			
Original evaluability criteria	9	6	3
Final Evaluability Criteria			
Follow-up evaluation <4 days posttherapy	21	8	13
Follow-up evaluation >8 days posttherapy	23	16	7
Total in final FDA nonevalauble cohort	53	30	23
Drug Therapy			
Insufficient duration of therapy			
Original evaluability criteria	6	4	2
Final Evaluability Criteria			
Levofloxacin <7 days or cefuroxime <10 days	17	6	11
Levofloxacin >10 days or cefuroxime >11 days	10	4	6
Total in final FDA nonevaluable cohort	33	14	19
Unevaluable for Safety	15	9	6
Effective Concomitant Therapy	3	1	2
Protocol Violation	1	1	0
TOTAL Reasons	105	55	50
TOTAL Patients	93	52	41

13.3.2. Reasons for Microbiologic Nonevaluability

Of the 458 clinically evaluable patients in the original FDA evaluable patient pool, the medical officer determined that 62% (283/458) of these were microbiologically evaluable according to the microbiologic evaluability criteria listed under section 11.2.2. Of the clinically evaluable patients, 38% (175/458) were microbiologically unevaluable according to the microbiologic evaluability criteria listed under section 11.2.2. The reasons for microbiologic nonevaluability for the original FDA medical officer's analysis of evaluability are as summarized in Table 13.3.2, below. With the addition of the further restriction on dosage duration and days for posttherapy follow-up evaluation, the pool of clinically and microbiologically nonevaluable patients was expanded to include patients made nonevaluable by these additional criteria. The statistician was unable to provide the medical officer with specific numbers for patients made microbiologically unevaluable by the application of these more stringent evaluability. However, the final microbiologically evaluable patient cohort consisted of 245 patients: 116 levofloxacin-treated patients and 129 cefuroxime-treated patients.

Table 13.3.2
Reasons for Microbiologic Nonevaluability:
Original FDA Microbiologically Evaluability Criteria (Study M92-024)

	Clinically Evaluable/ Microbiologically Unevaluable			Clinically and Microbiologically Unevaluable		
	ALL	LEVO	Cefuroxime	ALL	LEVO	Cefuroxime
No Admission Pathogen	173	91	82	18	12	6
Unevaluable for Safety/Lost-to-Follow-Up	--	--	--	8	4	4
Insufficient duration of therapy	--	--	--	3	2	1
Protocol Violation						
Inappropriate Bacteriologic Culture	--	--	--	5	3	2
Other	1	1	0	--	--	--
Residual Sputum at Posttherapy Visit not Cultured	2	0	2	--	--	--
Total: Microbiologically Nonevaluable Patients FDA Evaluable Patients: All Microorganisms	175	91	84	34	12	6
Total: Microbiologically Nonevaluable Patients FDA Evaluable Patients: All Microorganisms	175			34		
	209					

13.2. Clinical Efficacy as per Medical Officer:

Using the medical officer's clinical evaluability criteria delineated in Section 11.2.1 of this review and the later modifications to the dosage duration and follow-up clinical evaluation evaluability criteria, a total of 399 clinically evaluable patients were selected from the intent-to-treat cohort: 196 levofloxacin-treated patients and 203 cefuroxime-treated patients. The overall cure rate at the posttherapy evaluation was 68% (134/196) for the levofloxacin-treated cohort and 67% (137/203) for the cefuroxime-treated cohort. The 95% confidence interval around the difference in overall cure rates for the two treatment arms was $_{203,196}(-10.5,8.8)_{67\%,68\%}$ [1]. Thus, the overall clinical cure rates for the two treatment arms meet statistical criteria for equivalence. Cure rates by investigator are summarized in Table 13.2.A, below. The investigators Deabate and Faris reported higher clinical cure rates than the majority of investigators, but these higher cure rates were balanced in both treatment arms. Investigator McElvaine reported the highest cure rate in the levofloxacin treatment arm, and this was significantly higher than the cure rate in the cefuroxime treatment arm.

Table 13.2.A
Posttherapy Clinical Cure Rates By Investigator:
FDA Clinically Evaluable Subjects (Study M92-024)

	Levofloxacin						Cefuroxime Axetil					
Investigator	N*	Cure		Improve		Fail	N	Cure		Improve		Fail
Deabate	40	33	(83)	7	(18)	0 (0)	46	40	(87)	6	(13)	0 (0)
Faris	15	12	(80)	3	(20)	0 (0)	18	15	(83)	3	(17)	0 (0)
McElvaine	16	14	(88)	2	(13)	0 (0)	14	10	(71)	4	(29)	0 (0)
Russell	29	20	(69)	7	(24)	2 (7)	29	20	(69)	8	(28)	1 (3)
Other	96	55	(57)	34	(35)	7 (7)	96	52	(54)	30	(31)	14 (15)
Total	196	134	(68)	53	(27)	9 (5)	203	137	(67)	51	(25)	15 (7)

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

The difference in overall cure rates for all centers combined was not statistically significant in FDA's microbiologically evaluable patient group and the drugs are considered therapeutically equivalent; 95% confidence interval for cefuroxime axetil minus levofloxacin $_{203,196}(-10.5,8.8)_{67\%,68\%}$.

[1] Dr. Nancy Silliman. Statistical Review of NDA 20-634 and 20-635.

Of the clinically cured and clinically improved patients are grouped into one category of "clinical success", the levofloxacin-treated patients had an overall success rate of 95% (187/196) and the cefuroxime-treated patients had an overall success rate of 93% (188/203). Overall success rates by investigator are summarized in Table 13.2.B, below. The 95% confidence intervals for (1) individual investigators and (2) the overall clinically evaluable cohort all overlapped zero, indicating that the two treatments meet regulatory criteria for statistical equivalence. The analysis by investigator/investigative site failed to reveal any bias added to the overall result by an anomalous result from any one center.

Table 13.2.B
Posttherapy Clinical Success Rates By Investigator:
FDA Clinically Evaluable Subjects (Study M92-024)

Investigator	Levofloxacin		Cefuroxime Axetil		95% Confidence Interval[c]
	N[a]	Success[b]	N	Success	
Deabate	40	40 (100)	46	46 (100)	N/A
Faris	15	15 (100)	18	18 (100)	N/A
McElvaine	16	16 (100)	14	14 (100)	N/A
Russell	29	27 (93)	29	28 (97)	(-11.4, 18.3)
Other	96	89 (93)	93	82 (88)	(-14.0, 4.9)
Total	196	187 (95)	203	188 (93)	(-7.9, 2.3)

[a]Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[b]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 (cefuroxime axetil minus levofloxacin) in clinical success rate.

13.3. Microbiologic Efficacy as per Medical Officer

Using the medical officer's clinical and microbiologic evaluability criteria delineated in Sections 11.2.1 and 11.2.2 of this review, as well as the further modifications to the dosage duration and follow-up visit criteria, a total of 245 patients were both clinically and microbiologically evaluable, 116 levofloxacin-treated patients and 129 cefuroxime-treated patients. There are no specific recommendations in the "Points-to-consider" document for the number of isolates required for specific pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

The cure rates by pathogen for the respiratory pathogens request by the sponsor in the proposed draft labeling are listed in Table 13.2.A, below. The clinical cure rates in the levofloxacin-treated patients are acceptable for *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*, but are suboptimal for *Moraxella catarrhalis* and *Staphylococcus aureus*.

Table 13.3.A
Poststudy Clinical Cure Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Study M92-024)

Pathogen	Levofloxacin								Cefuroxime Axetil							
	N*	Cure		Improve		Fail			N*	Cure		Improve		Fail		
Haemophilus influenzae	40	29	(73)	9	(23)	2	(5)		31	16	(52)	14	(45)	1	(3)	
Haemophilus parainfluenzae	28	23	(82)	5	(18)	0	(0)		31	24	(77)	4	(13)	3	(10)	
Moraxella (Branhamella) catarrhalis	20	13	(65)	6	(30)	1	(5)		26	18	(69)	4	(15)	4	(15)	
Staphylococcus aureus	8	3	(38)	4	(50)	1	(13)		32	23	(72)	6	(19)	3	(9)	
Streptococcus pneumoniae	10	8	(80)	1	(10)	1	(10)		10	9	(90)	1	(10)	0	(0)	

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

The clinical success rates, defined as the combined group of patients who were clinically "cured" or "improved" at the posttherapy evaluation, are listed by pathogen in Table 13.2.B, below. In the levofloxacin-treated patients, the overall clinical success rates are within acceptable limits for all major pathogens.

Table 13.3.B
Poststudy Clinical Success Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Study M92-024)

Pathogen	Levofloxacin					Cefuroxime Axetil			
	N[a]	Clinical Success[b]		Fail		N[a]	Clinical Success		Fail	
Haemophilus influenzae	40	38	(95)	2	(5)	31	30	(97)	1	(3)
Haemophilus parainfluenzae	28	28	(100)	0	(0)	31	28	(90)	3	(10)
Moraxella (Branhamella) catarrhalis	20	19	(95)	1	(5)	26	22	(85)	4	(15)
Staphylococcus aureus	8	7	(87)	1	(13)	32	29	(91)	3	(9)
Streptococcus pneumoniae	10	9	(90)	1	(10)	10	10	(100)	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.
[b] The category of "Clinical Success" is defined by those patients considered clinically cured or improved at the post-therapy evaluation.

Microbiologic eradication rates and confidence intervals are listed by investigator in Table 13.3.C, below. There does not appear to be any bias introduced into the overall result by any one center, since all confidence interval overlap zero.

Table 13.3.C
Microbiologic Eradication Rates and Confidence Intervals By Investigator: FDA Microbiologically Evaluable Subjects (Study M92-024)

Investigator	Levofloxacin		Cefuroxime Axetil		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
Deabate	35	35 (100)	42	42 (100)	N/A
Russell	14	12 (86)	20	18 (90)	(-24.3, 32.9)
Other	67	60 (90)	67	52 (78)	(-25.8, 1.9)
Total	116	107 (93)	129	112 (87)	(-13.8, 3.0)

[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 (cefuroxime axetil minus levofloxacin) in microbiologic eradication rate.

The microbiologic eradication rates by pathogen for the major categories of pathogens and the specific pathogens requested by the sponsor in the proposed labeling are listed in Table 13.3.D, on the following page. The microbiologic eradication rates for levofloxacin-treated patients are statistically equivalent to the eradication rates for cefuroxime-treated patients, as indicated by the 95% confidence intervals that overlap zero. In addition, the absolute eradication rates for levofloxacin-treated patients for all major pathogens are acceptable, although the absolute eradication rate of 75% for *S. aureus* is on the low end of the acceptable range.

Table 13.3.D
Overall Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects[a] (Study M92-024)

Pathogen Category/Pathogen	Levofloxacin		Cefuroxime Axetil		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	33	30 (91)	56	49 (88)	(-18.9, 12.1)
Gram-negative aerobic pathogens	133	125 (94)	138	125 (91)	(-10.5, 3.7)
Total by pathogen	166	155 (93)	194	174 (90)	(-10.0, 2.6)
Total by subject	116	107 (92)	129	112 (87)	(-13.8, 3.0)
Pathogen					
Haemophilus influenzae	40	36 (90)	29	23 (79)	(-31.1, 9.7)
Haemophilus parainfluenzae	28	28 (100)	30	28 (93)	(-19.0, 5.7)
Moraxella (Branhamella) catarrhalis	20	20 (100)	25	22 (88)	(-29.2, 5.2)
Staphylococcus aureus	8	6 (75)	32	29 (91)	-
Streptococcus pneumoniae	10	9 (90)	10	10 (100)	(-18.6, 38.6)

[a]Numbers shown in parentheses are percentages for that category.
[b]A two-sided confidence interval for the difference (cefuroxime axetil minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

13.4. Overall Success Rates:

The overall success rates, defined by the population of patients who were clinically cured or improved at posttherapy evaluation and had microbiologic eradication of their admission pathogen, are summarized by investigator in Table 13.4, below. The overall success rate for patients with all pathogens isolated at admission was 91%, for the levofloxacin-treated arm and 86% for the cefuroxime-treated arm. for the evaluable patient cohort as a whole, indicating that the overall success rates for the two treatment arms are statistically equivalent. The 95% confidence interval around the difference in overall success rates of the two treatment arms overlapped zero for the individual study sites, indicating that no individual study site biased the overall result.

Table 13.4
Overall Success Rates[a] and Confidence Intervals By Study Center: FDA Microbiologically AND Clinically Evaluable Subjects (Study M92-024)

Investigator	Levofloxacin		Cefuroxime Axetil		95% Confidence Interval[d]
	N[b]	Overall Success[c]	N	Overall Success	
Deabate	35	35 (100)	42	42 (100)	N/A
Russell	14	12 (86)	20	18 (90)	(-24.3, 32.9)
Other	67	59 (88)	66	50 (76)	(-26.7, 2.1)
Total	116	106 (91)	128	110 (86)	(-14.2, 3.3)

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

14. Safety Results as per Sponsor

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any post-admission data were available. Subjects were classified according to the drug that was received. Four hundred eighty-four (98.4%) of 492 subjects enrolled were evaluated for safety. Of the 484 subjects, 243 received levofloxacin and 241 received cefuroxime axetil. Eight subjects (five in the levofloxacin treatment group and three in the cefuroxime axetil treatment group) were lost to follow-up with no safety information and were therefore excluded from the safety analysis.

Table 14.1
Subjects Excluded from the Safety Analysis

Subject Number	Age/Sex	Investigator	Reasons for Exclusion
Levofloxacin			
	28/M	Ginsberg	Lost to follow-up, no available data
	71/M	Hunter	Lost to follow-up, no available data
	20/F	Zervos	Lost to follow-up, no available data
	22/F	McElvaine	Lost to follow-up, no available data
	36/M	DeAbate	Lost to follow-up, no available data
Cefuroxime axetil			
	36/F	McElvaine	Lost to follow-up, no available data
	23/F	McElvaine	Lost to follow-up, no available data
	34/M	DeAbate	Lost to follow-up, no available data

Cross-reference: Appendix 13.

14.2. Overview of Safety Data

The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal and nervous systems, and consisted primarily of headache, diarrhea, nausea, and dizziness. The nature and frequency of adverse events were generally comparable across the two treatment groups. Of the 25 subjects with adverse events considered marked in severity, 13 subjects were in the levofloxacin group and 12 were in the cefuroxime group. Twenty-four (9.9%) levofloxacin-treated subjects and 19 (7.9%) cefuroxime-treated subjects had adverse events considered by the investigator to be probably or definitely related to study drug (drug-related). Of the four subjects with marked drug-related adverse events, two were in the levofloxacin treatment group (pruritus in one subject and nausea in one subject) and two were in the cefuroxime axetil treatment group (chest pain and rhinitis in one subject and diarrhea in one subject). Fifteen subjects discontinued study drug due to adverse events, seven subjects in the levofloxacin treatment group and eight subjects in the cefuroxime group. Nine subjects in the levofloxacin treatment group and five subjects in the cefuroxime axetil treatment group reported serious or potentially serious adverse events, all of which were unrelated or remotely related to the study drug and most likely related to the subjects' underlying condition. No deaths occurred during the study. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs occurred infrequently and were comparable across treatment groups.

14.3. Treatment-Emergent Adverse Events

14.3.1. Summary of All Adverse Events

One-hundred twenty-seven (52.3%) of 243 safety-evaluable subjects in the levofloxacin treatment group and 124 (51.5%) of 241 safety-evaluable subjects in the cefuroxime axetil treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. Body systems with the highest reported incidence of adverse events were the gastrointestinal system and the central and peripheral nervous system. The frequency of adverse events was similar in the two treatment groups. The overall proportions of subjects experiencing an adverse event (52.3% and 51.5% for levofloxacin- and cefuroxime axetil-treated subjects, respectively) did not show a statistically significant difference (i.e., the 95% confidence interval for the difference in rates includes zero). All body systems had calculated confidence intervals that included zero, indicating no statistically significant difference in frequency.

Table 14.3.1.A
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol M92-024)

	Levofloxacin (N=243)		Cefuroxime axetil (N=241)		
Body System	N	(%)	N	(%)	95% Confidence Interval[a]
Gastrointestinal System Disorders	64	(26.3)	73	(30.3)	(-4.3, 12.2)
Central & Peripheral Nervous System Disorders	48	(19.8)	33	(13.7)	(-12.9, 0.8)
Psychiatric Disorders	20	(8.2)	14	(5.8)	(-7.2, 2.3)
Body as a Whole–General Disorders	20	(8.2)	21	(8.7)	(-4.7, 5.7)
Respiratory System Disorders	16	(6.6)	18	(7.5)	(-3.9, 5.6)
Skin and Appendages Disorders	14	(5.8)	8	(3.3)	(-6.4, 1.5)
Reproductive Disorders, Female	7	(5.7)	3	(2.9)	(-6.6, 3.0)
Hearing and Vestibular Disorders	6	(2.5)	1	(0.4)	(-4.4, 0.3)
Vision Disorders	5	(2.1)	5	(2.1)	(-2.7, 2.8)
Urinary System Disorders	5	(2.1)	2	(0.8)	(-3.6, 1.1)
Musculo-Skeletal System Disorders	4	(1.6)	7	(2.9)	(-1.6, 4.1)
Special Senses (Other), Disorders	4	(1.6)	7	(2.9)	(-1.6, 4.1)
Resistance Mechanism Disorders	4	(1.6)	3	(1.2)	(-2.7, 1.9)
Autonomic Nervous System Disorders	3	(1.2)	7	(2.9)	(-1.1, 4.4)
Vascular (Extracardiac) Disorders	3	(1.2)	1	(0.4)	(-2.6, 1.0)
Metabolic and Nutritional Disorders	2	(0.8)	6	(2.5)	(-0.8, 4.1)
Heart Rate and Rhythm Disorders	2	(0.8)	1	(0.4)	(-2.0, 1.2)
Liver and Biliary System Disorders	1	(0.4)	0	(0.0)	(-1.4, 0.6)
Cardiovascular Disorders, General	1	(0.4)	2	(0.8)	(-1.2, 2.0)
Fetal Disorders	1	(0.4)	0	(0.0)	(-1.4, 0.6)
Application Site Disorders	1	(0.4)	0	(0.0)	(-1.4, 0.6)
White Cell and RES Disorders	0	(0.0)	1	(0.4)	(-0.6, 1.4)
Platelet, Bleeding & Clotting Disorders	0	(0.0)	1	(0.4)	(-0.6, 1.4)
Total With Adverse Events (%)	127	(52.3)	124	(51.5)	(-8.9, 8.3)

RES = Reticuloendothelial System.
[a] Two-sided 95% confidence interval around the difference (cefuroxime axetil 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 122 and the total number of women who received cefuroxime axetil was 102.

The most frequently reported adverse events were headache (13.2% incidence rate for levofloxacin-treated subjects versus 10.0% for cefuroxime axetil-treated subjects), diarrhea (7.4% versus 12.4%), nausea (7.4% versus 4.6%), and dizziness (7.0% versus 3.7%). The two treatment groups were generally comparable with respect to the type and incidence of adverse events.

Table 14.3.1.B
Incidence of Frequently Reported (≥2%)
Adverse Events Summarized by Body System:
Subjects Evaluable for Safety (Protocol M92-024)

	Levofloxacin (N=243)		Cefuroxime axetil (N=241)	
Body System/Primary Term	N	(%)	N	(%)
All Body Systems	127	(52.3)	124	(51.5)
Central & Peripheral Nervous System Disorders				
Headache	32	(13.2)	24	(10.0)
Dizziness	17	(7.0)	9	(3.7)
Gastrointestinal System Disorders				
Diarrhea	18	(7.4)	30	(12.4)
Nausea	18	(7.4)	11	(4.6)
Flatulence	12	(4.9)	4	(1.7)
Constipation	10	(4.1)	7	(2.9)
Vomiting	10	(4.1)	4	(1.7)
Abdominal Pain	9	(3.7)	9	(3.7)
Dyspepsia	6	(2.5)	14	(5.8)
Mouth Dry	4	(1.6)	7	(2.9)
Reproductive Disorders, Female[a]				
Vaginitis	7	(5.7)	2	(2.0)
Body As A Whole-General Disorders				
Fatigue	6	(2.5)	1	(0.4)
Chest Pain	2	(0.8)	8	(3.3)
Respiratory System Disorders				
Dyspnea	6	(2.5)	0	(0.0)
Sinusitis	2	(0.8)	5	(2.1)
Psychiatric Disorders				
Insomnia	5	(2.1)	3	(1.2)
Nervousness	5	(2.1)	2	(0.8)
Special Senses Other, Disorders				
Taste Perversion	4	(1.6)	7	(2.9)
Immune System Disorders				
Mouth Dry	2	(0.8)	5	(2.1)

[a] Primary term reported by ≥2% 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 122 and the total number of women who received cefuroxime axetil was 102.

The majority of adverse events were assessed as mild in severity. Thirteen subjects in the levofloxacin treatment group reported one or more adverse events of marked severity, including marked dyspnea and headache in two subjects each. Twelve subjects in the cefuroxime axetil treatment group also reported one or more marked adverse events, including diarrhea and chest pain in two subjects each. No other adverse events of marked severity occurred in more than one subject within a given treatment group, and most were considered by the investigator as unrelated or remotely related to the study drug. Of the four subjects with marked drug-related adverse events, two were in the levofloxacin treatment group (pruritus in one subject and nausea in one subject) and two were in the cefuroxime axetil treatment group (chest pain and rhinitis in one subject and diarrhea in one subject). Six of the 25 subjects with marked adverse events discontinued study drug treatment (three subjects in the levofloxacin treatment group and three subjects in the cefuroxime treatment group). Nine subjects had marked adverse events that were considered serious or potentially serious (four subjects in the levofloxacin treatment group and five subjects in the cefuroxime treatment group).

Table 14.3.C
Subjects with Adverse Events of Marked Severity:
Subjects Evaluable for Safety (Protocol M92-024)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship To Drug[a]
Levofloxacin				
	72	F	Nausea	Probable
	57	M	Asthenia	None
	51	M	Respiratory Insufficiency‡	None
	50	F	Abdominal Pain	Remote
	72	F	Moniliasis	Possible
	65	M	Headache	Remote
	33	F	Vomiting	Remote
			Headache	Remote
	62	M	Dyspnea‡	None
			Bacterial Infection‡	None
			Fever‡	None
	70	M	Skin Disorder[b]	None
	80	F	Arrhythmia‡	None
	38	F	Pruritus	Definite
	56	M	Dyspnea‡	None
	33	M	Hepatic Function Abnormal[c]	None
Cefuroxime Axetil				
	78	M	Gastrointestinal Hemorrhage‡	None
	83	M	Diarrhea	Possible
	70	M	Respiratory Disorder[d],‡	Remote
	37	M	Fracture Pathological[e]	None
	65	M	Pneumonia‡	None
	30	M	Diarrhea	Definite
	78	M	Syncope‡	None
	58	M	Upper Respiratory Tract Infection	None
	55	M	Chest Pain	Probable
			Rhinitis	Probable
	68	M	Headache	Possible
			Headache	Possible
	68	M	Chest Pain‡	Remote
	42	F	Nausea	Possible

[a] Based on investigator's assessment.
[b] Frostbite.
[c] Elevated liver enzymes (SGOT and SGPT).
[d] Acute exacerbation of COPD.
[e] Fractured ribs due to coughing.
* Subject discontinued due to this adverse event. (See Table 25)
** Subject also had a markedly abnormal laboratory value. (See Table 30)
‡ Serious or potentially serious adverse event. (See Table 26)

Twenty-four (9.9%) subjects in the levofloxacin treatment group and 19 (7.9%) subjects in the cefuroxime axetil treatment group had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug. Drug-related adverse events reported by ≥1.0% of levofloxacin-treated subjects were vaginitis (4.1%), nausea (2.5%), and diarrhea (1.6%). Drug-related adverse events reported by ≥1.0% of cefuroxime axetil-treated subjects were diarrhea (2.5%), taste perversion (1.7%), and vaginitis (2.0%). In general, the profile of adverse events in these different subgroups was comparable to that observed in the study population as a whole. However, the overall incidence of adverse events was higher in the levofloxacin group than in the cefuroxime group among women (59.8% vs. 51.0%) and lower in the levofloxacin group than in the cefuroxime group among men (44.6% vs. 51.8%). The differences among women were due primarily to dizziness and other adverse events in the central and peripheral nervous system. In both treatment groups, there were relatively few reports of dizziness among men. In addition, when comparing the two treatment groups across different age groups, adverse events tended to be more prevalent in the

levofloxacin group than in the cefuroxime group in the 46-64 year-old age group (58.7% vs. 41.3%, due primarily to differences in central and peripheral nervous system events), but less prevalent in the levofloxacin group than in the cefuroxime group among subjects ≥65 years of age (44.4% vs. 54.1%, due primarily to differences in GI events and adverse events in the body as a whole).

14.4. Deaths or Discontinuations due to Adverse Events

Fifteen subjects discontinued the study drug due to adverse events, including seven in the levofloxacin treatment group and eight in the cefuroxime axetil treatment group. The treatment-limiting adverse event was considered serious or potentially serious in one levofloxacin-treated subject [redacted]-dyspnea) and one cefuroxime-treated subject syncope). No deaths occurred during the study.

Table 14.4
Subjects who Discontinued due to Adverse Events:
Subjects Evaluable for Safety (Protocol M92-024)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day Of Onset*	Severity	Relationship To Study Drug†	Duration of Therapy (Days)
Levofloxacin							
	72	F	Dizziness	1	Moderate	Possible	1
			Nausea	1	Marked	Probable	
	68	F	Arthralgia	4	Moderate	Possible	3
			Moniliasis	4	Moderate	Probable	
	24	F	Abdominal Pain	4	Mild	Possible	4
	38	F	Rash	4	Moderate	Definite	6
			Pruritus	5	Marked	Definite	
	44	F	Urticaria	5	Moderate	Possible	5
	80	F	Anxiety	3	Moderate	Remote	3
			Dizziness	3	Moderate	Remote	
			Headache	3	Moderate	Remote	
			Nausea	3	Moderate	Remote	
	56	M	Dyspnea‡	4	Marked	None	4
Cefuroxime Axetil							
	61	F	Urticaria	3	Mild	Probable	4
	64	M	Headache	5	Mild	Possible	8
	80	M	Rash	4	Moderate	Possible	5
	30	M	Diarrhea	3	Marked	Definite	3
	78	M	Syncope‡	2	Marked	None	2
	46	M	Bullous Eruption	7	Moderate	Possible	9
	55	M	Chest pain	9	Marked	Probable	10
			Rhinitis	10	Marked	Probable	
	61	F	Diarrhea	2	Mild	Probable	6
			Abdominal Pain	3	Mild	Probable	

* Relative to start of therapy (Day 1).
† Based on investigator's assessment.
* NOTE: See Section VIII for relevant erratum.
‡ Serious or potentially serious adverse event. (See Table 26)
** Subject also had a markedly abnormal laboratory value. (See Table 30)

14.5. Serious or Potentially Serious Adverse Events

Nine subjects in the levofloxacin treatment group and five subjects in the cefuroxime axetil treatment group reported a serious or potentially serious adverse event during or up to approximately three weeks after completing study therapy. Two of the nine subjects who had serious or potentially serious adverse events in the levofloxacin treatment group reported the adverse event after the posttherapy visit; these adverse events were not collected on the CRF and thus are not included in the database for this individual study report but do appear on the RWJPRI serious adverse event reporting database and in the

pooled safety database for the NDA Integrated Safety Summary. Of the 14 subjects with serious or potentially serious adverse events, two subjects withdrew from the study because of the adverse event. In all cases, the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug, and in most cases was attributed to the subject's underlying condition.

Table 14.5
Subjects with Serious Adverse Events:
Subjects Evaluable for Safety (Protocol M92-024)

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	Respiratory Insufficiency	2	Marked	None	7
	48	F	Chest Pain	8	Mild	None	7
	69	M	Myocardial Infarction	28 (21PT)	-	Remote	7
			Cardiac Arrest		-	Remote	
	44	F	Cardiac Failure	20 (8PT)	Moderate	Remote	12
	62	M	Dyspnea	11 (4PT)	Marked	None	7
			Infection Bacterial		Marked	None	
			Fever		Marked	None	
	80	F	Arrhythmia	15 (8PT)	Marked	None	7
	56	M	Dyspnea	4	Marked	None	4
	61	M	Dyspnea	14 (7PT)	Moderate	Remote	7
			Syncope	13 (6PT)	-	Remote	7
	58	M	Atrial Fibrillation	13 (6PT)	-	Remote	7
			Cerebrovascular Disorder		-	Remote	
Cefuroxime Axetil							
	78	M	Gastrointestinal Hemorrhage	12 (2PT)	Marked	None	10
	70	M	Respiratory Disorder[d]	6	Marked	Remote	6
	65	M	Pneumonia	6	Marked	None	6
	78	M	Syncope	2	Marked	None	2
			Tachycardia[e]	6	-	Remote	
	68	M	Chest Pain	7	Marked	Remote	8

[a] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days postherapy, relative to the last day of study drug administration.
[b] Based on investigator's assessment.
[c] These serious adverse events occurred after the scheduled postherapy visit and therefore do not appear on the case report form or in the database for this individual study report. However, these events were collected as part of the RWJPRI serious adverse event reporting database and therefore are reflected in the pooled safety database for the NDA Integrated Safety Summary.
[d] Acute exacerbation of COPD.
[e] This adverse event does not appear in the individual study report database but was captured as serious in the RWJPRI serious adverse event reporting database; it is therefore reflected as serious in the pooled safety database of the NDA Integrated Safety Summary.
[f] Subject discontinued due to this adverse event. (See Table 25)
[g] Subject also had markedly abnormal laboratory value. (See Table 30)

14.6. Dosage Reductions and Concomitant Therapies

15 subjects had study drug therapy stopped due to adverse events, and 14 subjects reported serious or potentially serious adverse events. Several of these treatment-limiting adverse events and serious or potentially serious adverse events required treatment with concomitant therapies. These cases are summarized in Table 14.6, on the following page.

Table 14.6
Subjects who Required Concomitant Therapy for Adverse Events: Subjects Evaluable for Safety (Protocol M92-024)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset[a]	Severity	Concomitant Therapy
Levofloxacin						
	60	F	Vaginitis	17 (10PT)	Moderate	Fluconazole
	45	F	Vaginitis	9 (2PT)	Mild	Miconazole
	46	F	Vaginitis	6	Mild	Miconazole
	37	F	Vaginitis	11 (4PT)	Moderate	Traconazole
	44	F	Vaginitis	6	Moderate	Miconazole
	61	F	Ulcerative Stomatitis	5	Moderate	Nystatin
Cefuroxime Axetil						
	18	F	Diarrhea	3	Moderate	Brompheniramine maleate
	46	F	Vaginitis	12 (1PT)	Moderate	Miconazole
	76	M	Diarrhea	1	Moderate	Lomotil® (Diphenoxylate and atropine)
			Diarrhea	10	Moderate	Lomotil® (Diphenoxylate and atropine)

[a] Includes events considered by the investigator to be probably or definitely related to study drug, except for those resting in study drug discontinuation or considered serious or potentially serious as discussed in Sections IV.I.3b and IV3.c.
[b] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy, relative to the last day of edy drug administration.

14.7. Clinical Laboratory Tests

14.7.1. Overall Changes

A summary of the mean changes from admission to posttherapy for selected laboratory analytes (blood chemistry and hematology) by treatment group is presented in Table 28. No summaries are provided for basophils, monocytes, bicarbonate, or urinalysis parameters. There were no clinically significant mean changes from baseline for any laboratory analyte in the levofloxacin-treated or cefuroxime axetil-treated group, with comparable results in both groups. A Kolmogorov-Smirnov test was used to compare the two treatment groups with respect to the cumulative distribution of percentage changes in laboratory test results from admission to posttherapy. No statistically significant differences between the two treatment groups were observed except for a marginally significant difference for uric acid ($p=0.05$). The clinical relevance of this finding is unknown and will be further addressed in the Integrated Summary of Safety.

14.7.2. Individual Subject Changes

Summaries displaying the percentage of subjects with low, normal, or high values (relative to the RWJPRI reference range) at admission and posttherapy and changes from admission to posttherapy are presented for selected blood chemistry and hematology laboratory tests. The distribution of subjects with low, normal, or high values was comparable in the treatment groups at both the pretherapy and posttherapy timepoints, and showed little change from pretherapy to posttherapy.

Table 14.7.2
Means and Mean Changes from Admission to Posttherapy for Laboratory Analytes: Subjects Evaluable for Safety with Data Available at Admission and Posttherapy (Protocol M92-024)

	Levofloxacin							Cefuroxime axetil						
		Admission		Posttherapy		Change			Admission		Posttherapy		Change	
Laboratory Test	N	Mean	(SD)	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	Mean	(SD)
Blood Chemistry														
Glucose (mg/dL)	229	101.3	(42.97)	102.3	(36.04)	0.9	(30.99)	229	103.0	(43.13)	108.4	(56.58)	5.5	(40.18)
Calcium (mg/dL)	231	9.0	(0.45)	9.0	(0.49)	0.0	(0.48)	233	9.0	(0.42)	9.0	(0.42)	-0.1	(0.44)
Sodium (mEq/L)	231	138.0	(2.50)	138.3	(2.74)	0.3	(2.69)	233	138.0	(2.45)	138.9	(2.54)	0.1	(2.45)
Potassium (mEq/L)	228	4.3	(0.44)	4.3	(0.44)	0.0	(0.46)	230	4.3	(0.39)	4.3	(0.41)	0.0	(0.42)
Chloride (mEq/L)	231	102.6	(3.39)	103.3	(3.72)	0.6	(3.46)	233	102.4	(3.44)	102.9	(3.62)	0.5	(3.31)
Phosphorus, Inorg. (mg/dL)	227	3.6	(0.62)	3.6	(0.61)	0.0	(0.90)	230	3.6	(0.60)	3.5	(0.58)	-0.1	(0.66)
Blood Urea Nitrogen (mg/dL)	231	13.2	(5.50)	13.7	(5.74)	0.6	(4.31)	233	13.1	(4.80)	13.8	(5.16)	0.7	(3.81)
Lactic Dehydrogenase (U/L)	229	176.5	(47.09)	167.0	(40.40)	-8.5	(44.34)	229	179.7	(70.89)	173.6	(48.17)	-6.1	(74.46)
Total Protein (g/dL)	231	7.3	(0.59)	7.1	(0.59)	-0.2	(0.47)	233	7.3	(0.51)	7.2	(0.52)	-0.1	(0.42)
Albumin (g/dL)	229	3.9	(0.37)	3.9	(0.35)	-0.1	(0.28)	233	3.9	(0.32)	3.9	(0.32)	0.0	(0.28)
Uric Acid (mg/dL)	231	5.4	(1.56)	5.5	(1.46)	0.1	(0.67)	232	5.5	(1.60)	5.5	(1.61)	0.0	(0.81)
Creatinine (mg/dL)	231	1.1	(0.25)	1.1	(0.26)	0.0	(0.14)	233	1.2	(0.23)	1.2	(0.27)	0.0	(0.20)
Alkaline Phosphatase (U/L)	229	82.9	(52.06)	80.1	(54.31)	-2.8	(12.97)	232	80.3	(23.76)	77.1	(23.72)	-3.2	(12.45)
SGOT (U/L)	231	26.4	(18.96)	25.2	(20.65)	-1.2	(17.94)	233	28.6	(72.59)	24.4	(20.30)	-4.3	(72.79)
SGPT (U/L)	231	26.4	(26.24)	26.6	(46.36)	0.1	(38.77)	233	29.4	(80.91)	24.7	(23.84)	-4.6	(79.18)
Total Bilirubin (mg/dL)	229	0.5	(0.21)	0.5	(0.20)	0.0	(0.18)	233	0.5	(0.27)	0.5	(0.22)	0.0	(0.25)
Hematology														
Hemoglobin (g/dL)	223	14.5	(1.46)	14.4	(1.44)	-0.2	(0.67)	226	14.7	(1.49)	14.6	(1.52)	-0.1	(0.82)
Hematocrit (%)	217	43.1	(4.54)	42.5	(4.25)	-0.5	(2.75)	221	43.6	(4.51)	43.2	(4.57)	-0.4	(2.85)
WBC ($\times 10^3/\mu L$)	223	8.7	(2.79)	8.0	(2.60)	-0.7	(2.47)	226	8.6	(2.65)	7.9	(2.72)	-0.7	(2.59)
RBC ($\times 10^6/\mu L$)	223	4.8	(0.53)	4.7	(0.51)	-0.1	(0.27)	226	4.9	(0.52)	4.8	(0.54)	0.0	(0.27)
Neutrophils ($\times 10^3/\mu L$)	223	5.7	(2.57)	5.0	(2.24)	-0.7	(2.29)	226	5.7	(2.49)	5.0	(2.55)	-0.6	(2.44)
Lymphocytes ($\times 10^3/\mu L$)	223	2.1	(0.82)	2.2	(0.76)	0.1	(0.67)	226	2.1	(0.79)	2.1	(0.76)	0.0	(0.65)
Eosinophils ($\times 10^3/\mu L$)	223	0.2	(0.15)	0.2	(0.17)	0.0	(0.12)	226	0.2	(0.23)	0.2	(0.15)	0.0	(0.15)
Platelet Count ($\times 10^3/\mu L$)	222	284.5	(77.96)	301.4	(84.99)	16.9	(62.74)	224	275.9	(77.20)	286.9	(77.71)	11.0	(62.49)

N=Number of subjects with admission and posttherapy results

14.7.3. Marked Abnormalities

The laboratory values were classified as markedly abnormal according to standard criteria developed by RWJPRI, which take into account the posttherapy value of the analyte and the change or percentage change from admission. The incidence of markedly abnormal test results for individual analytes within a given treatment group for subjects who had admission data available was low (≤2.2%) and comparable across treatment groups. Twenty-nine subjects (12 in the levofloxacin group and 17 in the cefuroxime axetil group) had a total of 33 markedly abnormal test results after therapy start. Overall, six subjects in each treatment group had abnormal glucose levels: two levofloxacin-treated subjects and five cefuroxime axetil-treated subjects had increased glucose levels; four levofloxacin-treated subjects and one cefuroxime axetil-treated subject had decreased glucose levels. One subject in the levofloxacin group and four subjects in the cefuroxime axetil group had markedly abnormal liver function tests (elevations in SGOT or SGPT). Three subjects in the levofloxacin group and six subjects in the cefuroxime axetil group had markedly abnormal hematology tests (decreased neutrophils or lymphocytes).

Table 14.7.3.A
Incidence of Treatment-emergant Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety (Protocol M92-024)

	Levofloxacin		Cefuroxime axetil	
Laboratory Test	Proportion	%	Proportion	%
Blood Chemistry				
Elevated Glucose	2/230	0.9	5/229	2.2
Decreased Glucose	4/230	1.7	1/229	0.4
Decreased Potassium	1/228	0.4	0/231	0.0
Elevated Phosphorous	1/228	0.4	0/230	0.0
Decreased Phosphorous	1/228	0.4	0/230	0.0
Elevated LDH	0/229	0.0	1/230	0.4
Elevated Creatinine	0/231	0.0	1/234	0.4
Elevated SGOT	1/231	0.4	2/234	0.9
Elevated SGPT	1/231	0.4	3/234	1.3
Hematology				
Decreased Neutrophils	1/225	0.4	1/226	0.4
Decreased Lymphocytes	2/225	0.9	5/226	2.2

* 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 14.7.3.B
Subjects with Treatment-emergant Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety (Protocol M92-024)

Subject Number	Age	Sex	Laboratory Test[a] (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[b]		Follow-up Value (Therapy Day)	Duration of Therapy (Days)
Levofloxacin									
	67	F	Glucose (<70 or >200 mg/dL)	113.0	241.0	10	(3PT)	–	7
	88	F	Glucose (<70 or >200 mg/dL)	89.0	57.0	21	(14PT)	–	7
	73	F	Lymphocytes (<1.0 x 10⁹/μL)	0.34	0.12	14	(7PT)	–	7
	46	F	Glucose (<70 or >200 mg/dL)	98.0	59.0	21	(14PT)	–	7
	72	M	Glucose (<70 or >200 mg/dL)	88.0	58.0	14	(7PT)	–	7
	40	M	Neutrophils (<1.0 x 10⁹/μL)	1.79	0.99	16	(9PT)	–	7
	49	F	Glucose (<70 or >200 mg/dL)	131.0	247.0	16	(9PT)	–	7
	35	F	Glucose (<70 or >200 mg/dL)	81.0	54.0	14	(7PT)	–	7
	53	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.30	1.90	28	(21PT)	–	7
			Potassium (<3.0 or >6.0 mEq/L)	3.80	2.8	28	(21PT)	–	
	33	M	SGOT (>75 IU/L)	56.0	251.0	16	(9PT)	59.0 23 (16PT)	7
			SGPT (>75 IU/L)	118.0	655.0	16	(9PT)	154.0 23 (16PT)	
	33	F	Lymphocytes (<1.0 x 10⁹/μL)	1.26	0.84	12	(5PT)	–	7
	40	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	2.40	11.60	12	(5PT)	–	7
Cefuroxime axetil									
	48	M	Glucose (<70 or >200 mg/dL)	146.0	271.0	15	(5PT)	–	10
	78	M	Lymphocytes (<1.0 x 10⁹/μL)	1.45	0.88	17	(7PT)	–	10
	68	F	Glucose (<70 or >200 mg/dL)	128.0	224.0	15	(5PT)	–	10
	67	F	Creatinine (>1.5 mg/dL)	1.10	3.6	17	(7PT)	1.10 19 (5PT)	10
	76	M	Lymphocytes (<1.0 x 10⁹/μL)	1.63	0.67	17	(7PT)	–	10
	80	M	Glucose (<70 or >200 mg/dL)	167.0	383.0	6	(1PT)	–	5
	83	M	Glucose (<70 or >200 mg/dL)	70.0	253.0	16	(6PT)	–	10
	32	M	SGPT (>75 IU/L)	28.0	78.0	15	(5PT)	–	10
	65	M	Lymphocytes (<1.0 x 10⁹/μL)	2.15	0.33	7	(1PT)	–	6
	39	M	SGPT (>75 IU/L)	31.0	100.0	15	(5PT)	–	10
	76	M	Lymphocytes (<1.0 x 10⁹/μL)	1.51	0.93	17	(7PT)	–	10
	19	M	Lactic Dehydrogenase (>600 U/L)	249.0	667.0	17	(7PT)	–	10
			SGOT (>75 IU/L)	32.0	207.0	17	(7PT)	–	
			SGPT (>75 IU/L)	24.0	214.0	17	(7PT)	–	
	58	F	Glucose (<70 or >200 mg/dL)	113.0	57.0	16	(6PT)	–	10
	76	M	Glucose (<70 or >200 mg/dL)	140.0	260.0	17	(6PT)	–	11
	77	F	Lymphocytes (<1.0 x 10⁹/μL)	1.49	0.92	15	(5PT)	–	10
	49	F	Neutrophils (<1.0 x 10⁹/μL)	2.27	0.91	15	(5PT)	–	10
	31	M	SGOT (>75 IU/L)	34.0	76.0	15	(5PT)	–	10

[a] Only range given in table. For complete criteria see Attachment 24a.
[b] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy, relative to the last day of stdy drug administration.
* Subject discontinued due to adverse event. (See Table 25)
‡ Subject also had serious or potentially serious adverse event. (See Table 26)

14.8. Physical Examinations and Vital Signs

There were no clinically significant mean changesfrom admission to posttherapy in levofloxacin-treated or cefuroxime axetil-treated subjects, with comparable results in the two groups. There were also no clinically significant treatment-emergent vital sign changes in significant treatment-emergent- -physical examination abnormalities.

Table 14.8
Summary of Changes in Vital Signs From Admission to Posttherapy: Subjects Evaluable for Safety (Study M92-024)

	Levofloxacin				Cefuroxime axetil			
		Admission	Posttherapy	Change		Admission	Posttherapy	Change
Vital Sign	N*	Mean (SD)	Mean (SD)	Mean (SD)	N*	Mean (SD)	Mean (SD)	Mean (SD)
Oral Temperature (°F)	237	98.5 (0.99)	98.0 (0.76)	-0.5 (0.95)	238	98.6 (1.00)	98.0 (0.90)	-0.5 (1.12)
Respiratory Rate (breaths/min)	237	19.5 (3.63)	18.1 (3.33)	-1.4 (3.38)	236	19.7 (3.82)	18.3 (2.95)	-1.4 (3.68)
Pulse Rate (beats/min)	238	81.9 (12.89)	79.6 (11.83)	-2.4 (12.25)	237	82.7 (13.18)	80.9 (12.83)	-1.8 (12.01)
Systolic Blood Pressure (mm Hg)	237	128.3 (21.55)	126.3 (20.67)	-2.0 (16.74)	238	127.9 (18.95)	127.5 (18.73)	-0.4 (14.56)
Diastolic Blood Pressure (mm Hg)	237	77.3 (11.53)	76.9 (11.22)	-0.4 (10.18)	238	78.0 (11.65)	77.9 (11.30)	-0.1 (10.47)

* N=Number of subjects with admission and posttherapy vital signs.

15.Conclusions from Protocol M92-024:

15.1 Protocol design and implementation issues:

15.1.1. Protocol M92-024 has significant flaws in the protocol design including:

15.1.1.1. The protocol was a completely unblinded study. This is particularly significant in light of the fact that all of the endpoints are clinical and, thus, subjective and subject to bias by both (1) **observer/expectation bias** from the investigator and (2) **reporting/recall bias** in the patient reporting the symptoms[1].

15.1.1.2. The windows for clinical evaluation at only the End-of-therapy were inappropriate not in keeping with the IDSA guidelines and did not include late follow-up to allow for a definitive test-of-cure evaluation from which could be derived a stable point estimate for the clinical cure rate. In this protocol, the EOT evaluation was conducted too early to assess a stable cure rate and there were no later EOS evaluations, as recommended by the IDSA Guidelines, to assess (1) clinical failures (early relapses) resulting from partial response to study drug or superinfection and (2) late relapses from reinfection with the same organism or infection with another organism.

15.1.1.3. Original windows for follow-up culture were too close to the end of therapy to preclude suppression of regrowth by residual antibiotic levels or post-antibiotic effect

15.1.1.4. Inadequate documentation of the patients baseline (clinical symptoms of chronic bronchitis in the absence of acute exacerbation) clinical status to allow for accurate assessment of the clinical categories of "cured" and "improved" at the posttherapy follow-up. Since patient with chronic bronchitis are symptomatic in their "healthy" baseline status, the accurate assessment of response to therapy is dependent on comparison of posttherapy symptoms with the patient's baseline symptoms of chronic bronchitis in the absence of an acute exacerbation.

15.1.1.5. There were multiple protocol amendments submitted during the course of the study, including deletion of the inclusion/exclusion criteria from the evaluability criteria and deletion of the poststudy clinical evaluation. The issue was raised by the Medical Officer as to whether these changes were in response to protocol violations by the investigators, but the Medical Team leader did not feel that an investigation by the Division of Scientific Investigations was warranted at this time.

15.1.2. Protocol M92-024 has significant flaws in the protocol implementation including:

15.1.2.1. Omission of culture of persistent sinus secretions at the follow-up visits (both EOT and EOS), with overuse of the designation of "presumed eradication" in cases where documentation of microbiologic outcome was possible.

15.1.2.2. Changes in drug dosage and duration were made during the course

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[1] Sackett DL. Bias in Clinical Research. J Chronic Dis 32:51-63, 1979.

of the study, indicating that dose-ranging had not been adequately worked out in Phase 2.

15.1.2.3. Changes in the days of the post-therapy follow-up evaluation were made during the course of the study

15.1.2.4. The end-of-study evaluation was dropped from the protocol during the course of the study, which was in violation of the IDSA Guidelines for follow-up after treatment for acute exacerbation of chronic bronchitis

15.2. Efficacy Results:

15.2.1 Clinical Efficacy Results

The **clinical cure rate** of levofloxacin was statistically equivalent to cefuroxime axetil in Protocol M92-040. The clinical cure rate for the levofloxacin arm was 68% (134/196), and that for the cefuroxime axetil arm was 67% (137/203), with the 95% confidence interval around the difference being $_{203,196}(-10.5 \text{ to } 8.8)_{67\%,\ 68\%}$. Thus, levofloxacin meets regulatory criteria for approval for the treatment of acute exacerbation of chronic bronchitis based on the demonstration of statistical equivalence to an approved competitor. The clinical cure rate in the levofloxacin arm in Protocol K90-070 was 65% (62/95), and, thus, was comparable to the 68% clinical cure rate in the levofloxacin arm of Protocol M92-024.

The **clinical success rate** (clinically cured plus improved) of levofloxacin was statistically equivalent to cefuroxime axetil in Protocol M92-040. The clinical success rate for the levofloxacin arm was 95% (187/196), and that for the cefuroxime axetil arm was 93% (188/203), with the 95% confidence interval around the difference being $_{203,196}(-7.9 \text{ to } 2.3)_{93\%,\ 95\%}$. Thus, levofloxacin meets regulatory criteria for approval for the treatment of acute exacerbation of chronic bronchitis based on the demonstration of statistical equivalence to an approved competitor. The clinical success rate in the levofloxacin arm in Protocol K90-070 was 95% (187/196), and, thus, was comparable to the 68% clinical cure rate in the levofloxacin arm of Protocol M92-024.

The **overall success rate** (clinically cured or improved plus microbiologically eradicated) of levofloxacin was statistically equivalent to cefuroxime axetil in Protocol M92-040. The overall success rate for the levofloxacin arm was 91% (106/116), and that for the cefuroxime axetil arm was 86% (110/128), with the 95% confidence interval around the difference being $_{128,106}(-14.2 \text{ to } 3.3)_{86\%,91\%}$. Thus, levofloxacin meets regulatory criteria for approval for the treatment of acute exacerbation of chronic bronchitis based on the demonstration of statistical equivalence to an approved competitor. The overall success rate in the levofloxacin arm in Protocol K90-070 was 93% (57/61), and, thus, was comparable to the 68% clinical cure rate in the levofloxacin arm of Protocol M92-024.

15.2.2. Microbiologic Efficacy Results

Microbiologic eradication rates for **levofloxacin** for the pathogens requested by the sponsor in the proposed package labeling (*S. pneumoniae, H. Influenzae, H. parainfluenzae, M. catarrhalis* and *S. aureus)* are above 75% in Protocol M92024. In fact, the microbiologic rates for the pathogens other than *S. aureus* (*S. pneumoniae, H. Influenzae, H. Parainfluenzae, M. catarrhalis)* are all above 90% in this protocol. *S. aureus*, on the other hand, had eradication rates of 75% in this protocol. For *S. pneumoniae, H. Influenzae, H. Parainfluenzae, M. catarrhalis* the 95% confidence intervals for the difference between the eradication rates of levofloxacin and comparator overlapped zero, indicating that the two treatments were statistically equivalent in this regard. However, because of the low numbers of individual isolates, the calculation of confidence intervals around the difference in eradication rates was not possible for *S. aureus* in Protocol M92-024. **The eradication rates by individual pathogen are discussed in greater detail and in conjunction with the eradication rates from Protocol K90-070 in the Recommendations Section that follows this review.**

15.3. Issues regarding microbial resistance to the fluoroquinolone antibiotics:

The use of levofloxacin for the treatment of acute exacerbation of chronic bronchitis in the community will, in general, be empiric, thus, its coverage for organisms in which there could be pre-existing or rapid development of resistance may be suboptimal and may not be known with great accuracy.

15.3.1. Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*.

Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*, with methicillin-resistant *S. aureus* (MRSA) developing resistance at a more rapid rate than methicillin-sensitive *S. aureus* (MSSA). Ciprofloxacin-resistance in *S. aureus* is well documented, with reports resistance developing during therapy with these agents[2]. One study surveyed the development of ciprofloxacin-resistance in methicillin-resistant *S. aureus* (MRSA) in patients treated with the antibiotic for nonstaphylococcal infections in a VA Medical Center. These authors reported that 79% of MRSA isolates were resistant to ciprofloxacin one year after introduction of the drug, and 91% of MRSA isolates were resistant to

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[2] Daum TE, Schaberg DR. Increasing resistance of *S. aureus* to ciprofloxacin. Antimicrob Agents Chemother 34:1862-3, 1990; Blumberg HM, Rimland D, et.al. Rapid development of ciprofloxacin resistance in Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. J Infect Dis 163:1279-85, 1991; Mulligan ME, Ruane PJ, et.al. Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization. Am J Med 82 (Suppl.4A):215-9, 1987; Piercy EA, Barbaro D, et.al. Ciprofloxacin for methicillin-resistant Staphylococcus aureus infections. Antimicrob Agents Chemother 33:128-30, 1989; Scaefler S. Methicillin-resistant strains of Staphylococcus aureus resistant to the quinolones. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Widespread quinolone resistance among methicillin resistant S. aureus. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Ciprofloxacin resistance in epidemic methicillin-resistant *S. aureus*. Lancet 2:843, 1988.

ciprofloxacin two years after introduction of the drug[3]. Piercy et.al. reported development of resistance in 16% (6/37) of patients who were being treated with ciprofloxacin for MRSA colonization and Mulligan et.al. reported 32% (7/22) of treatment episodes were associated with the development of ciprofloxacin-resistant MRSA during the course of antibiotic therapy[4]. Resistance among methicillin-susceptible *S. aureus* (MSSA) has been less widespread than with MRSA, but has still been reported[5].

While the mechanism of resistance of *S. aureus* to quinolones is not completely understood, there are authors who suggest that the rapid emergence of ciprofloxacin resistance in *S. aureus* may be due to the fact that a single-step point mutation alone can lead to high-level resistance[6]. For *S. aureus*, the frequency of alterations in DNA gyrase caused by single-step mutations increases from 1 in 10^2 to 1 in 10^5 when bacteria are exposed to concentrations close to the minimal inhibitory concentration. The frequency of single-step mutation to fluoroquinolone resistance in *S. aureus* ranges from 1.5 x10-5 at twice the MIC to ≤3.6 x 10 -12 at eight times the MIC; and high level resistance occurs with serial exposure of bacteria to increasing concentrations of fluoroquinolones[7].

15.3.2. Quinolone-resistance has been documented to occur in *Streptococcus pneumoniae*. The mechanism for pneumococcal resistance to the quinolones is also a one-step point mutation (single amino acid substitution) in the DNA gyrase leading to high level resistance[8]. Quinolone resistance to ciprofloxacin is more prevalent than resistance to ofloxacin, with one paper in 1992 reporting 95% of pneumococcal isolates susceptible to ofloxacin and

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[3] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[4] Piercy EA. Antimicrob Agents Chemother 33:128-30, 1989; Mulligan ME, Ruane PJ, et.al. Am J Med 82 (Suppl.4A):215-9, 1987.

[5] Scaefler S. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Lancet 2:843, 1988; Daum TE, Schaberg DR. Antimicrob Agents Chemother 34:1862-3, 1990.

[6] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991; Oshita Y, Hiramatsu K. A point mutation in *norA* gene is responsible for quinolone resistance in *Staphylococcus aureus*. Biochem Biophys Res Commun 172:1028-34, 1990; Yoshida H, Bogaki M, et.al. Nucleotide sequence and characterization of the Staphylococcus *norA* gene, which confers resistance to the quinolones. J Bacteriol 172:6942-9, 1990; Neu HC. Bacterial resistance to the fluoroquinolones. Rev Infect Dis 10(suppl.1):57-63, 1988; Sreedharan S, Oram M. DNA gyrase *gyrA* mutations in ciprofloxacin-resistant strains of *S. aureus*: close similarity with quinolone resistant mutations in *E. coli*. J Bacteriol 172:7260-2, 1990.

[7] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[8] Piddock LJV, Wise R. The selection and frequency of streptococci with decreased susceptibility to ofloxacin and the other quinolones. J Antimicrobial Chemo 22(suppl C):45-51, 1988.

only 68% of isolates susceptible to ciprofloxacin[9]. However, it should be noted that development of resistance to antimicrobial agents is a time-dependent phenomenon, and that ciprofloxacin has been in use longer than ofloxacin. Data presented by the Center for Disease Control[10] at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy showed that there could be significant development of resistance to ofloxacin in the period of one year, such that the point prevalence for pneumococcal intermediate resistance to ofloxacin was 1% in 1993 and 9.5% in 1994. However, it should be noted that there was no absolute resistance detected in this study. Pharmacokinetic/pharmacodynamic data have been used to attempt to predict the clinical efficacy of antimicrobial agents against specific microorganisms. In the case of the quinolone antimicrobials, the inhibitory quotient, defined as the AUC/MIC ratio (the ratio of the Area Under the Concentration-time Curve (AUC) of the antibiotic to the minimum inhibitory concentration (MIC) of the *S. pneumoniae* isolate) has been shown to be predictive of clinical efficacy, with an AUC/MIC value of 40 being the breakpoint for *S. pneumonaie*[11]. Levofloxacin, being the active isomer of ofloxacin, achieves higher blood level of the active isomer, and thus has a better inhibitory quotient for *S. pneumonaie*, as described in the table below. However, it should be noted that the MIC90 of some strains of *S. pneumonaie* is now ≥4 mcg/mL for both ciprofloxacin and ofloxacin. At this higher MIC, the inhibitory quotient for levofloxacin falls below the breakpoint of 40. Thus, the margin for coverage of organisms with even a marginal drift in *MIC* afforded even by the higher blood levels of levofloxacin is borderline.

It should be noted that all these calculations are theoretical based on the pharmacokinetic/pharmacodynamic data of these compounds. For ofloxacin, there remains a discrepancy between the inadequacy of the inhibitory quotients and the clinical efficacy, with the clinical efficacy being better than would be predicted by the marginal inhibitory quotient against *S. pneumonaie*.

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[9] Jones RN, Reller LB, Rosati LA. Ofloxacin, a new Broad Spectrum Fluoroquinolone: Results from a Multicenter, National Comparative Activity Surveillance Study. Diag. Microbial Infect Dives 15:425-34, 1992.

[10] Butler JC, Hofman J, Elliot JA, et.al. Late breaking abstract. 35th ICAAC, San Francisco, CA, September 17-20, 1995.

[11] Dr. David C. Hooper . Presented at the 35th ICAAC, San Francisco, CA, September, 1995.

Table 15.3.A

Inhibitory quotients against *Streptococcus pneumonaie* for several of the Fluoroquinolone Antibiotics: Calculated for MICs of 2 mcg/mL and 4 mcg/mL

Quinolone Antimicrobial	Inhibitory Quotient (AUC/MIC) for MIC 2 mcg/mL		Inhibitory Quotient (AUC/MIC) for MIC 4 mcg/mL	
	MIC	AUC/MIC	MIC	AUC/MIC
Ciprofloxacin	2 mcg/mL	11.6	4 mcg/mL	5.8
Ofloxacin	2 mcg/mL	43.5	4 mcg/mL	21.8
Levofloxacin	2 mcg/mL	60.7	4 mcg/mL	30.4

15.4. Issues regarding the CNS penetration of levofloxacin:

There is inadequate data regarding the CNS levels of levofloxacin. This is particularly important in assessing the adequacy of this drug for coverage against CNS seeding in bacteremic pneumococcal pneumonia. However, also for CNS coverage in sinusitis (particularly *S. pneumoniae* and *S. aureus*, given that the venous drainage of the sinus is posterior into the venous drainage of the CNS.

According to the biopharmaceutics reviewer, the pharmacokinetics and distribution of levofloxacin are comparable to that of ofloxacin, such that extrapolation of the CSF penetration of ofloxacin to levofloxacin can be used to calculate the theoretical CSF penetration of levofloxacin. The CNS penetration ofloxacin is generally 40-50% of its blood level. Theoretically, if the CNS levels of levofloxacin were 50% of the blood levels of the drug, the inhibitory quotient (AUC/MIC) within the CNS for S. pneumoniae (at an MIC of 2 MIC/mL) would be approximately 30, which is below the breakpoint of 40 which correlates with clinically efficacy for the quinolones. Thus, the coverage for *S. pneumoniae* within the CNS could, hypothetically, be marginal, particularly for pneumococcal bacteremia. Again, this is based on a theoretical calculation using a breakpoint calculated by Hooper for use win predicting the clinical efficacy of the fluoroquinolones. The reader is referred to Section 15.2.2. for a discussion of the use of the inhibitory quotient in extrapolating pharmacokinetic/pharmacodynamic data to clinical efficacy.

Recommendations for the Use of Levofloxacin in the Treatment of Acute Exacerbation of Chronic Bronchitis:

1. Clinical Efficacy in the Treatment of Acute Exacerbation of Chronic Bronchitis (Protocols K90-070 and M92-024):

Protocol K90-070 demonstrated that the **clinical cure rate** of levofloxacin (65%) in the treatment of acute exacerbation of chronic bronchitis meets statistical criteria for equivalence to the comparison arm of cefaclor (58%). Protocol M92-024 demonstrated that the **clinical cure rate** of levofloxacin (68%) in the treatment of acute exacerbation of chronic bronchitis meets statistical criteria for equivalence to the comparison arm of cefuroxime axetil (67%). These results are summarized in Tables I and II, below.

Table I
Clinical Response Rates by Protocol:
FDA Clinically Evaluable Subjects (Protocols K90-070 and MR92-024)

Protocol	Levofloxacin						Cefaclor (K90-070) Cefuroxime axetil (M92-024)					
	N[a]	Cure		Improve		Fail	N	Cure		Improve		Fail
K90-070	95	62	(65)	31	(33)	2 (2)	127	74	(58)	49	(39)	4 (3)
M92-024	196	134	(68)	53	(27)	9 (5)	203	137	(67)	51	(25)	15 (7)
Total	291	196	(67)	84	(29)	11 (4)	330	211	(64)	100	(30)	19 (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".

Table II
Clinical Cure Rates and Confidence Intervals By Protocol:
FDA Clinically Evaluable Subjects (Protocols K90-070 and MR92-024)

Protocol	Levofloxacin			Cefaclor (K90-070) Cefuroxime (M92-024)			95% Confidence Interval[c]
	N[a]	Cure		N	Cure		
K90-070	95	62	(65)	127	74	(58)	(-20.8, 6.8)
M92-024	196	134	(68)	203	137	(67)	(-10.5, 8.8)
Total	291	196	(67)	330	211	(64)	(-10, 4)

[b]Clinical success is defined as either clinical cure or clinical improvement.
[c]Two-sided confidence interval for the difference (competitor minus levofloxacin AND cefuroxime minus levofloxacin) in clinical success rate.

Protocol K90-070 demonstrated that the **clinical success rate** (defined as the combined percentage of patients who were clinically cured or improved at the posttherapy clinical evaluation) of levofloxacin (98%) in the treatment of acute exacerbation of chronic bronchitis meets statistical criteria for equivalence to the comparison arm of cefaclor (97%). Protocol M92-024 demonstrated that the **clinical success rate** of levofloxacin (95%) in the treatment of acute exacerbation of chronic bronchitis meets statistical criteria for equivalence to the comparison arm of cefuroxime axetil (93%). These results are summarized in Table III, below.

Table III
Clinical Success Rates and Confidence Intervals by Protocol:
FDA Clinically Evaluable Subjects (Protocols K90-070 and MR92-024)

Protocol	Levofloxacin			Cefaclor (K90-070) Cefuroxime (M92-024)			95% Confidence Interval[c]
	N*	Success**		N	Success		
K90-070	95	93	(98)	127	123	(97)	(-6.2, 4.1)
M92-024	196	187	(95)	203	188	(93)	(-7.9, 2.3)
Total	291	280	(96)	330	311	(94)	(-5, 1)

*N=Number of patients for that category
**Clinical success is defined as either clinical cure or clinical improvement. [c]Two-sided confidence interval for the difference (competitor minus levofloxacin AND cefuroxime minus levofloxacin) in clinical success rate.

Protocol K90-070 demonstrated that the **overall success rate** (defined as the combined percentage of patients who were clinically cured or improved at the posttherapy clinical evaluation PLUS had eradication of their admission pathogen) of levofloxacin (92%) in the treatment of acute exacerbation of chronic bronchitis meets statistical criteria for equivalence to the comparison arm of cefaclor (91%). Protocol M92-040 demonstrated that the **overall success rate** of levofloxacin (91%) in the treatment of acute exacerbation of chronic bronchitis meets statistical criteria for equivalence to the comparison arm of cefuroxime axetil (96%). These results are summarized in Table IV, on the following page.

Table IV
Overall Success Rates[a] and Confidence Intervals by Protocol: FDA Microbiologically AND Clinically Evaluable Subjects

Protocol	Levofloxacin		Cefaclor (K90-070) Cefuroxime (M92-024)		95% Confidence Interval[d]
	N[b]	Overall Success[c]	N	Overall Success	
K90-070	61	56 (92)	64	58 (91)	(-12.7, 10.3)
M92-024	116	106 (91)	128	110 (86)	(-14.2, 3.3)
Total	167	162 (97)	192	174 (91)	(-7, 5)

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

Thus, the data from Protocols K90-070 and M92-024 meet regulatory criteria for equivalence in the comparison of levofloxacin to an approved comparator using three definitions of successful treatment outcome. The Division is, therefore, justified in recommending the use of levofloxacin for the treatment of acute exacerbation of chronic bronchitis based on the clinical criteria of equivalence to an approved comparator drug.

2. Microbiologic Efficacy in the Treatment of Acute Exacerbation of Chronic Bronchitis (Protocols K90-070 and M92-024):

2.1. Clinical Cure Rates by Pathogen:

Table V
Clinical Response for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Protocols K90-070 and M92-024)

Pathogen	Levofloxacin				Cefaclor (K90-070) Cefuroxime (M92-024)			
	N[a]	Cure	Improve	Fail	N[a]	Cure	Improve	Fail
Haemophilus influenzae	54	33 (61)	19 (35)	2 (4)	50	24 (48)	24 (48)	2 (4)
Haemophilus parainfluenzae	32	27 (84)	5 (16)	0 (0)	39	28 (72)	8 (21)	3 (8)
Moraxella (Branhamella) catarrhalis	30	18 (60)	10 (33)	2 (7)	30	20 (67)	6 (20)	4 (13)
Staphylococcus aureus	12	6 (50)	5 (42)	1 (8)	34	24 (71)	7 (21)	3 (9)
Streptococcus pneumoniae	19	15 (79)	3 (16)	1 (5)	15	12 (80)	3 (20)	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 VI

Clinical Cure Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects (Protocols K90-070 and M92-024)

Pathogen	Levofloxacin		Cefaclor (K90-070) Cefuroxime (M92-024)		95% Confidence Interval[c]
	N[a]	Cure	N[a]	Cure	
Haemophilus influenzae	54	33 (61)	50	24 (48)	(-32, 6)
Haemophilus parainfluenzae	32	27 (84)	39	28 (72)	(-31, 7)
Moraxella catarrhalis	30	18 (60)	30	20 (67)	(-17, 31)
Staphylococcus aureus	12	6 (50)	34	24 (71)	(-11, 53)
Streptococcus pneumoniae	19	15 (79)	15	12 (80)	(-26, 28)

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.
[c]two-sided confidence interval for the difference (cefaclor minus levofloxacin AND cefuroxime minus levofloxacin) in microbiologic eradication rate.

2.2. Microbiologic Eradication Rates by Protocol:

Overall microbiologic eradication rates are listed by protocol in Table VII, below. In both protocols, the 95% confidence intervals around the difference in eradication rate (comparator minus levofloxacin) overlap zero, indicating statistical equivalence of the two treatment arms for this outcome.

Table VII

Microbiologic Eradication Rates and Confidence Intervals by Protocol: FDA Microbiologically Evaluable Subjects (Protocols K90-070 and M92-024)

Investigator	Levofloxacin		Cefaclor (K90-070) Cefuroxime (M92-024)		95% Confidence Interval[c]
	N[a]	Eradication[b]	N	Eradication	
K90-070	61	57 (93)	65	58 (89)	(-15.6, 7.1)
M92-024	116	107 (93)	129	112 (87)	(-13.8, 3.0)
Total	177	164 (93)	194	170 (88)	(-11, 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]Numbers shown in parentheses are percentages for that category.
[c]two-sided confidence interval for the difference (cefaclor minus levofloxacin AND cefuroxime minus levofloxacin) in microbiologic eradication rate.

2.3. Microbiologic Eradication Rates by Pathogen:

Microbiologic eradication rates for the pathogens requested by the sponsor in the proposed package labeling (*S. pneumoniae, H. Influenzae, H. parainfluenzae, M. catarrhalis* and *S. aureus)* are above 75% in both protocol K90-070 and M92-024. In fact, the microbiologic rates for the pathogens other than *S. aureus* (*S. pneumoniae, H. Influenzae, H. Parainfluenzae, M. catarrhalis)* are all above 88% in both protocols. *S. aureus*, on the other hand, had eradication rates of 75%

in both protocols. In all cases, the 95% confidence intervals for the difference between the eradication rates of levofloxacin and comparator overlapped zero, indicating that there was the two treatments were statistically equivalent. However, because of the low numbers of individual isolates, the calculation of confidence intervals around the difference in eradication rates was not possible for *S. aureus, S. pneumoniae, H. parainfluenzae, M. catarrhalis* in Protocol K90-070 and for *S. aureus* in Protocol M92-024. These results are summarized in Table VIII, on the following page.

Table VIII
Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects (Protocols K90-070 and M92-024)

Pathogen Category/Pathogen	Levofloxacin		Cefaclor (K90-070) Cefuroxime (M92-024)		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	47	42 (89)	65	58 (89)	(-12, 12)
Gram-negative aerobic pathogens	193	181 (94)	202	182 (90)	(-9, 1)
Total by pathogen	240	223 (93)	267	240 (90)	(-2, 8)
Total by subject	177	164 (93)	194	170 (88)	(-11, 1)
Pathogen					
Haemophilus influenzae	52	47 (90)	46	36 (78)	(-26, 2)
Haemophilus parainfluenzae	32	32 (100)	34	32 (94)	(-14, 2)
Moraxella catarrhalis	30	30 (100)	29	26 (90)	(-21, 1)
Staphylococcus aureus	12	9 (75)	34	31 (91)	(-10, 42)
Streptococcus pneumoniae	18	16 (89)	15	15 (100)	(-3, 25)

[a]Numbers shown in parentheses are percentages for that category.
[b]A two-sided confidence interval for the difference (cefaclor minus levofloxacin AND cefuroxime minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

2.2. Microbiologic eradication rates of levofloxacin for individual pathogens isolates from patients with acute exacerbation of chronic bronchitis:

2.2.1 *Streptococcus pneumoniae*:

The total number of isolates of *Streptococcus pneumoniae* from levofloxacin-treated patients was 18: 8 in K90-070 and 10 in M92-024. The eradication rate of *Streptococcus pneumoniae in levofloxacin-treated patients* was 88% in Protocol K90-070 and 90% in Protocol M92-024. In addition, the 95% confidence interval for the difference in eradication rates between levofloxacin and cefuroxime (Protocol M92-024) overlapped zero, indicating statistical equivalence. Thus, although the total number of isolates is suboptimal, the absolute and relative eradication rates all support the inclusion of this organism in the labeling. However, the issues surrounding the resistance of this organism to the quinolone antibiotics need to be considered, since the use of this antibiotic in general medical practice for the treatment of acute exacerbation of chronic bronchitis will, in general, be empiric.

2.2.2. *Haemophilus influenzae*:

The total number of isolates of *Haemophilus influenzae* from levofloxacin-treated patients was 52: 12 in K90-070 and 40 in M92-024. The eradication rate of *Haemophilus influenzae* in levofloxacin-treated patients was 92% in Protocol K90-070 and 90% in Protocol M92-024. In addition, the 95% confidence intervals for the difference in eradication rates between (1) levofloxacin and cefaclor in Protocol K90-070 and (2) levofloxacin and cefuroxime in Protocol M92-024 both overlapped zero, indicating statistical equivalence. Thus, the total number of isolates is adequate, and the absolute and relative eradication rates all support the inclusion of this organism in the labeling.

2.2.3. *Haemophilus parainfluenzae*:

The total number of isolates of *Haemophilus parainfluenzae* from levofloxacin-treated patients was 32: 4 in K90-070 and 28 in M92-024. The eradication rate of *Haemophilus influenzae* in levofloxacin-treated patients was 100% in Protocol K90-070 and 100% in Protocol M92-024. In addition, the 95% confidence intervals for the difference in eradication rates between levofloxacin and cefuroxime in Protocol M92-024 overlapped zero, indicating statistical equivalence. Thus, the total number of isolates is adequate, and the absolute and relative eradication rates all support the inclusion of this organism in the labeling.

2.2.4. *Moraxella catarrhalis*:

The total number of isolates of *Moraxella catarrhalis* from levofloxacin-treated patients was 30: 10 in K90-070 and 20 in M92-024. The eradication rate of *Moraxella catarrhalis* in levofloxacin-treated patients was 100% in Protocol K90-070 and 100% in Protocol M92-024. In addition, the confidence intervals for the difference in eradication rates between levofloxacin and cefuroxime in Protocol M92-024 overlapped zero, indicating statistical equivalence. Thus, the total number of isolates is

adequate, and the absolute and relative eradication rates all support the inclusion of this organism in the labeling.

2.2.5. *Staphylococcus aureus*:

The total number of isolates of *Staphylococcus aureus* from levofloxacin-treated patients was 12: 4 in study K90-070 and 8 in study M92-024. The eradication rate of *Staphylococcus aureus* in levofloxacin-treated patients was 75% in Protocol K90-070 and 75% in Protocol M92-024. In addition, the 95% confidence intervals for the difference in eradication rates between levofloxacin and cefuroxime in Protocol M92-024 overlapped zero, indicating statistical equivalence. Thus, although the eradication rate for *S. aureus* in one protocol is statistically equivalent to comparator, the total number of isolates is suboptimal and the absolute eradication rates are borderline. The inclusion of this organism in the labeling is equivocal.

In summary, given the eradication rates in the NDA database, the Division is justified in granting *H. influenzae, H. parainfluenzae, S. pneumoniae and M. catarrhalis* for the product labeling in the indication of acute exacerbation of chronic bronchitis. The number of isolates of these four organisms is adequate to assess the eradication rates for all of these organisms with the exception of *S. pneumoniae*. Only 18 isolates of *S. pneumoniae* were obtained in the combined protocols, and this is borderline, though not entirely unacceptable, for assessing an eradication rate for this organism. The medical officer will defer to the team leader in granting *S. aureus* for the labeling, because of the low number of organisms and the borderline absolute eradication rates. The team leader may wish to recommend a repeat study with adequate numbers of *S. aureus* for inclusion of this organism in the labeling, but this must be continent upon follow-up surveillance for resistance to this organism, as discussed below. The extensive discussion above regarding the resistance of both *S. aureus* and *S. pneumoniae* to quinolone antibiotics emphasizes the Medical Officer's concerns regarding the long term efficacy of levofloxacin for this indication.

3. Subsequent clinical study for the treatment of *Staphylococcus aureus* in acute exacerbation of chronic bronchitis:

The medical officer considers the data to support a claim for the treatment of AECB resulting from infection with *Staphylococcus aureus* to be marginal. This is based on the following reasons: (1) the low eradication rates of *S. aureus* to levofloxacin documented in this database, (2) the low number of isolates of *S. aureus* in these two protocols (3) the rapid development of resistance (at times during therapy) of *S. aureus* to the other quinolones. If the sponsor would like *S. aureus* included in the label for this indication, the Medical Officer recommends a rigorous subsequent study rigorous characterization of the microbiology of clinical and microbiologic failures to assess for the development of resistance in *S. aureus* during the course of therapy.

4. Phase 4 agreement requiring surveillance for the development of resistance to levofloxacin:

The extensive discussion above regarding the resistance of both *S. aureus* and *S. pneumoniae* to these agents emphasizes the medical officer's concerns regarding the long term efficacy of levofloxacin for this indication. The Medical officer would recommend that a condition of the approval be a Phase 4 surveillance program to document the development of resistance to this antimicrobial so that product labeling can be updated accordingly.

4.1. Streptococcus pneumoniae:

According to a DAIDP advisory committee recommendation in October 1991, there exist significant concern about the resistance of *S. pneumonaie* to the quinolone antibiotics, such that there was a recommendation of a labeling change warning of the development of resistance in *S. pneumoniae* and recommending that the "quinolones not be used as first line agent for the treatment of infection due to presumed or confirmed [pneumonia] *S. pneumonaie*". As per the discussion of inhibitory quotients of several of the quinolone antibiotics for *S. pneumonaie*, there does not exist a large safety margin for levofloxacin in regards to the achievable blood levels (AUC) and the MIC of this organism. In addition, the eradication rate of *S. pneumoniae* in both Protocol K90-070 and Protocol M92-024 is below the historic susceptibility rate of 95% for ofloxacin against *S. pneumoniae*. Since granting *S. pneumoniae* as a pathogen requires that the Division overturn a recommendation of this advisory committee, the Medical Officer would thus recommend some type of post-marketing surveillance for the development of resistance in this organism.

4.2. *Staphylococcus aureus*:

Although the Medical Officer cannot recommend without reservation the use of levofloxacin for the treatment of acute exacerbation of chronic bronchitis due to *S. aureus*, the use of this antibiotic for the treatment of this indication will generally be empiric, and, therefore, involve empiric coverage of this organism. Thus, the development of resistance in this organism is important to the labeling regardless of whether or not *S. aureus* is included in the labeling, as this drug will most frequently be used empirically in the treatment of community-acquired acute exacerbation of chronic bronchitis.

Medical Officer's Review of NDA 20-634
Levaquin® (levofloxacin) Tablets
Medical Officer's Review of NDA 20-635
Levaquin® (levofloxacin) Intravenous Injection

Indication: Community-acquired Pneumonia

Overview of Clinical Studies:

1. **Pivotal studies conducted primarily in the United States:**
   - 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
   - 1.2. **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
2. **Supportive Foreign Study:**
   - 2.1. **3355E-CLN025** : 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

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Protocol: Study K90-071:
Study Title:
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 cefuroxime (500 mg PO BID for 7-14 days) OR ceftriaxone sodium (1 GM IV BID or 2 GM IV QD for 7-14 days) in the treatment of community-acquired pneumonia in adults

Study dates: DATE STUDY INITIATED: November 11, 1992
DATE STUDY COMPLETED: January 25, 1995.

1. Study Objective:
The objective of this study was to compare the safety and efficacy of 488 mg levofloxacin administered orally, or 500 mg levofloxacin administered intravenously, once daily, for a total of 7 to 14 days with that of ceftriaxone sodium, 1 to 2 grams administered intravenously once or twice daily, or 500 mg cefuroxime axetil administered orally twice daily for a total of 7 to 14 days, in the treatment of community-acquired pneumonia in adults.

2. Protocol design:

This was a randomized, open-label, active-control, multicenter study designed to evaluate the safety and efficacy of levofloxacin compared with ceftriaxone sodium or cefuroxime axetil in the treatment of community-acquired pneumonia. This study was conducted in the United States and Canada. Approximately 528 adult subjects were to have been enrolled to ensure clinically evaluable data from a minimum of 366 subjects (183 subjects per treatment group). Enrollment could continue until sufficient numbers of evaluable subjects with infections due to critical pathogens had entered. Subjects were assigned randomly to receive either levofloxacin 488 mg orally or 500 mg intravenously, once daily for 7 to 14 days, or one of the two following comparative agents: ceftriaxone sodium 1 to 2 grams given intravenously once a day or in equally divided doses twice a day, but not to exceed 4 grams/day, or cefuroxime axetil 500 mg orally twice daily.

2.1 Randomization:

The randomization of the protocol was accomplished by a computer-generated schedule prepared by RWJPRI and supplied to each investigator. The schedule was generated using random permuted blocks of four and stratified by study center to assign subjects in equal numbers to receive either levofloxacin or ceftriaxone sodium/cefuroxime axetil on an open-label basis. Subjects received an identification number in consecutive order of study entry. Rosters of potential subjects were to be maintained by the investigators and were to be designed to document that subjects were neither enrolled in the study nor preferentially assigned to either treatment arm on the basis of disease severity.

2.2. Study drug administration and treatment duration

2.2.1. Study drug administration and treatment duration for levofloxacin and comparator

Treatment with either study drug or comparator was to continue for 7 to 14 days, as clinically indicated. Subjects treated with intravenous levofloxacin could have been switched to oral levofloxacin at any time at the discretion of the investigator. Likewise, subjects treated with parenteral ceftriaxone sodium could have been switched to oral cefuroxime axetil and at any time during the study at the discretion of the investigator. The total duration of therapy on either the levofloxacin or comparative regimen was not to exceed 7 to 14 days. If, in the opinion of the investigator, a subject required a longer duration of therapy, the subject could have been continued on the same study drug without any break in dosing. The investigator was to contact the RWJPRI medical monitor for approval to extend therapy in such cases. As further described below, the dosing regimens described above represent amendments to the original protocol which did not include an intravenous formulation of levofloxacin and allowed for a lower total daily dose of ceftriaxone sodium.

2.2.2. Study drug administration and treatment duration for antimicrobials added to the comparator arm for coverage of atypical pathogens

If *M. pneumoniae* or *C. pneumoniae* were suspected in subjects randomized

to receive one of the comparative therapies, erythromycin 500 mg administered orally or intravenously four times daily could have been added to the treatment regimen. If *Legionella* was suspected, erythromycin 0.5 to 1 gram, administered orally or intravenously four times daily could have been added to the treatment regimen. If routine cultures performed at admission for subjects receiving comparative therapies failed to reveal an organism and/or the subject had a suspected atypical pathogen (*M. pneumoniae, C. pneumoniae, or L. pneumophila)*, erythromycin 500 mg taken orally, or 0.5-1 gram given intravenously, may have been added four times daily. Subjects randomized to treatment with levofloxacin were not to receive erythromycin. Subjects randomized to a comparative treatment who were not able to tolerate erythromycin could have been treated with doxycycline at an appropriate dose. As with levofloxacin and ceftriaxone, subjects treated with parenteral erythromycin could have been switched to oral erythromycin at any time during the study at the discretion of the investigator.

2.3. Clinical Assessment:

The protocol defined the window for assessment of posttherapy clinical progress and any adverse events was to have been the 5-7 Days Posttherapy visit. However, the window for posttherapy evaluation was broadened by amendment to the original protocol to include any visit from 1-10 day posttherapy. Other evaluations included: physical examination; culture and Gram stain of respiratory specimens, if possible; chest X-ray; and collection of samples for hematology, serum chemistry, serology and urinalysis. Additionally, two specimens for blood culture were to have been collected for any subject who had positive cultures at admission. Subjects who had an infiltrate on the admission chest X-ray but negative routine cultures were to have been followed up at a poststudy visit (21 to 28 days posttreatment). Convalescent serologies were to have been obtained. Subjects in whom a persistent infiltrate (no documented improvement from the baseline chest X-ray) was noted on the posttherapy chest X-ray and/or subjects with persistent symptoms or relapse at the follow-up telephone contact were to return to the site 21 to 28 days posttherapy for assessment, which consisted of the following: vital signs, culture and Gram stain of respiratory specimens, chest examination for clinical signs of pneumonia, chest X-ray, clinical response assessment. Efficacy evaluations, included assessments of clinical signs and symptoms, clinical response (assessed as cured, improved, failed, or unable to evaluate at posttherapy and as cured, improved, relapsed, or unable to evaluate at poststudy) and microbiologic response by pathogen (assessed as eradicated, persisted, persisted with acquisition of resistance or unknown) and by infection(assessed as eradicated, persisted, or unknown). Clinical symptoms were to be recorded as present or absent after completion of therapy (five to seven days posttherapy). Clinical symptoms were also to be recorded as present-or absent by the investigator at the telephone contact 21 to 28 days after the end of therapy. Posttherapy and poststudy microbiologic response was to be assessed by The R.W. Johnson Pharmaceutical Research Institute (RWJPRI).— Safety evaluations included the assessment of treatment-emergent adverse events; laboratory tests of hematology, blood chemistry, and urinalysis; and physical examinations

including vital sign measurements.

2.4. Protocol Amendments

The study protocol was amended several times after the study was initiated. The first amendment, dated March 3, 1993, added an intravenous formulation of levofloxacin and, thus, deleted the requirement that subjects were to have been appropriate candidates for oral therapy only. In addition, changes were made as follows:

(I) the requirement that subjects have clinical signs and symptoms of community-acquired pneumonia was changed to clinical signs and symptoms of lower respiratory tract infection and initial chest X-ray compatible with pneumonia;
(ii) exclusion criteria were expanded to include infection due to mycobacteria, subjects with empyema, and subjects with HIV infection and a CD4 count <200, while the existing criteria of suspicion of septic shock and use of tranquilizers were deleted from the exclusion criteria;
(iii) the ceftriaxone sodium regimen was changed from 1 gram i.v. every 12 hours or 2 grams i.v. every 24 hours to 1 to 2 grams given once daily or equally divided doses given twice daily and it was clarified that the dose was not to exceed 4 grams/day;
(iv) collection of samples for peak and trough levofloxacin plasma levels at selected sites was deleted;
(v) diagnostic criteria for atypical pathogens were added;
(vi) the requirement for collection of a plasma sample in the event of a serious adverse event was added;
(vii) the requirement that Ery-tab ® have been the erythromycin formulation used was deleted, and provisions were made to include intravenous erythromycin as well as the oral regimen;
(viii) dosage adjustment in the presence of renal impairment was clarified;
(ix) *C. pneumoniae* was added as an atypical pathogen to have been studied;
(x) biopsies and pleural fluid were added as acceptable media for culture for admission procedures and the requirement for PT and PTT determination for subjects receiving anticoagulant therapy was specified;
(xi) the requirement for three specimens for blood culture was changed to two (preferably three);
(xii) requirement of theophylline blood levels for subjects receiving this therapy was deleted;
(xiii) provision was added to allow for dosing of subjects with suspected *L. pneumophila* with erythromycin 0.5 to 1 gram i.v. four times daily;
(xiv) an acceptable second systemic antimicrobial agent was changed from zidovudine (AZT) to antiviral agent;
(xv) a provision was added to allow subjects without an isolated pathogen at admission or a pathogen resistant to study drug(s) to continue if clinical improvement was noted;
(xvi) the requirement for an on-study chest X-ray was deleted and the need for a repeat poststudy chest X-ray was changed from "if indicated" to "required" for subjects with a significant infiltrate on posttherapy X-ray and qualified as "if indicated" for subjects followed poststudy for serology;
(xvii) the requirement of a repeat DNA probe for *M. pneumoniae* at both the posttherapy and poststudy evaluation was deleted;
(xviii) severity of admission diagnosis was to have been recorded on the potential subject roster;
(xix) resistance to study drug was added as a reason a subject would have been considered unevaluable for microbiologic efficacy;

The second protocol amendment, dated October 5, 1993, changed the dosing instructions to allow for the treatment of inpatients with the oral formulations; the minimum of three days of i.v. therapy was deleted. The collection of cost-efficacy data was added. In addition, changes were made as follows:

(i) clarification that the requirement of a blood sample for the determination of levofloxacin levels to have been drawn at the time of a serious adverse event was for

subjects assigned to receive levofloxacin;
(ii) a requirement to obtain samples for hematology, serum chemistry, and urinalysis was added to the on-therapy evaluation;
(iii) the definition of "unable to evaluate" for clinical response was changed by adding "subject lost to follow-up and not returning for posttherapy or poststudy evaluation";
(iv) evaluability criteria were modified to state cases of polymicrobial infection with at least one pathogen susceptible to the assigned study drug could have been considered evaluable and requirements for a subject to have been considered for microbiologic efficacy were clarified;
(v) a positive DFA test, urinary antigen detection test, or DNA probe test could have been considered diagnostic of infection due to *L. pneumophila*
(vi) specifics of "clinical picture consistent with pneumonia" were defined in the inclusion criteria;
(vii) the following were deleted as exclusion criteria: conditions requiring thoracic surgical procedure or suspected septic shock, infection acquired in an institutional setting other than a hospital, and tuberculosis;
(viii) admission specimens for blood culture were specified as having been applicable to hospitalized subjects;
(ix) a change was made allowing for subjects receiving ceftriaxone sodium to have been dosed twice daily, if clinically indicated;
(x) posttherapy evaluation was changed to indicate repeat serologies for *M. pneumoniae, L. pneumophila, and C. pneumonia* were required for all subjects, while culture and Gram stain of respiratory specimens were to have been done, if possible;
(xi) the requirement of a poststudy chest X-ray for subjects being seen only to obtain convalescent serologies was deleted;
(xii) susceptibility data for *C. pneumoniae* were added;
(xiii) provisions for enrolling subjects who had received prior antimicrobial therapy were defined;
(xiv) allowance was made for subjects receiving a comparative therapy who required an additional therapy to have been treated with doxycycline, if they were unable to tolerate erythromycin;
(xv) required urinary antigen detection test for *L. pneumophila* at admission was added for all subjects;
(xvi) documentation of eligible subjects was added to the potential subject roster;
(xvii) provision was made for adjustment of erythromycin, doxycycline, and cefuroxime axetil dosages for subjects with renal impairment;
(xviii) requirement for DFA confirmation (Legionella) was replaced by nonculture methods;
(xix) minimum inhibitory concentration (MIC) and disk zone requirements for increased doses of levofloxacin were deleted;
(xx) the MIC and inhibition zone diameter for *H. influenzae* were specified.

The protocol was amended for a third time on March 9, 1994, to clarify provisions for enrollment of subjects who received or failed previous nonstudy antimicrobial therapy and to further clarify the exclusion criteria regarding subjects with seizure disorders or unstable psychiatric conditions. In addition, the definition of the clinical response of "improved" was modified to clarify that subjects who required additional antimicrobial therapy could not have been considered clinically improved and the definition of "unable to evaluate" was further clarified, as was the provision for contacting the RWJPRI medical monitor before extending therapy. 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 fewer than five days of therapy could have been considered evaluable;
(ii) requirement that bacteriologic cultures have been obtained between 1-10 days PT rather than 2-9 days PT for subjects to have been 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 have been excluded from the efficacy analysis;
(iv) deletion of resistance to study drug as a criterion for classifying a subject as

microbiologically unevaluable;
(v) subjects receiving doxycycline in accordance with the protocol were defined as evaluable.

3. Diagnostic criteria:

3.1. Clinical: The diagnosis was based on having had at least ~~two~~ of the following signs and symptoms of community-acquired pneumonia:

- fever (oral temperature ≥38 C or 100.4 F or rectal temperature ≥39 C or 102.2 F)
- cough
- production of purulent sputum (<10 epithelial cells and >25 WBC per low power field)
- chest pain
- shortness of breath
- evidence of pulmonary consolidation on physical examination (rales on auscultation, dullness to percussion, or egophony).

3.2. Radiographic: chest X-ray showing an infiltrate compatible with acute infection

3.3. Microbiologic: culture of purulent sputum (<10 epithelial cells and >25 WBC per low power field)

4. Inclusion and exclusion criteria:

Subjects may have been included in the study if they satisfied the following inclusion and exclusion criteria, as outlined in Sections 4.1 and 4.2, respectively.

4.1. Inclusion criteria:

There were multiple revisions to the inclusion criteria during the course of the study, and these changes are outlined in chronological order in the following paragraphs.

4.1.1. Inclusion criteria as per Original Protocol dated June 10, 1992:

Subject must have been at least 18 years old with clinical signs and symptoms of community-acquired pneumonia including chest X-ray with an infiltrate compatible with acute infection, gram stain revealing numerous neutrophils and few or no squamous epithelial cells.

4.1.2. Inclusion criteria as per Amendment #1 dated March 3, 1993:

Subject must have been at least 18 years old with clinical signs and symptoms of a lower respiratory tract infection and an initial chest X-ray compatible with acute pneumonia

4.1.3. Inclusion criteria as per Amendment #2 dated October 5, 1993:

The inclusion criteria in Protocol Amendment #2 were unchanged from Protocol Amendment #1, dated March 3, 1993.

4.1.4. Inclusion criteria as per Amendment #3 dated March 9, 1994:

The inclusion criteria in Protocol Amendment #3 were unchanged from Protocol Amendment #2, dated October 5, 1993.

4.2. Exclusion criteria:

A subject was to have been excluded from the study if any of the exclusion criteria were met. There were multiple revisions to the exclusion criteria during the course of the study, and these changes are outlined in chronological order in the following paragraphs.

4.2.1. Exclusion criteria as per Original Protocol dated June 10, 1992:

- previous allergic or serious adverse reaction to any member of the quinolone or cephalosporin classes of antimicrobials, or a severe reaction to penicillin
- diagnosis of cystic fibrosis, tuberculosis, or an infection due to fungus, parasite, virus, or other organism resistant to either study regimen
- severe renal failure
- presence of neutropenia
- high likelihood of death during the course of study
- presence of any seizure or major psychiatric disorder
- pregnant women or nursing mothers.

4.2.2. Exclusion criteria as per Amendment #1 dated March 3, 1993:

- previous allergic or serious adverse reaction to any member of the quinolone or cephalosporin classes of antimicrobials, or a severe reaction to penicillin
- diagnosis of cystic fibrosis, tuberculosis, or an infection due to fungus, parasite, virus, **mycobacteria** or other organism resistant to either study regimen
- Conditions requiring a thoracic surgical procedure (e.g., empyema)
- Severe renal failure (creatinine clearance < 20 mL/min)
- Presence of neutropenia (< 500 PMN's/mm^3)
- High likelihood of death during the course of the study
- Infection acquired in a hospital
- Subjects with septic shock
- Stipulations for use of a second systemic antimicrobial regimen with the levofloxacin treatment regimen: Subjects who develop bacterial pneumonia while receiving AZT or a systemic antifungal **or antiviral agent** were eligible for study entry and may continue these medications.
- **History** of any seizure disorder or major psychiatric disorder requiring the administration of major tranquilizers
- **Subjects with empyema**
- pregnant women or nursing mothers.
- Use of an investigational agent within 30 days prior to entry into the study
- Previous treatment under this protocol.
- **Subjects with HIV infection and CD4 count <200.**
- Reasons why any subjects were not enrolled must have been documented on the Potential Subject Roster.

4.2.3. Exclusion criteria as per Amendment #2 dated October 5, 1993:

- previous allergic or serious adverse reaction to any member of the quinolone or cephalosporin classes of antimicrobials, or a severe reaction to penicillin
- diagnosis of cystic fibrosis, tuberculosis, or an pulmonary infection due to fungus, parasite, virus, mycobacteria or other organism resistant to either study regimen
- severe renal failure (creatinine clearance < 20 mL/min)
- presence of neutropenia (< 500 PMN's/mm^3)
- high probability of death during the course of study
- history of any seizure disorder or major psychiatric disorder
- pregnant women or nursing mothers.
- Infection acquired in a hospital or other institutional setting
- Stipulations for use of a second systemic antimicrobial regimen with the levofloxacin treatment regimen: Subjects who develop bacterial pneumonia while receiving AZT an antifungal or antiviral agent were eligible for study entry and may continue these medications.
- History of any seizure disorder or major psychiatric disorder
- Subjects with empyema
- Pregnant women or nursing mothers
- Use of an investigational agent within 30 days prior to entry into the study
- Previous treatment under this protocol.
- Subjects with HIV infection and CD4 count <200.

4.2.4. Exclusion criteria as per Amendment #3 dated March 9, 1994:

- previous allergic or serious adverse reaction to any member of the quinolone or cephalosporin classes of antimicrobials, or a severe reaction to penicillin
- diagnosis of cystic fibrosis, tuberculosis, or an pulmonary infection due to fungus, parasite, virus, mycobacteria or other organism resistant to either study regimen
- severe renal failure
- presence of neutropenia (< 500 PMN's/mm^3)
- high probability of death during the course of study
- history of any seizure disorder or major psychiatric disorder
- Presence of seizure disorder
- Unstable psychiatric conditions.
- pregnant women or nursing mothers.
- Infection acquired in a hospital
- Stipulations for use of a second systemic antimicrobial regimen with the levofloxacin treatment regimen: Subjects who develop bacterial pneumonia while receiving AZT or an antifungal or antiviral agent were eligible for study entry and may continue these medications.
- Presence of any seizure disorder or major psychiatric disorder requiring the administration of major tranquilizers
- Unstable psychiatric conditions
- Subjects with empyema
- Pregnant women or nursing mothers
- Use of an investigational agent within 30 days prior to entry into the study
- Previous treatment under this protocol.
- Subjects with HIV infection and CD4 count <200.

5. Dosage and Administration:

5.1. Study Drug Administration:

5.1.1. As per Original Protocol dated June 10, 1992:

Equal numbers of subjects were to have been assigned to each treatment regimen according to a computer-generated randomization schedule prepared by the sponsor. The following two regimens were to have been utilized:

1. **Levofloxacin** 488 mg (5 x 97.6 mg tablets) PO q24h for 7-14 days
2. **Ceftriaxone sodium** 1 gm IV q12h or 2 gm IV q24h for 7-14 days (for those subjects enrolled as inpatients) OR **Cefuroxime axetil** 500 mg PO q12h for 7-14 days (for those subjects enrolled as outpatients)

- Duration of ceftriaxone sodium therapy was to have been a minimum of three days. The subject may then have been placed on cefuroxime axetil 500 mg (2 x 250 mg tablets) PO q12h for the remainder of therapy, if clinically indicated.
- For those subjects receiving levofloxacin who had pathogens isolated with an MIC greater than 1.0 mcg/mL but less than or equal to 4.0 mcg/mL (or zone size greater than or equal to 13 mm but less than 18 mm for both ofloxacin and levofloxacin disks) and/or who were not clinically improving, the dosage may have been increased to 488 mg PO or 500 mg IV q12h.
- For those subjects receiving the comparative therapies, Ery-Tab® (Abbott Laboratories, North Chicago, IL) **Erythromycin** 500 mg IV or PO qid may have been added, if *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* was suspected. **If *Legionella pneumophila* was suspected, erythromycin 0.5-1 gm IV qid may have been added.** If these pathogens were confirmed by culture or by DFA (Legionella), these subjects may have been continued on erythromycin alone.
- Outpatient subjects randomized to the active-control regimen were to have received cefuroxime axetil 500 mg PO q12h for the duration of therapy.

5.1.2. As per Protocol Amendment #1 dated March 3, 1993:

Equal numbers of subjects were to have been assigned to each treatment regimen according to a computer-generated randomization schedule prepared by the sponsor. The following two regimens were to have been utilized:

1. Levofloxacin 488 mg (5 x 97.6 mg tablets) PO q24h for 7-14 days **(for those subjects enrolled as outpatients) OR Levofloxacin 500 mg IV q24h for 7-14 days (for those subjects enrolled as inpatients). The intravenous levofloxacin was to have been diluted in 80 mL D_5W (dextrose) to achieve a total volume of 100 mL for infusion over a period of one (1) hour. Duration of levofloxacin IV therapy was to have been a minimum of three days. The subject may then receive levofloxacin 488 mg PO q24h for the remainder of therapy, if clinically indicated.**

2. Ceftriaxone sodium 1 gm IV q12h or 2 gm IV q24h for 7-14 days **1 to 2 grams given once a day or in equally divided doses twice a day** (for those subjects enrolled as inpatients) OR Cefuroxime axetil 500 mg PO q12h for 7-14 days (for those subjects enrolled as outpatients)

- Duration of ceftriaxone sodium therapy was to have been a minimum of three days. **The total daily dose of ceftriaxone sodium should not exceed 4 grams/day.** The subject may then have been placed on cefuroxime axetil 500 mg (2 x 250 mg tablets) PO q12h for the remainder of therapy, if clinically indicated.
- For those subjects receiving the comparative therapies, Ery-Tab® (Abbott Laboratories,

North Chicago, IL) Erythromycin 500 mg IV or PO qid may have been added, if *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* was suspected. If *L. pneumophila* was suspected, erythromycin 0.5-1 gm IV qid may have been added. If these pathogens were confirmed by culture or by DFA (Legionella), these subjects may have been continued on erythromycin alone.

- Outpatient subjects randomized to the active-control regimen were to have received cefuroxime axetil 500 mg PO q12h for the duration of therapy.

5.1.3. Protocol Amendment #2 dated October 5, 1993:

Equal numbers of subjects were to have been assigned to each treatment regimen according to a computer-generated randomization schedule prepared by PRI. The following two regimens were to have been utilized:

1. Levofloxacin 488 mg (5 x 97.6 mg tablets) PO q24h for 7-14 days (for those subjects enrolled as outpatients) OR Levofloxacin 488 mg (5 x 97.6 mg tablets) PO or 500 mg IV q24h for 7-14 days (for those subjects enrolled as inpatients) The intravenous levofloxacin was to have been diluted in 80 mL D5W (dextrose) to achieve a total volume of 100 mL for infusion over a period of one (1) hour. Duration of levofloxacin IV therapy was to have been a minimum of three days. Subjects who began therapy on IV levofloxacin may have been switched to the oral formulation at any time, as the subject may then receive levofloxacin 488 mg PO q24h for the remainder of therapy, if clinically indicated.
2. Ceftriaxone sodium 1 gm IV q12h or 2 gm IV q24h for 7-14 days 1 to 2 grams IM or IV given once a day or in equally divided doses twice a day or cefuroxime axetil 500 mg PO q12h (for those subjects enrolled to have been treated as inpatients) OR Cefuroxime axetil 500 mg PO q12h for 7-14 days (for those subjects enrolled to have been treated as outpatients).

- Total duration of ceftriaxone sodium and/or cefuroxime axetil therapy was to have been 7-14 days. The total daily dose of ceftriaxone sodium should not exceed 4 grams/day. Subjects who began therapy on ceftriaxone sodium may have been switched to cefuroxime axetil at any time, as clinically indicated. The subjects may then have been placed on cefuroxime axetil 500 mg (2 x 250 mg tablets) PO q12h for the remainder of therapy, if clinically indicated. For subjects assigned to levofloxacin therapy who, at enrollment, have hypotension (diastolic blood pressure <60 mmHg) in the absence of volume depletion, altered mental status, who require intubation, mechanical ventilation, or have a baseline respiratory rate >28 minutes the dosage of levofloxacin may have been increased to 488 mg PO or 500 mg IV q12h. For those subjects receiving levofloxacin who have pathogens isolated with an MIC greater than 1.0 mcg/mL but less than or equal to 4.0 mcg/mL (or zone size greater than or equal to 13 mm but less than 18 mm for both ofloxacin and levofloxacin disks) and/or who were not clinically improving, the dosage of levofloxacin may have been increased to 488 mg PO or 500 mg IV q12h.

- For those subjects receiving the comparative therapies, Ery-Tab® (Abbott Laboratories, North Chicago, IL) Erythromycin 500 mg IV or PO qid may have been added, if *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* was suspected. If *L. pneumophila* infection was suspected, erythromycin 0.5-1 gm PO or IV qid may have been added. If these pathogens are confirmed by culture or by DFA (Legionella) nonculture methods, these subjects may have been continued on erythromycin alone (or doxycycline) monotherapy.

5.1.4. Protocol Amendment #3 dated March 9, 1994:

Equal numbers of subjects were to have been assigned to each treatment regimen according to a computer-generated randomization schedule prepared by PRI. The following two regimens were to have been utilized:

1. Levofloxacin 488 mg (5 x 97.6 mg tablets) PO q24h for 7-14 days (for those subjects enrolled as outpatients) OR Levofloxacin 500 mg IV q24h for 7-14 days (for those subjects enrolled as inpatients). The intravenous levofloxacin was to have been diluted in 80 mL D_5W (dextrose) to achieve a total volume of 100 mL for infusion over a period of one (1) hour. Duration of levofloxacin IV therapy was to have been a minimum of three days. Subjects who began therapy on IV levofloxacin may have been switched to the oral formulation at any time, and the subject may then receive levofloxacin 488 mg PO q24h for the remainder of therapy, if clinically indicated.
2. Ceftriaxone sodium 1 gm IV q12h or 2 gm IV q24h for 7-14 days, 1 to 2 grams IM or IV given once a day or in equally divided doses twice a day or cefuroxime axetil 500 mg PO q12h (for those subjects enrolled to have been treated as inpatients) or Cefuroxime axetil 500 mg PO q12h for 7-14 days (for those subjects enrolled to have been treated as outpatients).

- Total duration of ceftriaxone sodium and/or cefuroxime axetil therapy was to have been 7-14 days. The total daily dose of ceftriaxone sodium should not exceed 4 grams/day. Subjects who began therapy on ceftriaxone sodium may have been switched to cefuroxime axetil at any time, as clinically indicated.
- If, in the opinion of the investigator, a subject requires a longer duration of any study therapy, the PRI medical monitor should have been contacted.
- For subjects assigned to levofloxacin therapy who, at enrollment, have hypotension (diastolic blood pressure <60 mmHg) in the absence of volume depletion, altered mental status, who require intubation, mechanical ventilation, or have a baseline respiratory rate >28 per minute the dosage of levofloxacin may have been increased to 488 mg PO or 500 mg IV q12h.
- For those subjects receiving the comparative therapies, Erythromycin 500 mg IV or PO qid may have been added, if *M. pneumoniae*, or *C. pneumoniae* was suspected. If *L. pneumophila* infection was suspected, erythromycin 0.5-1 gm PO or IV qid may have been added. If these pathogens were confirmed by culture or) nonculture methods, these subjects may have been continued on erythromycin alone (or doxycycline) monotherapy.

5.1.5. As per Clinical Trial Report from CANDA submission:

Subjects were assigned randomly to receive either levofloxacin or ceftriaxone sodium/cefuroxime axetil. 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 or a 100 mL solution containing 500 mg of levofloxacin in D5W once daily as a one-hour intravenous infusion. Subjects given the intravenous formulation could then receive the oral formulation if clinically indicated. The duration of therapy was to have been 7 to 14 days. Subjects assigned to the comparative control group received either 1 to 2 grams ceftriaxone sodium given intravenously once daily or in equally divided doses given twice daily, or two 250-mg cefuroxime axetil tablets twice daily for a total daily dose of 1000 mg. The drug could have been given intramuscularly when

intravenous access was not available. The total dose of ceftriaxone sodium was not to exceed 4 grams/day. If *M. pneumoniae* or *C. pneumoniae* were suspected in subjects randomized to receive a comparative therapy, erythromycin 500 mg, administered orally or intravenously four times daily, could have been added to the treatment regimen. If *Legionella* was suspected, erythromycin 0.5 to 1 gram administered orally or intravenously four times daily could have been added to the treatment regimen. Subjects who began therapy on ceftriaxone sodium may have been switched to cefuroxime axetil at any time, as clinically indicated. Subjects unable to tolerate erythromycin could have been treated with doxycycline inappropriate doses. The total duration of therapy was to have been 7 to 14 days. If, in the opinion of the investigator, a subject required a longer duration of therapy, the subject could have been continued on the same study drug without any break in dosing. The investigator was to contact RWJPRI for approval to extend therapy in these cases. The levofloxacin dosage could have been increased, at the discretion of the investigator, to 488 mg orally or 500 mg i.v. every 12 hours for subjects with severe infection, defined as those with hypotension (diastolic blood pressure <60 mmHg) in the absence of volume depletion; subjects with altered mental status; subjects who required intubation or mechanical ventilation, or subjects who had a baseline respiratory rate >28 breaths per minute; or subjects with bacteremia. The levofloxacin dosage was to have been reduced for subjects with calculated creatinine clearance values of 20 to 50 mL/min. These subjects were to receive an initial (loading) dose of 500 mg i.v. or 488 mg p.o. of levofloxacin followed by levofloxacin 500 mg i.v. or 488 mg orally every 48 hours. Subjects who had creatinine clearances of 20 to 50 mL/min and who were receiving levofloxacin every 12 hours were to have their dosage interval adjusted to every 24 hours. For subjects with renal impairment who were randomized to receive comparative treatment, medication was to have been adjusted in accordance with package instructions.

5.2. Concomitant use of medications and other antimicrobial agents: The use of other medications during the study was to have been 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 might decrease bioavailability of study drug. However, if administration of an antacid was necessary, it was to have been administered at least two hours before or after study drug administration. If the administration of any other medication (e.g., aspirin) was required, it was reported on the subject's case record form.

6. Efficacy Criteria per Sponsor:

Efficacy evaluations included evaluation of clinical signs and symptoms, clinical response ratings (assessed as cured, improved, failed, or unable to evaluate at posttherapy and as cured, improved, relapsed, or unable to evaluate at poststudy), and microbiologic eradication rates by pathogen (assessed as eradicated, persisted, persisted with acquisition of resistance, or unknown) and by infection (assessed as eradicated, persisted, or unknown). Microbiologic response in the group of subjects evaluable for microbiologic efficacy represented the secondary efficacy variable for this study. Safety evaluations included the incidence of treatment-emergent adverse events; laboratory tests of hematology, blood chemistry, and urinalysis; and physical examinations including vital signs.

7. Schedule and procedures for Efficacy and Safety Evaluations

7.1. Clinical Efficacy Evaluation:

7.1.1. Clinical Signs and Symptoms:

Clinical symptoms of a lower respiratory tract infection including chills, increased cough, production of purulent sputum, increased sputum, pleuritic chest pain, and shortness of breath were to be indicated by the investigator as present or absent at **admission**, at the **posttherapy visit** (five to seven days after the end of therapy), and at the **poststudy follow-up** telephone contact and/or visit (21 to 28 days after the end of treatment). Clinical signs of pneumonia obtained from a chest examination (diminished breath sounds, rales, egophony, rhonchi, or wheezes) were to be assessed and graded by the investigator as none, mild, moderate, or severe at admission and at the posttherapy visit (five to seven days after the end of therapy). In addition, the investigator was to examine the chest X-ray for the presence or absence of acute infiltrates or other pulmonary abnormalities. For subjects with a significant persistent infiltrate and no documented improvement on the previous chest X-ray compared with baseline, persistent symptoms at the posttherapy evaluation, or possible relapse at the follow-up telephone contact, the chest examination and chest X-ray were to be repeated at a poststudy visit (21 to 28 days posttherapy).

7.1.2. Clinical Response Rating:

7.1.2.1. Clinical Response Rating: Posttherapy Evaluation

At the posttherapy visit five to seven days after the end of therapy, the investigator was to assess 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 and an improvement in or resolution of chest X-ray findings.
> **Clinically Improved:** Incomplete resolution of signs, symptoms and chest X-ray findings and no additional antimicrobial therapy required. Subjects who were lost to follow-up but who had "clinical improvement" listed as the reason for change in study drug administration from intravenous to oral route of administration were assigned posttherapy clinical response ratings of "Clinically Improved".
> **Clinical Failure:** No response to therapy.
> **Unable to evaluate:** Not able to evaluate because subject lost to follow-up.

7.1.2.2. Clinical Response Rating: Poststudy Evaluation

At the poststudy visit (Posttherapy Days 21-28), which was required for subjects with a significant persistent infiltrate on chest X-ray at the posttherapy evaluation and subjects with persistent symptoms or relapse at the poststudy telephone contact, the investigator was to assess clinical response as cured, improved, relapse, or unable to evaluate by comparing poststudy and posttherapy symptoms, signs from chest examination, and chest X-ray findings. The definitions for these assessments are as follows:

> **Clinical Cure:** Resolution of signs and symptoms associated with active infection and improvement in or resolution of chest X-ray findings.
> **Clinically Improved:** Continued incomplete resolution of signs and symptoms with no deterioration or relapse since the posttherapy evaluation and no additional antimicrobial therapy required.
> **Clinical Relapse:** Resolution or improvement of signs and symptoms at the posttherapy evaluation (Posttherapy Clinical Response of Cure or Improved) followed by reappearance or worsening of signs and symptoms of infection.
> **Unable to Evaluate:** Not able to evaluate because subject lost to follow-up and did not return for poststudy evaluation.

For purposes of statistical summaries and analyses, a poststudy clinical response was based on the results of the clinical evaluation during the poststudy visit or (if there was no poststudy visit) on the results of the follow-up telephone contact. For subjects who had a poststudy evaluation, the poststudy clinical response was determined by the investigator. For subjects who had no poststudy evaluation and had a follow-up telephone contact, the clinical response was determined as follows:

> - If a subject was cured or improved posttherapy, and a relapse of symptoms occurred, then the poststudy clinical response was "RELAPSE."
> - If a subject was cured at posttherapy, and a relapse of symptoms had not occurred, then the poststudy clinical response was "CURED."
> - If a subject was improved at posttherapy, a relapse of symptoms had not occurred, and persistent symptoms were not resolved, then the poststudy clinical response was "IMPROVED."
> - If a subject was improved at posttherapy, a relapse of symptoms had not occurred, and persistent symptoms were resolved then the poststudy response was "CURED."

For subjects with no poststudy clinical evaluation and no follow-up telephone contact, the poststudy clinical response was not determined.

7.2. Microbiologic Efficacy Evaluation:

7.2.1. Specimen Collection

7.2.1.1. Respiratory Secretions

Respiratory specimens were to be obtained including deep expectorated or suctioned sputum, transtracheal aspirate, pleural fluid, bronchial brushings, biopsies, or washings. Respiratory specimens were to be collected within 48 hours prior to admission for culture, Gram stain, and susceptibility tests. Specimens also were to have been cultured for *M. pneumoniae, L. pneumophila, and C. pneumoniae*, if the local laboratory had the capability to perform these cultures. Optional studies included a direct fluorescent antibody test (DFA) of sputum or bronchoalveolar lavage

fluid for *L. pneumophila* and a DNA probe test for detection of infection caused by Legionella sp. The Infectious Disease Laboratory at Indiana University Medical Center (Indianapolis, IN) was used for Chlamydia evaluation. If the subject could produce sputum, specimens were to be obtained at the posttherapy visit (five to seven days after the end of therapy) and poststudy visit (21 to 28 days after the end of therapy) for culture, susceptibility testing, and Gram stain.

7.2.1.2. Blood Culture

At least two separate specimens for blood cultures were to be obtained from each hospitalized subject within 48 hours before therapy was started. Cultures were to be repeated during therapy (Days 2-4) and at the posttherapy visit (Posttherapy Days 5-7), if at least one of the admission blood cultures was positive.

7.2.1.3. Serology

Blood samples were to be obtained from each subject at admission (within 48 hours before therapy start) and posttherapy (Posttherapy Days 5-7) for serologic studies of *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. These evaluations were to be repeated at the poststudy (Posttherapy Days 21-28) visit.

7.2.1.4. Urinary Antigen Testing

Urine specimens were to be obtained at admission (within 48 hours before therapy start). A urinary antigen detection test for *L. pneumophila* was to be performed for all subjects.

7.2.2. Susceptibility Testing

Susceptibility to levofloxacin, ceftriaxone sodium, and cefuroxime axetil was to be determined for all aerobic pathogens (with the exception of *M. pneumoniae, L. pneumophila, and C. pneumoniae)*. The MIC susceptibility was to be the primary susceptibility criterion. If the MIC values were not available, disks were to be used to determine susceptibility. Disk susceptibility testing was to be performed for all aerobic pathogens with the exception of *M. pneumoniae, L. pneumophila, and C. pneumoniae* in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) methods using 5-μg levofloxacin disks provided by RWJPRI for levofloxacin susceptibility, and ceftriaxone sodium and cefuroxime axetil disks provided by the study center for susceptibility to these comparative therapies. Minimum inhibitory concentrations for levofloxacin, ceftriaxone sodium, and cefuroxime axetil were to be determined using a broth microdilution susceptibility assay for all aerobic pathogens, excluding *M. pneumoniae, L. pneumophila, and C. pneumoniae*. MIC determinations were to be preformed by R. M. Alden Research Laboratory (Santa Monica, CA).

7.2.3. Diagnosis of Infection Due to Atypical Pathogens

Diagnosis of infection due to *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* was to be made on the basis of the clinical, radiologic, serologic, and other diagnostic criteria, as described in the following case definitions:

7.2.3.1. Legionella case definition:

Clinical and radiologic evidence of pneumonia in association with one or more of the following:

(I) a single IgM enzyme-linked immunosorbent assay (ELISA) titer ≥1:256 or a four-fold increase or decrease in titer from admission to posttherapy or poststudy;
(ii) a single IgG ELISA titer ≥1:256 or a four-fold increase or decrease in titer from admission to posttherapy or poststudy;
(iii) a positive DFA on sputum, bronchial lavage, or tracheal aspirate;
(iv) a positive culture at admission for *L. pneumophila* from respiratory specimens; or
(v) a positive urine antigen test.

7.2.3.2. Chlamydia pneumoniae case definition:

Respiratory signs and symptoms compatible with *C. pneumoniae* infection in association with one or more of the following:

(I) a single microimmunofluorescence IgM titer ≥1:32 or a four-fold increase or decrease in titer from admission to posttherapy or poststudy;
(ii) a single microimmunofluorescence IgG titer >1:512;
(iii) a positive admission sputum or nasopharyngeal culture; or
(iv) a positive culture from pleural fluid or other pertinent respiratory tissue or fluid.

7.2.3.3. Mycoplasma case definition:

Clinical and radiologic evidence of pneumonia in association with one or more of the following:

(I) a single IgM ELISA titer ≥1:16 or a four-fold increase or decrease in titer from admission to posttherapy or poststudy;
(ii) a single IgG ELISA titer ≥1:128 or a four-fold increase or decrease in titer from admission to posttherapy or poststudy;
(iii) a positive culture from sputum or other respiratory fluid or material.

The criteria described above for diagnosis of *C. pneumoniae* and *Mycoplasma* infections using a single IgG titer have been modified from those specified in the protocol. The protocol stated that a single IgG titer ≥1:64 or a four-fold increase or decrease in the IgG titer from admission to posttherapy or poststudy were diagnostic for *C. pneumoniae*; the modified criterion described above in the case definition was used for diagnosis of *C. pneumoniae* infections using a single IgG titer. For *Mycoplasma*, the protocol contained an error indicating that a single IgG ELISA titer ≥1:28 (rather than the correct titer of ≥1:128) was diagnostic for infection.

7.3. Efficacy Criteria

7.3.1. Clinical Response

The primary efficacy variable was clinical response, assessed by the investigator as cured, improved, failed, or unable to evaluate at the **posttherapy** visit (five to seven days after the end of therapy) and as cured, improved, relapsed, or unable to evaluate at the **poststudy** contact or visit (Posttherapy Days 21 to 28). The clinical cure rate was to be evaluated by determining the percentage of clinically evaluable subjects who were cured, and the clinical success rate was to be based on the percentage of clinically evaluable subjects who were cured or improved.

7.3.2. Microbiologic Response

The secondary efficacy variable of microbiologic response to treatment was to be evaluated by RWJPRI in terms of pathogen and infection eradication rates. Microbiologic response was to be assessed for cultures of respiratory specimens, blood pathogens (bacteremia) and for atypical pathogens, including *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*. A culture or nonculture evaluation was to be considered valid if it was obtained at least one day posttherapy and if the subject was not receiving any effective concomitant antimicrobial agent.

7.3.2.1. Microbiologic Response: Cultures of Respiratory Specimens:
The microbiologic response for pathogens isolated at admission was to be determined by evaluating the posttherapy/early termination or poststudy culture results. Results were categorized as follows:

Eradicated: Eradication of the admission pathogen as evidenced by failure to isolate the pathogen in a valid posttherapy/early termination or poststudy culture. If clinical improvement occurs such that no sputum was produced and invasive procedures for culture were contraindicated, then the pathogen was presumed eradicated.

Persisted: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/early termination or poststudy culture. If a subject was discontinued due to clinical failure or resistant pathogen or was considered a clinical failure upon completion of therapy and eradication of the admission pathogen was not confirmed by valid culture results, then 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 termination or poststudy culture with documented acquisition of resistance.

Unknown: No posttherapy/early termination or poststudy culture results available due to lost-to-follow-up, lost culture, or culture not done when specimen was available. The response was unknown if the culture was performed on the last day of therapy or if the culture was done while the subject was receiving an effective antimicrobial agent for reasons other than clinical failure, unless persistence was verified or presumed.

7.3.2.2. Microbiologic Response: Blood Pathogens:
The microbiologic response for blood pathogens was to be based on posttherapy blood culture results of subjects with confirmed bacteremia at admission. Bacteremia was defined as at least one positive blood culture obtained at admission. Microbiologic response for each admission pathogen

was to be determined for subjects with blood culture results available posttherapy as follows:

Blood Culture 1	Blood Culture 2	Clinical Response*	Microbiologic Response
Negative	Negative	All	Eradicated
Negative	Unknown	Cure/Improved	Eradicated
Negative	Unknown	Failure	Persisted
Positive	Positive	All	Persisted
Positive	Negative	All	Persisted
Positive	Unknown	All	Persisted

* 'All' includes cured, improved, failure, and unable to evaluate.

Microbiologic response for subjects with no blood culture results available posttherapy or poststudy was to be determined as follows:

Blood Culture 1	Blood Culture 2	Clinical Response	Microbiologic Response
Unknown	Unknown	Cure/Improved	Eradicated
Unknown	Unknown	Failure	Persisted
Unknown	Unknown	Relapse	Unknown
Unknown	Unknown	Unable to Evaluate	Unknown

7.3.2.3. Microbiologic Response: Atypical Pathogens

The microbiologic response for *M. pneumoniae, L. pneumophila, or C. pneumoniae* was to be based on clinical response, and was determined as follows:

Clinical Response	Microbiologic Response
Cured or Improved	Eradicated
Failure	Persisted
Relapse	Unknown
Unable to Evaluate	Unknown

7.3.2.4. Microbiologic Response: Subject's Infection

The microbiologic response for the subject's infection at posttherapy or poststudy was also to be determined and 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 no known results for at least one pathogen isolated at admission with no pathogen persisting.

7.3.2.5. Superinfection

A superinfection was to be defined as a new infection, found at any site during therapy, which was caused by a new pathogen (not recognized as the original causative agent), and which was documented by culture results. A superinfection was to have been associated with clinical signs and symptoms of infection and required antimicrobial therapy.

7.4. Safety Evaluations

7.4.1. Treatment-Emergent Adverse Events

Adverse events were defined as treatment-emergent signs and symptoms, i.e., events that were not present at admission or events that represented an increase in severity or frequency of a sign or symptom already present at admission. Each subject was to be assessed at each visit after admission through the posttherapy (Day 5-7) visit for possible adverse events that might have occurred throughout the study period. The investigator was to record all adverse events on the case record forms and grade their severity as mild, moderate, or marked. The investigator also was to assess the relationship of the adverse event to trial treatment using the following ratings: none, remote, possible, probable, or definite. Other information to be recorded on the subject's case record form included: the date of onset of the event, control measures taken (i.e., dosage reductions, discontinuation of study drug, or administration of remedial therapy), the outcome (resolved, persisted, or unknown), and the date of resolution of the event. Serious adverse events were defined as those events that presented a significant threat to the well-being of the subject. Serious adverse events included any event that was fatal, life-threatening, permanently or significantly disabling, required hospitalization or prolonged hospitalization, resulted in long-term outpatient treatment (greater than six months), or was a congenital anomaly, cancer, or overdose. Investigators were instructed to report all serious adverse events immediately to RWJPRI. A 5-cc venous blood sample for determination of levofloxacin plasma concentration was to have been obtained for those subjects assigned to levofloxacin therapy at the time of a serious adverse event.

7.4.2. Clinical Laboratory Tests

The following standard clinical laboratory evaluations were to be performed before dosing (admission) and at the posttherapy visit. Additional evaluations were to be made between Days 2 and 4 and every five days thereafter for hospitalized patients.

> **Hematology:** hemoglobin, hematocrit, white blood cell (WBC) count and differential, red blood cell (RBC) count, and platelet count. PT and PTT were obtained for subjects receiving concurrent treatment with anticoagulants.
> **Blood Chemistry:** glucose, blood urea nitrogen (BUN), total bilirubin, total protein, albumin, uric acid, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), creatinine, calcium, inorganic phosphorus, sodium,
> **Urinalysis:** pH, specific gravity, and microscopic examination for red blood cells, white blood cells, and nonamorphous crystals.

7.5. Physical Examinations and Vital Signs

Physical examinations, including vital sign measurements, were to be performed at admission, the posttherapy or early termination visit, and at the poststudy visit when this visit was required. Any physical examination abnormalities were to be noted on the case record forms. Vital sign measurements included oral temperature, respiration rate, pulse rate, and blood pressure. Weight was to be obtained at admission only.

8. Investigators and study sites:

Protocol MR92-040 was conducted by 51 investigators at a total of 96 separate sites, as delineated below.

Paul J. Alessi, D.O.	- Our Lady of Lourdes Medical Center, Camden NJ; USA
Ian M. Baird, M.D., FACP	- Riverside Methodist Hospitals, Columbus, OH; USA
Carl T. Boylen, M.D.[a]	- LAC/USC Medical Center, Los Angeles, CA; USA
Edwin T. Brankston, M.D.	- The Oshawa Clinic, Oshawa, Ontario; Canada
Kathryn S. Budzak, M.D.	- Dean Clinic, Madison WI; USA
F. Keith Bufford, M.D.	- Community Medical Arts Center, Tallassee, AL; USA
Thomas N. Decker, M.D.	- Dover Professional Center, Dover, NH; USA
	- Wentworth Douglas Hospital, Dover, NH; USA
Lala M. Dunbar, M.D./Ph.D.	- Louisiana State University Medical Center, East Campus and Charity Hospital of New Orleans/MCLA, New Orleans, LA; USA
	- University Hospital/MCLA, West Campus, New Orleans, LA; USA
Charles A. Ellis, Jr., M.D.	- Andover, MA; USA
John E. Ervin, M.D./FACP/FACR	- The Center for Pharmaceutical Research, PC, Kansas City, MO; USA
	- St. Joseph Health Center, Kansas City, MO; USA
Thomas M. File, Jr., M.D.	- Summa Health System, Akron, OH; USA
	- St. Thomas Hospital Campus, Akron, OH; USA
Joseph V. Follett, M.D.	- Internal Medicine Group, P.C., Cheyenne, WY; USA
	- United Medical Center West, Cheyenne, WY; USA
	- United Medical Center East, Cheyenne, WY; USA
Tim Gardner, M.D.	- Holy Family Hospital, Spokane, WA; USA
Ronald W. Geckler, M.D.	- Mercy Medical Center, Baltimore, MD; USA
Myles E. Gombert, M.D.	- Long Beach Memorial Hospital, Long Beach, NY; USA
Glenn Gomes, M.D.	- Medical Center of Baton Rouge, Baton Rouge, LA; USA
	- Ochsner Clinic of Baton Rouge, Baton Rouge, LA; USA
John Graham, M.D.	- Family Practice Associates, Nova Scotia; Canada
	- Camp Hill Medical Centre, Nova Scotia; Canada
Jon Green, M.D., Ph.D.	- Department of Veterans Affairs Northern California System of Clinics, Martinez, CA; USA
Stephen L. Green, M.D.	- Sentara Hampton General Hospital, Hampton, VA; USA
Anton Grunfeld, M.D.	- Vancouver General Hospital, Vancouver, British Colombia; Canada
Michael Habib, M.D.	- VA Medical Center, Tucson, AZ; USA
Daniel Havlichek, M.D. and	- E.W. Sparrow Hospital and Laboratory, Lansing, MI; USA
Gary E. Stein, Pharm.D.[b]	- Unity Hospital, Fridley, MN; USA
Marvin A. Heuer, M.D.[c] and	- Fridley Medical Center, Fridley, MN; USA
R. Douglas Thorsen, M.D.	- United Hospital, St. Paul, MN; USA
	- Westview Clinic, PA, West St. Paul, MN; USA
	- Research Support Unit, Minneapolis, MN; USA
Robert Holloway, M.D.	- DeKalb Medical Center, Decatur, GA; USA
	- DeKalb Medical Family Care Center, Decatur, GA; USA
	- Tucker Family Care Center, Tucker, GA; USA
	- Covington Family Care Center, Decatur, GA; USA
	- Insite Clinical Trials, Atlanta, GA; USA
	- Southeast Clinical Resources, Atlanta, GA; USA
Robert N. Hunt, M.D. and	- Heartland Research Center, South Bend, IN; USA
Alan R. Rosenthal, PharmD [d]	- Memorial Hospital of South Bend, South Bend, IN; USA
	- Michiana Community Hospital, South Bend, IN; USA
	- St. Joseph Hospital, Michawaka, Mishawaka, IN; USA
	- Memorial Hospital of Michigan City, Michigan City, IN; USA
	- Elkhart General Hospital, Elkhart, IN; USA
	- Health Family Center, Mishawaka, IN; USA
	- South Bend Clinic, South Bend, IN; USA
	- New Carlisle, IN; USA
	- Southbend Community Health Center, South Bend, IN; USA
	- McKinely Medical Clinic, Mishawaka, IN; USA
	- Michiana Family Clinic, South Bend, IN; USA
	- Michiana Internal Medicine Assoc., South Bend, IN; USA
	- Osceola Clinic, Inc., Osceola, IN; USA
	- Nappanee IN; The Medical Group, Michigan City, IN; USA
	- The Elkhart Clinic, Elkhart IN; USA
	- Family Practice Assoc., Elkhart, IN; USA

Keith Ironside, Jr., M.D.	- St. Vincent Hospital and Medical Center, Portland, OR; USA
Dennis M. Israelski, M.D.	- San Mateo County General Hospital, San Mateo, CA; USA
	- San Mateo County AIDS Program, San Mateo, CA; USA
	- AIDS Community Research Consortium, Redwood City, CA; USA
	- Santa Clara Valley Medical Center, San Jose, CA; USA
Manjari Joshi, M.D.	- RA Cowley Shock Trauma Center, Baltimore, MD; USA
	- Harbor Hospital Center, Baltimore, MD; USA
Fernando A. Keller, M.D.	- Schader, Hauser, Tabak and Keller Pulmonary Associates, M.D., PA., Miami, FL; USA
	- South Miami Hospital, Miami, FL; USA
Richard B. Kohler, M.D.	- Wishard Memorial Hospital, Indianapolis, IN; USA
Frank P. Maggiacomo,[a] D.O.	- Silver Lake Medical, Inc., Providence, RI; USA
	- Roger Williams Medical Center, Providence, RI; USA
	- Harbour Medical LTD, East Greenwich, RI; USA
	- Pawtaxet Valley Medical Surgical Services, Warwick, RI; USA
	- Midland Medical, Warwich, RI; USA
	- Elmhurst Extended Care, Providence, RI; USA
	- Cedar Crest Nursing Home, Cranston, RI; USA
Lionel A. Mandell, M.D.	- Hamilton Civic Hospitals Henderson General Division, Hamilton, Ontario; Canada
Barrie March, M.D.[b] , and Diann Clarens, PharmD.	- MeritCare Medical Center, Fargo, ND; USA
Richard R. Moyer, M.D.	- Mesaba Clinic, Hibbing, MN; USA
R. Dale Padgett, M.D.	- Bamberg, SC; Bamberg County Memorial Hospital, Bamberg, SC; USA
James N. Parsons, M.D.	- Mount Carmel Medical Center, Columbus, OH; USA
D. Keith Payne, M.D.	- LSU Medical Center, Shreveport, LA; USA
Rick Player, M.D.	- Cooper Green Hospital, Birmingham, AL; USA
	- SORRA Research Center, Birmingham, AL; USA
Joseph Plouffe, M.D.	- The Ohio State University Hospitals, Columbus, OH; USA
Alan R. Pollack, M.D.[b]	- Rockville Internal Medicine Group, Rockville, MD; USA
Philip J. Roos, M.D.[b]	- Jerry L. Pettis Memorial V.A. Hospital, Loma Linda, CA; USA Dennis
Ruff, M.D.	- San Antonio Regional Hospital, San Antonio, TX; USA
Joram Seggev, M.D.	- University of Nevada School of Medicine, University Medical Center, Las Vegas, NV; USA
John Segreti, M.D.	- Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; USA Mark
J. Shankman, M.D.	- Health Stop, Watertown and West Roxbury, MA; USA
Christopher E. Spooner, M.D.[b]	- Phoenix Infectious Disease Spec, Phoenix, AZ; USA
	- Phoenix Memorial Hospital, Phoenix, AZ; USA
James R. Taylor, M.D.[b]	- St. Joseph Hospital, Tacoma, WA; USA
	- Tacoma General Hospital, Tacoma, WA; USA
	- Pulmonary Consultants, Tacoma, WA; USA

a This investigator did not enroll any subjects.
b Drs. Havlicheck and Stein were co-principal investigators at this site. All tables and listings were under the name of Dr. Havlicheck.
c Dr. Thorsen replaced Dr. Heuer as principal investigator at these sites after the study started. Dr. Heuer's name was retained in the data base and thus all tables and listings were under the name of Dr. Heuer.
d Drs. Hunt and Rosenthal were co-principal investigators at this site. All tables and listings were under the name of Dr. Hunt.

9. Study Population:

Approximately 528 subjects, men and women who were 18 years of age or older with community-acquired pneumonia, were to have been enrolled in this study to ensure 366 clinically evaluable subjects (183 per treatment group) for efficacy analysis. Enrollment could continue until sufficient numbers of evaluable subjects with infections due to critical pathogens were enrolled.

10. Discontinuation from study:

Subjects could have been 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, including evaluation of signs and symptoms, physical

examination and vital signs, culture, susceptibility testing, and Gram stain of respiratory specimens, if possible, and clinical laboratory tests were to have been performed. The investigator was to record the reason for premature discontinuation on the subject's case record form.

11. Evaluability Criteria:

11.1. Evaluability criteria as per Sponsor:

11.1.1. Original evaluability criteria as outlined in original Protocol dated June 20, 1992:

To be evaluable for clinical efficacy, subjects were not to have been classified in any of the following categories:

A minimum of five days of therapy was required in order for a subject to have been classified as evaluable in the analyses of clinical and microbiologic response; subjects who had failed clinically (in the judgement of the investigator) and had taken more than 48 hours but fewer than five days of study drug were not classified as unevaluable due to insufficient course of therapy.

11.1.2. Evaluability criteria as outlined in Protocol Amendment #1 dated March 3, 1993:

1. **Safety Analysis**

To be evaluable for the safety analysis, a subject must have taken the study medication and must have relayed safety information.

2. **Efficacy Analysis**

A subject was to have been evaluable for microbiological efficacy unless categorized into one of the following groups:

1. Unevaluable for safety
2. Infection not bacteriologically proven. No pathogen identified in the admission respiratory or blood cultures, and there was no evidence of *Mycoplasma pneumoniae*, *Legionella pneumophila*, or *Chlamydia pneumoniae* based on serology results
3. **An admission pathogen was resistant to the assigned study drug.**
4. Insufficient course of therapy
   - Subject does not take the study drug for at least five days.
   - Subjects who take study drug for less than five days because they were judged a clinical failure by the investigator were evaluable. The pathogen(s) was(were) presumed to persist in these situations.
5. Effective concomitant therapy. Subject takes an effective systemic antimicrobial between time of admission culture and within 48 hours prior to start of therapy, or following therapy prior to test-of-cure culture (post-therapy). If the subject takes effective systemic antimicrobial therapy because the subject has been judged a clinical failure by the investigator, the subject was evaluable and the pathogen(s) was(were) presumed to persist. Concomitant administration of erythromycin to the control drug was to not affect subject's evaluability.
6. Inappropriate bacteriologic cultures
   - 6.1. Admission culture was greater than 48 hours prior to the start of therapy
   - 6.2. Post-therapy evaluation was not between 2-9 days post-therapy. If the subject was discontinued due to a persistent pathogen or clinical failure and the post-therapy culture was obtained on the last day of therapy, the subject was considered evaluable.
   - 6.3. Adequate microbiological data was not available. If the subject was a clinical failure and persistence of the pathogen(s) isolated on admission was (were) not confirmed by culture results, the pathogen(s) was (were) presumed to persist.
7. Lost to follow-up but relays safety information
8. Other protocol violation, e.g.,
   - i. Subject fails specific entrance criteria
   - ii. Subject re-enters study
   - iii. Subject does not take at least 70% of assigned study drug

iv. Subject takes study drug for more than 20 days (unless due to a persistent pathogen)

Subjects with no initial pathogen but a four-fold or greater rise or decrease or a single diagnostic titer of antibodies for *Mycoplasma pneumoniae, Legionella pneumophila,* or *Chlamydia pneumoniae* were evaluable for efficacy unless any of the following criteria were met:

1. Subject was not evaluable for safety
2. Insufficient course of therapy
3. Effective concomitant therapy
4. Lost to follow-up but relayed safety information
5. Other protocol violation

All the preceding subjects with no initial pathogen and evaluable for efficacy were to be evaluable for clinical response efficacy. The microbiological response of the pathogen was to be based on the clinical response of the subject. For this indication, an evaluable subject may have had a microbiological response of "unknown."
Additionally, a subject was to have been evaluable for clinical efficacy, unless the clinical diagnosis was unconfirmed or the subject was classified by categories a, c, d, f, d, e, g, and/or g, h above.

11.1.3. Evaluability criteria as outlined in Protocol Amendment #2 dated October 5, 1993:

1. Safety Analysis
To be evaluable for the safety analysis, a subject must have taken the study medication and must have relayed safety information.
2. Efficacy Analysis
A subject was to have been evaluable for microbiological efficacy unless categorized into one of the following groups:

1. Unevaluable for safety
2. Infection not bacteriologically proven. No pathogen identified in the admission respiratory or blood cultures, and there was no evidence of *Mycoplasma pneumoniae, Legionella pneumophila,* or *Chlamydia pneumoniae* based on serology results (or other diagnostic procedures)
   iii. Resistant to study drug. An admission pathogen was resistant to the assigned study drug. In a monomicrobial infection, the admission pathogen was resistant to the assigned study drug. If the infection was caused by more than one pathogen and at least one pathogen was susceptible to the assigned study drug, the case was to have been considered evaluable.
3. Insufficient course of therapy. Subject does not take the study drug for at least five days. Subjects who take study drug for less than five days because they were judged a clinical failure by the investigator were evaluable. The pathogen(s) was(were) presumed to persist in these situations.
4. Effective concomitant therapy. Subject takes an effective systemic antimicrobial between time of admission culture and within 48 hours prior to start of therapy, or following therapy prior to test-of-cure culture (post-therapy). If the subject takes effective systemic antimicrobial therapy because the subject has been judged a clinical failure by the investigator, the subject was evaluable and the pathogen(s) was(were) presumed to persist. Concomitant administration of erythromycin to the control drug was to not affect subject's evaluability.
5. Inappropriate bacteriologic cultures.
   5.1. Admission culture was greater than 48 hours prior to the start of therapy
   5.2. Post-therapy evaluation was not between 2-9 days post-therapy. If the subject was discontinued due to a persistent pathogen or clinical failure and the post-therapy culture was obtained on the last day of therapy, the subject was considered evaluable.
   5.3. Adequate microbiological data was not available. If the subject was a clinical failure and persistence of the pathogen(s) isolated on admission was (were) not confirmed by culture results, the pathogen(s) was (were) presumed to persist.
6. Lost to follow-up but relays safety information
7. Other protocol violation, e.g.,

7.1. Subject fails specific entrance criteria
7.2. Subject re-enters study
7.3. Subject does not take at least 70% of assigned study drug
7.4. Subject takes study drug for more than 20 days (unless due to a persistent pathogen).

Subjects with no initial pathogen but a fourfold or greater rise or decrease or a single diagnostic titer of antibodies for who were determined by culture or non-culture methods (Appendix-III) to have infection due to *Mycoplasma pneumoniae, Legionella pneumophila, or Chlamydia pneumoniae* were evaluable for microbiological efficacy unless any of the following criteria were met:

1.Subject was not evaluable for safety
2. Insufficient course of therapy
3.Effective concomitant therapy
4.Lost to follow-up but relayed safety information
5.Other protocol violation

All the preceding subjects with no initial pathogen and evaluable for microbiological efficacy were evaluable for clinical response efficacy. The microbiological response of the pathogen was based on the clinical response of the subject. For this indication, an evaluable subject may have a microbiological response of "unknown."
Additionally, a subject was to be evaluable for clinical efficacy, unless the clinical diagnosis was unconfirmed or the subject was classified by categories a, c, d, f, d, e, g, and/or g, h above.

11.1.4. Evaluability criteria as outlined in Protocol Amendment #3 dated March 9, 1994, 1994:

1. Safety Analysis
To be evaluable for the safety analysis, a subject must take the study medication and must relay safety information.
2. Efficacy Analysis
A subject was to have been evaluable for microbiological efficacy unless categorized into one of the following groups:
1. Unevaluable for safety
2. Infection not bacteriologically proven. No pathogen identified in the admission respiratory or blood cultures, and there was no evidence of *Mycoplasma pneumoniae, Legionella pneumophila,* or *Chlamydia pneumoniae* based on serology results (or other diagnostic procedures)
(deleted) c. Resistant to study drug. In a monomicrobial infection, the admission pathogen was resistant to the assigned study drug. If the infection was caused by more than one pathogen and at least one pathogen was susceptible to the assigned study drug, the case was to be considered evaluable. (deleted)
3. Insufficient course of therapy. Subject does not take the study drug for at least five days. Subjects who take study drug for greater than 48 hours but for less than five days because they were judged a clinical failure by the investigator were evaluable. The pathogen(s) was(were) presumed to persist in these situations.
4. Effective concomitant therapy. Subject takes an effective systemic antimicrobial between time of admission culture and within 48 hours prior to start of therapy, or following therapy prior to test-of-cure culture (post-therapy). If the subject takes effective systemic antimicrobial therapy because the subject has been judged a clinical failure by the investigator, the subject was evaluable and the pathogen(s) was(were) presumed to persist. Concomitant administration of erythromycin or doxycycline to the control drug was to not affect subject's evaluability.
5. Inappropriate bacteriologic cultures
   5.1. Admission culture was greater than 48 hours prior to the start of therapy
   5.2. Post-therapy culture/evaluation was not between 1-10 days post-therapy. If the subject was discontinued due to a persistent pathogen or clinical failure and the post-therapy culture was obtained on the last day of therapy, the subject was considered evaluable.
   5.3. Adequate microbiological data was not available. If the subject was a clinical failure and persistence of the pathogen(s) isolated on admission was (were) not confirmed by culture results, the pathogen(s) was (were) presumed to persist.
6. Lost to follow-up but relays safety information
7. Other protocol violation, e.g.,

1) Subject fails specific entrance criteria (deleted)
2) 1) Subject re-enters study
3) 2) Subject does not take at least 70% of assigned study drug
4) Subject takes study drug for more than 20 days (unless due to a persistent pathogen) (deleted)

Subjects who were determined by culture or non-culture methods to have infection due to *Mycoplasma pneumoniae, Legionella pneumophila,* or *Chlamydia pneumoniae* were evaluable for microbiological efficacy unless any of the following criteria were met:

1. Subject was not evaluable for safety
2. Insufficient course of therapy
3. Effective concomitant therapy (not including erythromycin or doxycycline allowed as comparative study therapy by protocol)
4. Lost to follow-up but relayed safety information
5. Other significant protocol violation

All the subjects meeting any of the serologic diagnositic criteria, as delineated above, who had no initial pathogen and were evaluable for microbiological efficacy, were also evaluable for clinical efficacy. The microbiological response of the pathogen was based on the clinical response of the subject.
Additionally, a subject was to have been evaluable for clinical efficacy, unless the clinical diagnosis was unconfirmed or the subject was classified by categories a, c, d, e.2, f, and/or g, above.

11.1.2.3. Microbiologic Efficacy as per study summary

A subject was evaluable for microbiologic efficacy if all criteria for clinical efficacy were met and the subject was not classified by any of the following:

1. Infection not bacteriologically proven.
2. 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 microbiologic culture/evaluation was not on Days 1-10 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 unavailable. If a subject was discontinued due to a clinical failure and the posttherapy culture was not obtained, the subject was not considered unevaluable for this reason.

The hierarchy.that guided the assignment of microbiologic unevaluability was:

1. Not evaluable for safety.
2. Infection not bacteriologically proven.
3. Clinical diagnosis unconfirmed.
4. Insufficient course of therapy.
5. Effective concomitant therapy.
6. Inappropriate bacteriologic culture.
7. Lost to follow-up but provided safety information.
8. Other protocol violation

For subjects who were determined by culture or nonculture methods to have infection due to *Mycoplasma pneumonia, Legionella pneumophila,* or *Chlamydia pneumoniae,* the hierarchy was:

1. Not evaluable for safety
2. Insufficient course of therapy
3. Effective concomitant therapy
4. Lost to follow-up but provided safety information
5. Other protocol violation

If a subject fit into more than one of these categories, the highest reason was reported as the primary reason. Final classification regarding evaluability rested with the RWJPRI

medical monitor.

11.2. Evaluability criteria as per Medical Officer:

11.2.1. Clinical Evaluability Criteria as per Medical Officer:

1. The subject met the inclusion criteria
2. The subject did **NOT** meet any of the exclusion criteria at the time of enrollment
3. A **posttherapy/end-of therapy/EOT** clinical evaluation and an **poststudy/end-of study/EOS** clinical evaluation were performed. The exceptions were for patients who:
   - 3.1. declared clinical failures on-therapy, at the posttherapy visit, or in the interval between the posttherapy and poststudy visits, but did not have a poststudy follow-up, here the failure declared at the earlier time point was carried forward
   - 3.2. declared clinical cures at the posttherapy evaluation (i.e., were completely asymptomatic, and had a normal chest X-ray at EOT visit), here the clinical cure was carried forward. This was specified by the sponsor in the original study protocol, and, therefore, could not be modified after the fact.
4. A symptomatic response could be evaluated at the **posttherapy** and (where applicable) the **poststudy** time point.
5. With regard to establishing time point for follow-up after treatment of community-acquired pneumonia, both (1) the **natural history of the disease** and (2) the **half-life of the antimicrobial agent** under investigation need to be taken into account. The windows for follow-up after an episode of community-acquired pneumonia was to have been the same for patients treated with any **antimicrobial agent with a relatively short half-life**. It was only in the case of a prolonged half-life that the window for follow-up needs to be extended because blood levels and tissue levels persist far beyond the last dose of the antimicrobial drug. For levofloxacin, whose serum half-life was 6.34-6.39 hours in the clinical tablet, the window of follow-up can be the same as for other antimicrobials with relatively short half-lives.

   5.1. The **IDSA Guidelines** recommend standard follow-up after an episode of community-acquired pneumonia as follows:

   > .Hospitalized patients should be assessed every day during the course of therapy and within 5-7 days after the completion of treatment[1]

   5.2. Recent **regulatory precedent** for the appropriate time point for test of cure has been established in other reviews of antimicrobial agents with short half-lives for the indication of community-acquired pneumonia, and these confirm the need for late post-therapy follow-up to determine a stable point-estimate for clinical cure at the test-of-cure evaluation[2].

The original protocol 90-070 specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to have been the primary clinical endpoint, but with an End-of-Study evaluation at 3-6 weeks post-therapy to provide a late follow-up assessment and stable-estimate for the test-of-cure. Protocol

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[1] Beam TR, Gilbert, DN, Kunin CM. Guidelines for the Evaluation of Anti-infective Drug Products. Clin Infect Dis 15(Suppl 1):S85, 1992

[2] Merepenam NDA Review. NDA 50706.

Amendment #1 also specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to have been the primary clinical endpoint, but the late follow-up at 3-6 weeks was deleted from the protocol under this. **Therefore, acknowledging that the 5-7 day posttherapy visit was suboptimal for establishing a stable point estimate of the test-of-cure, the medical officer had no choice but to use the only existing endpoint for the follow-up clinical evaluation as the time point for the primary clinical endpoint for the purposes of this evaluation.**

6. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

(i) A patient was **fully clinically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

- Within 48 hours prior to enrollment in the protocol
- During the treatment period
- From the end of the treatment period to the poststudy evaluation
- At the evaluation for clinical relapse

(ii) if the patient received an antimicrobial agent prior to enrollment in the study, but there was **a pathogenic organism isolated on admission culture**, the patient was considered **clinically evaluable**
(iii) if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **clinically unevaluable**.
(iv) if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **clinically evaluable (only) as a treatment failure**.

7. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

(i) for patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the amended protocol
(ii) for patients in the cefuroxime arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol
(iii) for patients in either the levofloxacin arm or the cefuroxime designated a clinical failure, a minimum of 72 hours of study drug was to have been taken
(iv) for the levofloxacin arm, no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 7-14 doses of therapy, as specified by the amended protocol.
(v) for patients in the cefuroxime arm, no more than two missed doses requiring extension of the dosing interval to complete the full 7-14 days of therapy specified by the protocol

8. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS

evaluation.

9. The patient had no known history of AIDS and was not HIV seropositive.

11.2.2. Microbiologic evaluability criteria as per Medical Officer:

1. A subject met criteria for clinical evaluability at all time points during the study
2. Pretherapy (admission) sputum culture was positive for a microorganism known to be pathogenic in lower respiratory tract infections or there was evidence of infection by an atypical pathogen (see criteria for the diagnosis of atypical pathogens, below)
3. Any residual secretions present at the EOT visit were sent for culture. The medical officer would not accept the category of "presumed eradication" in cases in which there were persistent secretions that were not cultured. The medical officer felt that it was incumbent upon the sponsor and investigators to document eradication when and where possible.

   (i) Only in cases where there were no residual secretions would the designation "clinical cure/presumed eradication" be accepted.
   (ii) If there residual **purulent** secretions that were not cultured, the medical officer defaulted to "presumed persistence".
   (iii) If there residual **nonpurulent** secretions that were not cultured, the medical officer defaulted to "microbiologically unevaluable".
   (iv) In cases of clinical failure, a microbiologic assessment of "presumed persistence" was universally applied.

4. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

   (i) A patient was **fully microbiologically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

   - For the 48 hour period prior to enrollment (see exception under item (ii) below)
   - During the treatment period
   - From the end of the treatment period to the poststudy evaluation
   - At the evaluation for clinical relapse

   (ii) if the patient received **pretherapy** antimicrobial treatment with another antibiotic, the patient was microbiologically evaluable if there was a pathogen isolated on admission culture. If no pathogen was isolated on admission culture, the patient was both clinically and microbiologically unevaluable.
   (iii) if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **microbiologically unevaluable**.
   (iv) if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **microbiologically evaluable (only) as a persistent pathogen**.

5. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

   (I) for patients in the levofloxacin arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the amended protocol
   (ii) for patients in the cefuroxime arm who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the protocol
   (iii) for patients in either the levofloxacin arm or the cefuroxime designated a clinical failure at EOT, a minimum of 72 hours of study drug was to have been taken
   (iv) for the levofloxacin arm, no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 7-14 doses of therapy, as specified by the amended protocol.
   (v) for patients in the cefuroxime arm, no more than two missed doses requiring extension of the dosing interval to complete the full 7-14 days of therapy specified by the protocol

6. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

7. Diagnostic criteria for an atypical pathogen were defined as follows:

7.1. *Chlamydia pneumoniae*

Respiratory signs and symptoms compatible with *Chlamydia pneumoniae*, in association with one or more of the following[3]:

A. A single microimmunofluorescence IgM titer ≥ 1:16 (in the absense preexisting IgG) or a fourfold increase or decrease in the IgM titer at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

or

B. A single microimmunofluorescence IgG titer ≥ 1:512 or a fourfold increase or decrease in the IgG titer at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

or

C. A positive admission sputum or nasopharyngeal culture for *Chlamydia pneumoniae*

or

D. A positive culture from pleural fluid or other pertinent respiratory tissue or fluid

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[3] Grayston JT, Campbell LA, Kuo CC, et.el. A New Respiratory Tract Pathogen: *Chlamydia pneumoniae* Strain TWAR. J Infect Dis 161:618-25, 1990; New and Emerging Etiologies for Community-acquired Pneumonia with Implications for Therapy: A Prospective Multicenter Study of 359 cases. Medicine 69(5):307-316, 1990; Ekman MR, Leinonen M. Evaluation of Serological Methods in the Diagnosis of *Chlamydia pneumoniae* Pneumonia during and Epidemic in Finland. Eur J Clin Microbiol Infect Dis. 12(10): 756-60, 1993; Grayston JT, Aldous MB. Evidence that *Chlamydia pneumoniae* causes Pneumonia and Bronchitis. J Infect Dis 168:1231-5, 1993; Grayston JT, Kou CC, Et.al. A new *Chlamydia psittaci* strain, TWAR, isolated in acute respriatory tract infections. NEJM 315(3):161-68, 1986.

7.2. *Legionella pneumophilia*

Clinical and radiologic evidence of pneumonia in association with one or more of the following[4]:

A. A single IGM ELISA > 1:256 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

B. A single IGG ELISA > 1:256 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

C. A positive DFA (direct fluorescence antibody test) on sputum, bronchial lavage or tracheal aspirate)

D. A positive culture at admission for *Legionella pneumophila* from sputum or other respiratory fluid or material

E. Positive urine antigen

7.3. *Mycoplasma pneumoniae*

Clinical and radiologic evidence of pneumonia in association with one or more of the following[5]:

A. A single IGM ELISA > 1:16 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

B. A single IGG ELISA > 1:28 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

C. A positive culture at admission for *Mycoplasma pneumoniae* from sputum or other respiratory fluid or material

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[4] Ostergard L, Anderson PL. Etiology of Community-acquired Pneumonia: Evaluation by Transtracheal Aspiration, Blood Culture, or Serology. Chest 104:1400-07, 1993; Ruf B, Schurmann D, Horbach I. Prevalence and diagnosis of Legionella Pneumonia: A 3-year Prosective Study with Emphasis on Application of Urinary Antigen Detection. J Infect Dis 1990:1341-48, 1990; Myburgh J, Nagel GJ, Petschel E. Efficacy and tolerance of a three day course of azithromycin in the treatment of community-acquired pneumonia. J Antimicrob Chemother 31 Suppl E: 163-9, 1993; Ruf B, Schurmann D. Prevalence and diagnosis of Legionella pneumonia: a 3-year proseptive study with emphasis on applicaiton of urinary antigen detection. J Infect Dis 162(6):1341-8, 1990.

[5] Fang GD, Fine M, et.al., New and Emerging Etiologies for Community-acquired Pneumonia with Implications for Therapy: A Prospective Multicenter Study of 359 Cases. Medicine 69(5):307-16, 1990; Uldum SA, Jensen JS, et.al., Enzyme Immunoassay for Detection of Immunoglobulin M (IgM) and IgG Antibodies to *Mycoplasma pneumoniae*. J Clin Microbiol 30(5):1198-1204, 1992; Jacobs E, Bennewitz A, et.al., Reaction pattern of human anti-Mycoplasma pneumoniae antibodies in enzyme-linked immunosorbent assays and immunoblotting. J Clin Microbiol 23:517-522, 1986; Jacobs E, Fuchte K, et.al., A 168-kilodalton protein of *Mycoplasma pneumoniae* antibodies in enzyme-linked immunoabsorbant assay. Eur J Clin Microbiol Infect Dis 5:435-40, 1986; van Griethuysen AJA, de Graf R, et.al., Evaluation of a commercial enzyme immunoassay for detection of *Mycoplasma pneumoniae* specific immunoglobulin G antibodies. Eur J Clin Microbiol Infect Dis 9:221-223, 1990.

12. Efficacy as per sponsor:

12.1 Overview of Analysis Groups:

Approximately 528 subjects, men and women who were 18 years of age or older with community-acquired pneumonia, were to have been enrolled in this study to ensure 366 clinically evaluable subjects (183 per treatment group) for efficacy analysis. Enrollment could continue until sufficient numbers of evaluable subjects with infections due to critical pathogens were enrolled. Approximately 4% of subjects were enrolled prior to the first amendment to the protocol, approximately 10% were enrolled between the first and second amendments, and approximately 21% were enrolled between the second and third amendments. Approximately 64% of subjects were enrolled after the third amendment.

Data presented in tables and figures in this review are the pooled safety and efficacy results from all study centers, with the exception of the data for one investigator (F.P. Maggiacomo, M.D.). The study was prematurely terminated at this site for administrative reasons and data for this investigator were not used in support of efficacy and were not included in the summary displays of safety or efficacy presented in this report, with the exception of two subjects with serious adverse events (one in each treatment group) who were discussed herein for completeness. This investigator was not terminated due to either lack of efficacy or serious adverse events, and no subjects from this center discontinued the study due to an adverse event. A prestudy (admission) culture was not obtained for subject 208; this subject was discontinued from the study on Day 4 for this reason. No other significant protocol variations were noted.

12.1.1. Demographics of Randomized Cohort:

Five hundred ninety subjects were enrolled in this study by 40 of the 47 investigators (six investigators did not enroll any subjects, and data for an additional 17 subjects enrolled by Dr. Maggiacomo were not included in the data summaries, as discussed earlier). The intent-to-treat group included 295 subjects who were randomized to the levofloxacin treatment group and 295 subjects who were randomized to the ceftriaxone/cefuroxime treatment group at the 40 centers. The demographic and baseline (admission) characteristics of the intent-to-treat group were summarized in Table 12.1.1 and were comparable between the levofloxacin and ceftriaxone/cefuroxime treatment groups. The mean age for all subjects was 49.7±18.1 years with a range of 18-96 years. Men accounted for 55.1% of all subjects enrolled and Caucasians for 63.6%. Three hundred ten (52.5%) of subjects were enrolled as outpatients, and 280 (47.5%) as inpatients. The majority (82.5%) of subjects had infections that were categorized as mild/moderate, with the remaining subjects (17.5%) having severe infections. There were no statistically significant differences ($p \geq 0.36$) between the two treatment groups for any of the demographic features tested (i.e., age, sex, race) for any of the analysis groups. Rosters of potential subjects 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 admission date and subject number assigned, if the subject was enrolled. The most frequent reason for not entering a potential subject was absence of signs and symptoms of pneumonia. Other reasons frequently noted included patient refusal or inability to give informed consent, other underlying disease, or conditions prohibited by the protocol, use of antibiotics, residence in a supervised care facility (e.g., nursing home) and allergy to penicillin.

Figure 12.1.1
Baseline Demographic Characteristics:
Modified Intent-to-Treat Cohort (Protocol K90-071)

	Levofloxacin (N=295)		Ceftriaxone/Cefuroxime (N=295)		Total (N=590)	
	No.	(%)	No.	(%)	No.	(%)
Sex						
Men	162	(54.9)	163	(55.3)	325	(55.1)
Women	133	(45.1)	132	(44.7)	265	(44.9)
Race						
Caucasian	187	(63.4)	188	(63.7)	375	(63.6)
Black	101	(34.2)	101	(34.2)	202	(34.2)
Oriental	1	(0.3)	1	(0.3)	2	(0.3)
Hispanic	6	(2.0)	3	(1.0)	9	(1.5)
Other	0	(0.0)	2	(0.7)	2	(0.3)
Age (Years)						
≤45	141	(47.8)	137	(46.4)	278	(47.1)
46-64	88	(29.8)	76	(25.8)	164	(27.8)
≥65	66	(22.4)	82	(27.8)	148	(25.1)
Mean±SD	49.0±17.8		50.3±18.5		49.7±18.1	
Range	[redacted]		[redacted]		[redacted]	
Weight (lbs.)						
N	279		280		559	
Mean±SD	169.6±43.8		173.3±45.2		171.4±44.5	
Range	[redacted]		[redacted]		[redacted]	
Missing	16		15		31	
Severity						
Severe	48	(16.3)	55	(18.6)	103	(17.5)
Mild/Moderate	247	(83.7)	240	(81.4)	487	(82.5)
Status						
Inpatient	138	(46.8)	142	(48.1)	280	(47.5)
Outpatient	157	(53.2)	153	(51.9)	310	(52.5)

Note: Values represent numbers of subjects except as otherwise indicated.

12.1.2. Discontinuation/ completion information:

Of the 590 subjects enrolled in the study, 295 received levofloxacin and 295

received ceftriaxone/cefuroxime (intent-to-treat group). Of the 277 subjects in the levofloxacin group with known discontinuation/completion information, 28 (10.1%) subjects discontinued therapy prematurely; 249 (89.9%) completed therapy according to the regimen prescribed by the investigator. Of the 277 subjects in the ceftriaxone/cefuroxime treatment group with known discontinuation/ completion information, 36 (13.0%) discontinued therapy prematurely; 241(87.0%) completed therapy. Discontinuation/completion information was unknown for 18 subjects in each of the two treatment groups. The most common single reasons for therapy discontinuation in both treatment groups were adverse events and clinical failure.

Figure 12.1.2.A
Discontinuation/Completion Information:
Modified Intent-to-treat Subjects (Protocol K90-071)

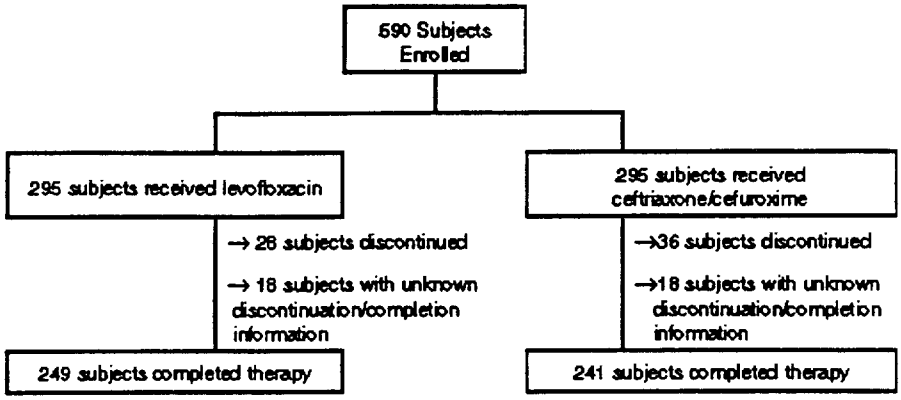

Table 12.1.2.B
Reasons for Premature Discontinuation:
Modified Intent-to-Treat Subjects (Protocol K90-071)

	Levofloxacin		Ceftriaxone/Cefuroxime	
Reason	No.	(%)*	No.	(%)*
Adverse Event	13	(4.7)	12	(4.3)
Clinical Failure	9	(3.2)	8	(2.9)
Presumptive Diagnosis Unconfirmed	1	(0.4)	1	(0.4)
Resistant Pathogen	0	(0.0)	3	(1.1)
Personal Reason	0	(0.0)	1	(0.4)
Other[b]	5	(1.8)	11	(4.0)
Total Discontinued	28	(10.1)	36	(13.0)
Total with Discontinuation/ Completion Information	277		277	
Total with Unknown Discontinuation/ Completion Information	18		18	

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

[b] Other reasons for discontinuation among levofloxacin-treated subjects included: subject not an appropriate study candidate (subjects [redacted]); diagnosis of tuberculosis (subject [redacted]) and problems with reimbursement of hospital costs while on study medication (subject [redacted]). Among subjects in the ceftriaxone/cefuroxime treatment group, other reasons for early discontinuation included: requiring additional antibiotic therapy (subjects [redacted] and [redacted]); diagnosis of tuberculosis (subjects [redacted]); protocol violation (subject [redacted]); diagnosis of large-cell carcinoma (subject [redacted]); T-cells too low (subject [redacted]); development of new case of pneumonia (subject [redacted]); no i.v. access and wrong oral antibiotic prescribed (subject [redacted]) and private pulmonary consult requested by a subject with worsening CHF (subject [redacted]).

12.1.3. Data set analyzed: Clinically and Microbiologically Evaluable Patients:

Two hundred twenty-six (76.6%) subjects in the levofloxacin treatment group and 230 (78.0%) subjects in the ceftriaxone/cefuroxime treatment group were clinically evaluable. One hundred twenty-eight (43.4%) subjects in the levofloxacin group and 144 (48.8%) subjects in the ceftriaxone/cefuroxime group were microbiologically evaluable. The main reasons that subjects were not clinically evaluable were insufficient course of therapy and inappropriate timing (outside of the 1-10-day posttherapy window used to determine evaluability) of posttherapy clinical evaluation (levofloxacin group) and no posttherapy evaluation and insufficient course of therapy (ceftriaxone/cefuroxime group), whereas the major reason that subjects were not microbiologically evaluable in the two treatment groups was absence of bacteriologically proven infection.

Table 12.1.3.A

Number of Subjects by Analysis Group and Study Center (Protocol K90-071)

	Levofloxacin			Ceftriaxone/Cefuroxime		
Investigator*	Intent-to Treat	Clinical Efficacy	Microbiologic Efficacy	Intent-to Treat	Clinical Efficacy	Microbiologic Efficacy
Alessi	5	4 (80.0)	4 (80.0)	6	5 (83.3)	3 (50.0)
Baird	7	6 (85.7)	3 (42.9)	7	4 (57.1)	3 (42.9)
Brankston	11	8 (72.7)	4 (36.4)	12	11 (91.7)	6 (50.0)
Budzak	4	4 (100.0)	3 (75.0)	4	3 (75.0)	2 (50.0)
Burford	3	3 (100.0)	3 (100.0)	3	3 (100.0)	2 (66.7)
Decker	1	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)
Dunbar	34	22 (64.7)	14 (41.2)	33	30 (90.9)	17 (51.5)
Ellis	2	1 (50.0)	1 (50.0)	4	4 (100.0)	2 (50.0)
Ervin	2	1 (50.0)	0 (0.0)	2	2 (100.0)	1 (50.0)
File	12	12 (100.0)	7 (58.3)	11	7 (63.6)	3 (27.3)
Follett	7	6 (85.7)	4 (57.1)	8	8 (100.0)	5 (62.5)
Gardner	2	2 (100.0)	1 (50.0)	2	2 (100.0)	0 (0.0)
Geckler	17	13 (76.5)	10 (58.8)	16	9 (56.3)	3 (18.8)
Gombert	8	6 (75.0)	3 (37.5)	8	4 (50.0)	4 (50.0)
Gomes	7	7 (100.0)	4 (57.1)	6	4 (66.7)	2 (33.3)
Graham	2	0 (0.0)	0 (0.0)	1	1 (100.0)	1 (100.0)
Green J.	2	2 (100.0)	1 (50.0)	2	2 (100.0)	1 (50.0)
Green S.	1	0 (0.0)	0 (0.0)	3	3 (100.0)	2 (66.7)
Grunfeld	6	3 (50.0)	2 (33.3)	5	3 (60.0)	2 (40.0)
Habb	8	7 (87.5)	6 (75.0)	6	6 (100.0)	5 (83.3)
Havlichek	2	2 (100.0)	0 (0.0)	4	4 (100.0)	2 (50.0)
Heuer	19	16 (84.2)	9 (47.4)	17	17 (100.0)	17 (100.0)
Holloway	10	8 (80.0)	2 (20.0)	10	5 (50.0)	1 (10.0)
Hunt	11	7 (63.6)	4 (36.4)	10	6 (60.0)	4 (40.0)
Ironside	2	2 (100.0)	1 (50.0)	4	2 (50.0)	1 (25.0)
Israelski	5	3 (60.0)	0 (0.0)	6	5 (83.3)	5 (83.3)
Joshi	5	2 (40.0)	1 (20.0)	4	4 (100.0)	4 (100.0)
Keller	4	2 (50.0)	0 (0.0)	4	4 (100.0)	3 (75.0)
Kohler	20	16 (80.0)	7 (35.0)	20	18 (90.0)	10 (50.0)
Mandell	2	2 (100.0)	1 (50.0)	3	1 (33.3)	1 (33.3)
Moyer	10	9 (90.0)	6 (60.0)	10	9 (90.0)	6 (60.0)
Padgett	4	2 (50.0)	0 (0.0)	4	3 (75.0)	1 (25.0)
Parsons	6	5 (83.3)	2 (33.3)	6	5 (83.3)	4 (66.7)
Payne	7	5 (71.4)	2 (28.6)	8	3 (37.5)	2 (25.0)
Player	24	22 (91.7)	14 (58.3)	23	15 (65.2)	8 (34.8)
Pburle	8	5 (62.5)	4 (50.0)	7	4 (57.1)	3 (42.9)
Ruff	4	4 (100.0)	1 (25.0)	4	3 (75.0)	1 (25.0)
Seggev	4	3 (75.0)	2 (50.0)	4	3 (75.0)	1 (25.0)
Segreti	6	4 (66.7)	2 (33.3)	6	6 (100.0)	5 (83.3)
Shankman	1	0 (0.0)	0 (0.0)	1	1 (100.0)	1 (100.0)
Total	295	226 (76.6)	128 (43.4)	295	230 (78.0)	144 (48.8)

Numbers shown in parentheses are percentages for that category.

* Six investigators (Boylan, March, Pollack, Roos, Spooner, and Taylor) did not enroll any subjects.

Table 12.1.3.B
Primary Reasons for Clinical or Microbiologic Nonevaluability: Sponsor's Modified Intent-to-Treat Cohort (Protocol K90-071)

Reasons	Levofloxacin (N=295)		Ceftriaxone/Cefuroxime (N=295)	
Clinical Efficacy				
Insufficient Course of Therapy	18		15	
Inappropriate Posttherapy Evaluation Date[b]	17		12	
No Posttherapy Evaluation	12		16	
Other Protocol Violation	10		9	
Clinical Diagnosis Unconfirmed	4		4	
Effective Concomitant Therapy	4		7	
Unevaluable for Safety	4		2	
Total Unevaluable For Clinical Efficacy	69	(23.4%)	65	(22.0%)
Microbiologic Efficacy				
Infection Not Bacteriologically Proven	125		113	
Inappropriate Posttherapy Evaluation Date[b]	13		9	
Insufficient Course of Therapy	11		11	
No Posttherapy Evaluation	6		7	
Other Protocol Violation	5		5	
Unevaluable for Safety	4		2	
Effective Concomitant Therapy	2		3	
Clinical Diagnosis Unconfirmed	1		1	
Total Unevaluable For Microbiologic Efficacy	167	(56.6%)	151	(51.2%)

[a] Subjects counted only once.
[b] A window of 1-10 days posttherapy was used for evaluability criteria.

12.1.4. Demographics of Clinically and Microbiologically Evaluable Cohort:

The demographic and baseline (admission) characteristics for the clinically and microbiologically evaluable subjects are shown in Table 12.1.4, below. The demographic and baseline characteristics of the subjects included in the clinically and microbiologically evaluable groups were comparable to the previously described intent-to-treat group with respect to age, sex, racial composition, and other baseline characteristics. The demographic and baseline characteristics of clinically evaluable and microbiologically evaluable subjects were comparable. There were no statistically significant differences ($p \geq 0.36$) found between the treatment groups for the variables tested (i.e., age, sex, race).

Table 12.1.4
Demographic and Baseline Characteristics:
Sponsor's Clinically and Microbiologically Evaluable Subjects (Protocol K90-071)

	Levofloxacin		Ceftriaxone/Cefuroxime	
	Clinically Evaluable (N=226)	Microbiologically Evaluable (N=128)	Clinically Evaluable (N=230)	Microbiologically Evaluable (N=144)
Sex				
Men	125	73	124	83
Women	101	55	106	61
Race				
Caucasian	147	86	151	101
Black	74	41	75	42
Hispanic	5	1	2	1
Other	0	0	2	0
Age (Years)				
≤45	107	61	108	62
46-64	71	38	61	47
≥65	48	29	61	35
N	226	128	230	144
Mean±SD	49.1±17.6	50.0±17.9	50.1±18.5	50.6±17.7
Range	[redacted]	[redacted]	[redacted]	[redacted]
Weight (lbs.)				
N	216	120	219	138
Mean±SD	171.0±43.6	167.5±40.2	174.8±46.1	175.0±46.3
Range	[redacted]	[redacted]	[redacted]	[redacted]
Missing	10	8	11	6
Severity				
Severe	36	21	37	28
Mild/Moderate	190	107	193	116
Status				
Inpatient	104	60	96	60
Outpatient	122	68	134	84

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.1.5. Extent of Exposure

The mean durations of i.v. and oral levofloxacin therapy were 3.2 days and 10.2 days, respectively, and the mean number of days of total therapy was 10.9. The median number of days of i.v., oral, and total therapy were 3, 10, and 10, respectively. Eighteen subjects received levofloxacin for more than 14 days. One hundred one subjects received both i.v. and oral levofloxacin therapy, 16 subjects received only i.v. therapy, and 178 subjects received only oral therapy. The mean duration of therapy was 12.2 days for subjects who received both i.v. and oral therapy, 4.2 days for subjects who received only i.v. therapy, and 10.8 days for subjects who received only oral therapy. The mean duration of ceftriaxone/cefuroxime therapy was 11.1 days and the median was 11 days. Sixty-five ceftriaxone/cefuroxime-treated subjects also received erythromycin or doxycycline; the mean duration of this therapy was 8.5 days and the median was 7 days.

Table 12.1.5
Extent of Exposure to Therapy:
Sponsor's Intent-to-treat Subjects (Protocol K90-071)

Extent of Therapy	Route of Therapy[a] I.v. (N=117)	Oral (N=279)	Either I.v. or Oral (N=295)
Days on Therapy[b]			
Unknown	0	15	15
1	12	4	8
1.5	1	0	0
2	34	5	8
3	31	4	3
3.5	2	2	0
4	17	2	2
4.5	1	0	0
5	10	5	3
5.5	1	0	0
6	1	5	3
6.5	0	1	0
7	2	31	15
8	1	15	10
9	2	9	8
9.5	0	1	0
10	1	73	61
11	0	19	13
12	1	17	14
13	0	6	12
14	0	54	62
15	0	7	10
16	0	0	3
17	0	2	2
18	0	0	1
22	0	2	2
Mean±SD	3.2±1.89	10.2±3.44	10.9±3.67
Median	3.0	10	10
Number of Doses			
Total with Dosing Information	117	264	280
Total with Missing Dosing Information	0	15	15
Mean±SD	3.3±1.98	10.3±3.73	11.0±4.00
Median	3.0	10.0	10.0
Range	[redacted]	[redacted]	[redacted]

[a] Subjects who received both i.v. and oral therapy are included in both the 'i.v.' and 'oral' categories.
[b] Days on therapy was defined as (last day - first day) + 1.

12.1.6. Concomitant Therapies

Concomitant therapies administered during the study that were considered to possibly have a clinically relevant interaction with quinolones are summarized in Table 12.1.6 along with the total number of subjects who received any concomitant therapy. Comparable percentages of subjects in the levofloxacin and ceftriaxone/cefuroxime treatment groups took concomitant therapies (92.9% subjects in the levofloxacin treatment groups and 93.9% subjects in the ceftriaxone/cefuroxime treatment group). Of interest, the most frequently administered were central nervous system-acting medications, which were taken by 62.4% and 56.3% subjects in the levofloxacin and ceftriaxone/cefuroxime groups, respectively.

Table 12.1.6
Summary of Concurrent Therapies:
Modified Intent-to-Treat Subjects (Protocol K90-071)

	Levofloxacin (N=295)		Ceftriaxone/Cefuroxime (N=295)	
Therapy Classification	No.	(%)	No.	(%)
Total Who Took Any Concomitant Therapy	274	(92.9)	277	(93.9)
Central Nervous System-Acting Drugs*	184	(62.4)	166	(56.3)
Antimicrobials	120	(40.7)	134	(45.4)
Antacids	71	(24.1)	68	(23.1)
NSAIDs	53	(18.0)	41	(13.9)
Vitamins & Nutritional Supplements	34	(11.5)	43	(14.6)
Bronchodilators	25	(8.5)	32	(10.8)
Anticoagulants	22	(7.5)	25	(8.5)
Antidiabetic Therapy	21	(7.1)	20	(6.8)

* Besides the traditional central nervous system-acting drugs (antipsychotics, antidepressants, antiepileptics, hypnotics, sedatives, antiparkinson agents, opioid analgesics, and anesthetics), other drugs with secondary central nervous system effects were included. See Appendices 10 and 11 for complete drug list.

12.2. Protocol Results

12.2.1. Overall Clinical Response

Clinical response to treatment represents the primary efficacy variable in this study. The clinical efficacy analyses focus mainly on the group of subjects evaluable for clinical efficacy. Supporting summaries and analyses are provided for intent-to-treat subjects, microbiologically evaluable subjects, and for the subsets of clinically evaluable subjects who did or did not receive one or more days of twice-daily levofloxacin administration. Posttherapy clinical response rates (cured, improved, and failed) for the levofloxacin and comparative treatment groups are summarized and presented by study center, pathogen, and method of evaluation (respiratory culture, blood culture, or serology/other diagnostic procedure), and by severity of infection (severe and mild/moderate). Subjects were considered to have severe infections if they fulfilled at least one of the following criteria: bacteremia, diastolic hypotension (diastolic blood pressure <60 mm Hg), or a baseline respiratory rate >28 breaths per minute. Subjects who did not meet any of these criteria were considered to have infections that were mild/moderate in severity.

12.2.1.1 Clinical Response at Posttherapy Evaluation (5 to 7 Days After Completion of Therapy)

Among clinically evaluable subjects in the levofloxacin treatment group, 72.1% were cured and 24.3% were improved, compared with 69.1% and 21.3% in the ceftriaxone/cefuroxime treatment group. Eight (3.5%) subjects in the levofloxacin treatment group and 22 (9.6%) subjects in the ceftriaxone/cefuroxime treatment group failed treatment. Of the 226 levofloxacin-treated clinically evaluable subjects, 213 (94.2%) received levofloxacin treatment at q24h or q48h intervals; clinical response rates for these subjects were cure for 154 (72.3%) subjects, improved for 52 (24.4%) subjects, and failed for 7 (3.3%) subjects. Similar posttherapy clinical response rates were observed for the 13 clinically evaluable subjects who received one or more days of twice-daily levofloxacin treatment. In the microbiologically evaluable group, levofloxacin treatment resulted in clinical response rates of 72.7% cure, 25.0% improvement, and 2.3% failure; ceftriaxone/cefuroxime treatment resulted in 65.3% cure, 22.9% improvement, and 11.8% failure. For the intent-to-treat group, levofloxacin treatment resulted in 63.7% cure, 26.8% improvement, and 7.1% failure; 2.4% of subjects could not be evaluated. Ceftriaxone/cefuroxime treatment resulted in 60.7% cure, 25.4%

improvement, and 11.5% failure; 2.4% of subjects could not be evaluated.

Table 12.2.1.A
Clinical Response Rate at Posttherapy Visit for Each Study Center: Sponsor's Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin						Ceftriaxone/Cefuroxime					
Investigator	N	Cured		Improved		Failed	N	Cured		Improved		Failed
Alassi	4	3	(75.0)	1	(25.0)	0 (0.0)	6	5	(100.0)	0	(0.0)	0 (0.0)
Baird	6	6	(100.0)	0	(0.0)	0 (0.0)	4	2	(50.0)	0	(0.0)	2 (50.0)
Brankston	8	6	(75.0)	2	(25.0)	0 (0.0)	11	6	(54.5)	4	(36.4)	1 (9.1)
Budzak	4	2	(50.0)	2	(50.0)	0 (0.0)	3	3	(100.0)	0	(0.0)	0 (0.0)
Burford	3	0	(0.0)	3	(100.0)	0 (0.0)	3	2	(66.7)	1	(33.3)	0 (0.0)
Decker	0	0	–	0	–	0 –	1	1	(100.0)	0	(0.0)	0 (0.0)
Dunbar	22	16	(72.7)	5	(22.7)	1 (4.5)	30	26	(86.7)	3	(10.0)	1 (3.3)
Ellis	1	1	(100.0)	0	(0.0)	0 (0.0)	4	3	(75.0)	1	(25.0)	0 (0.0)
Ervin	1	1	(100.0)	0	(0.0)	0 (0.0)	2	1	(50.0)	1	(50.0)	0 (0.0)
Fite	12	5	(41.7)	7	(58.3)	0 (0.0)	7	5	(71.4)	1	(14.3)	1 (14.3)
Follett	6	5	(83.3)	1	(16.7)	0 (0.0)	8	4	(50.0)	4	(50.0)	0 (0.0)
Gardner	2	1	(50.0)	0	(0.0)	1 (50.0)	2	1	(50.0)	0	(0.0)	1 (50.0)
Geckler	13	10	(76.9)	2	(15.4)	1 (7.7)	9	8	(88.9)	0	(0.0)	1 (11.1)
Gombert	6	6	(100.0)	0	(0.0)	0 (0.0)	4	3	(75.0)	1	(25.0)	0 (0.0)
Gomes	7	6	(85.7)	1	(14.3)	0 (0.0)	4	4	(100.0)	0	(0.0)	0 (0.0)
Graham	0	0	–	0	–	0 –	1	0	(0.0)	1	(100.0)	0 (0.0)
Green J.	2	1	(50.0)	1	(50.0)	0 (0.0)	2	2	(100.0)	0	(0.0)	0 (0.0)
Green S.	0	0	–	0	–	0 –	3	1	(33.3)	2	(66.7)	0 (0.0)
Grunfeld	3	2	(66.7)	1	(33.3)	0 (0.0)	3	3	(100.0)	0	(0.0)	0 (0.0)
Habib	7	6	(85.7)	1	(14.3)	0 (0.0)	6	4	(66.7)	1	(16.7)	1 (16.7)
Havlichek	2	1	(50.0)	1	(50.0)	0 (0.0)	4	2	(50.0)	2	(50.0)	0 (0.0)
Hauer	16	13	(81.3)	1	(6.3)	2 (12.5)	17	6	(35.3)	3	(17.6)	8 (47.1)
Holloway	8	4	(50.0)	3	(37.5)	1 (12.5)	5	3	(60.0)	1	(20.0)	1 (20.0)
Hunt	7	7	(100.0)	0	(0.0)	0 (0.0)	6	5	(83.3)	0	(0.0)	1 (16.7)
Ironside	2	2	(100.0)	0	(0.0)	0 (0.0)	2	2	(100.0)	0	(0.0)	0 (0.0)
Israelski	3	1	(33.3)	1	(33.3)	1 (33.3)	5	4	(80.0)	0	(0.0)	1 (20.0)
Joshi	2	0	(0.0)	1	(50.0)	1 (50.0)	4	2	(50.0)	0	(0.0)	2 (50.0)
Keller	2	2	(100.0)	0	(0.0)	0 (0.0)	4	2	(50.0)	2	(50.0)	0 (0.0)
Kohler	16	9	(56.3)	7	(43.8)	0 (0.0)	18	9	(50.0)	9	(50.0)	0 (0.0)
Mandell	2	1	(50.0)	1	(50.0)	0 (0.0)	1	0	(0.0)	1	(100.0)	0 (0.0)
Moyer	9	7	(77.8)	2	(22.2)	0 (0.0)	9	8	(88.9)	1	(11.1)	0 (0.0)
Padgett	2	2	(100.0)	0	(0.0)	0 (0.0)	3	2	(66.7)	1	(33.3)	0 (0.0)
Parsons	5	3	(60.0)	2	(40.0)	0 (0.0)	5	2	(40.0)	3	(60.0)	0 (0.0)
Payne	5	4	(80.0)	1	(20.0)	0 (0.0)	3	3	(100.0)	0	(0.0)	0 (0.0)
Player	22	15	(68.2)	7	(31.8)	0 (0.0)	15	13	(86.7)	2	(13.3)	0 (0.0)
Plouffe	5	5	(100.0)	0	(0.0)	0 (0.0)	4	4	(100.0)	0	(0.0)	0 (0.0)
Ruff	4	3	(75.0)	1	(25.0)	0 (0.0)	3	1	(33.3)	1	(33.3)	1 (33.3)
Seggar	3	3	(100.0)	0	(0.0)	0 (0.0)	3	2	(66.7)	1	(33.3)	0 (0.0)
Segreti	4	4	(100.0)	0	(0.0)	0 (0.0)	6	4	(66.7)	2	(33.3)	0 (0.0)
Shankman	0	0	–	0	–	0 –	1	1	(100.0)	0	(0.0)	0 (0.0)
Combined[b]	150	110	(73.3)	35	(23.3)	5 (3.3)	150	105	(70.0)	32	(21.3)	13 (8.7)
Total	226	163	(72.1)	55	(24.3)	8 (3.5)	230	159	(69.1)	49	(21.3)	22 (9.6)

Numbers shown in parentheses are percentages for that category.
[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Combined = centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Alassi, Baird, Brankston, Budzak, Burford, Decker, Ellis, Ervin, Fite, Follett, Gardner, Geckler, Gombert, Gomes, Graham, Green J., Green S., Grunfeld, Habib, Havlichek, Holloway, Hunt, Ironside, Israelski, Joshi, Keller, Mandell, Moyer, Padgett, Parsons, Payne, Plouffe, Ruff, Seggar, Segreti, and Shankman.

To allow for a dichotomous assessment of clinical response for clinically evaluable subjects, the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success" and the clinical response category "failed" was designated as the category of "Clinical Failure." Two-sided 95% confidence intervals for the difference in clinical success rates were calculated to evaluate therapeutic equivalence between treatments. Among clinically evaluable subjects, levofloxacin treatment resulted in a 96.5% clinical success rate and ceftriaxone/cefuroxime treatment resulted in a 90.4% clinical success rate, with a 95% confidence interval of [-10.7, -1.3] for the difference (ceftriaxone/cefuroxime minus levofloxacin) in success rates. The confidence interval, the upper limit of which lies below the upper bound of 10% suggested by the FDA's Anti-Infective "Points to Consider" guideline for establishing clinical equivalence of treatments with success rates greater than 90%, establishes that levofloxacin was at least equivalent to ceftriaxone/cefuroxime in terms of achieving clinical success. Confidence intervals computed for each study center

with 10 or more clinically evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers, with the exception of Dr. Heuer's center, where levofloxacin possibly demonstrated enhanced efficacy compared to ceftriaxone/cefuroxime. The cure rates for clinically evaluable subjects in the two treatment groups for all centers combined were similar, 72.1% for levofloxacin and 69.1% for ceftriaxone/cefuroxime, with a 95% confidence interval on the difference in cure rates of [-11.6, 5.6]. Similar cure rates were observed between the two treatment groups across the study centers, with the exception of Dr. Heuer's center, as noted above, and across the efficacy analysis groups. The results of the age, sex, and race subgroup analyses were similar to those for all evaluable subjects with two exceptions. The cure rate for clinically evaluable Black subjects treated with ceftriaxone/cefuroxime was higher than that of Caucasians (81.3% versus 62.3%). Additionally, cure rates in both treatment groups tended to decrease with age. The posttherapy clinical success rates for treatment with levofloxacin and ceftriaxone/cefuroxime were 90.5% and 86.1%, respectively, in the intent-to-treat group and 97.7% and 88.2%, respectively, in the microbiologically evaluable group. To evaluate consistency across all efficacy analysis groups in clinical success rates, 95% confidence intervals for the difference in success rates are provided. The individual confidence intervals for all three efficacy analysis groups are centered below zero and demonstrate the higher clinical success rates achieved in the levofloxacin group than in the ceftriaxone/cefuroxime group.

Table 12.2.1.B
Clinical Success/Failure Rates and Confidence Intervals by Study Center: Sponsor's Clinically Evaluable Subjects

	Levofloxacin			Ceftriaxone/Cefuroxime			
Investigator	N	Success[b]	Failure[b]	N	Success[b]	Failure[b]	95% CI[c]
Alessi	4	4 (100.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	(. , .)
Baird	6	6 (100.0)	0 (0.0)	4	2 (50.0)	2 (50.0)	(. , .)
Brankston	8	8 (100.0)	0 (0.0)	11	10 (90.9)	1 (9.1)	(. , .)
Budzak	4	4 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Bufford	3	3 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Decker	0	0 –	0 –	1	1 (100.0)	0 (0.0)	(. , .)
Dunbar	22	21 (95.5)	1 (4.5)	30	29 (96.7)	1 (3.3)	(-11.9, 14.3)
Ellis	1	1 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Ervin	1	1 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
File	12	12 (100.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	(. , .)
Follett	6	6 (100.0)	0 (0.0)	8	8 (100.0)	0 (0.0)	(. , .)
Gardner	2	1 (50.0)	1 (50.0)	2	1 (50.0)	1 (50.0)	(. , .)
Gackler	13	12 (92.3)	1 (7.7)	9	8 (88.9)	1 (11.1)	(. , .)
Gombert	6	6 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Gomes	7	7 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Graham	0	0 –	0 –	1	1 (100.0)	0 (0.0)	(. , .)
Green J.	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Green S.	0	0 –	0 –	3	3 (100.0)	0 (0.0)	(. , .)
Grunfeld	3	3 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Habib	7	7 (100.0)	0 (0.0)	6	5 (83.3)	1 (16.7)	(. , .)
Havlichek	2	2 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Hauer	16	14 (87.5)	2 (12.5)	17	9 (52.9)	8 (47.1)	(-66.4, -2.7)
Holloway	8	7 (87.5)	1 (12.5)	5	4 (80.0)	1 (20.0)	(. , .)
Hunt	7	7 (100.0)	0 (0.0)	6	5 (83.3)	1 (16.7)	(. , .)
Ironside	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Israelski	3	2 (66.7)	1 (33.3)	5	4 (80.0)	1 (20.0)	(. , .)
Joshi	2	1 (50.0)	1 (50.0)	4	2 (50.0)	2 (50.0)	(. , .)
Keller	2	2 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Kohler	16	16 (100.0)	0 (0.0)	18	18 (100.0)	0 (0.0)	(-3.1, 3.1)
Mandell	2	2 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Moyer	9	9 (100.0)	0 (0.0)	9	9 (100.0)	0 (0.0)	(. , .)
Padgett	2	2 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Parsons	5	5 (100.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	(. , .)
Payne	5	5 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Player	22	22 (100.0)	0 (0.0)	15	15 (100.0)	0 (0.0)	(-3.3, 3.3)
Plouffe	5	5 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Ruff	4	4 (100.0)	0 (0.0)	3	2 (66.7)	1 (33.3)	(. , .)
Segger	3	3 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Segreti	4	4 (100.0)	0 (0.0)	6	6 (100.0)	0 (0.0)	(. , .)
Shankman	0	0 –	0 –	1	1 (100.0)	0 (0.0)	(. , .)
Combined[d]	150	145 (96.7)	5 (3.3)	160	137 (91.3)	13 (8.7)	(-11.0, 0.3)
Total	**226**	**218 (96.5)**	**8 (3.5)**	**230**	**208 (90.4)**	**22 (9.6)**	**(-10.7, -1.3)**

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Numbers shown in parentheses are percentages for that category.
[c] Two-sided 95% confidence intervals for the difference (ceftriaxone/cefuroxime 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.
[d] Combined = centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Alessi, Baird, Brankston, Budzak, Bufford, Decker, Ellis, Ervin, File, Follett, Gardner, Gackler, Gombert, Gomes, Graham, Green J., Green S., Grunfeld, Habib, Havlichek, Holloway, Hunt, Ironside, Israelski, Joshi, Keller, Mandell, Moyer, Padgett, Parsons, Payne, Plouffe, Ruff, Segger, Segreti, and Shankman.

12.2.1.2. Clinical Response at Poststudy Evaluation (21 to 28 Days After Completion of Therapy)

Of the 205 clinically evaluable subjects in the levofloxacin treatment group who had a posttherapy clinical response of cured or improved and who had a clinical response poststudy, poststudy clinical responses were cure for 185 (90.2%) subjects, improved for 12 (5.9%) subjects, and relapse for 6 (2.9%) subjects. Among the 193 subjects in the ceftriaxone/cefuroxime group who met the aforementioned criteria, 178 92.2%) subjects had a poststudy clinical response of cure, 11 (5.7%) improved, and 4 (2.1%) relapse. Improvements in clinical responses from the posttherapy to the poststudy evaluations were noted for the 39 and 31 clinically evaluable subjects in the levofloxacin and ceftriaxone/cefuroxime groups, respectively, whose ratings changed from improved to cure. The subjects who relapsed are further discussed below.

for all but one of the admission pathogens isolated in ceftriaxone/cefuroxime-treated subjects; in the case of Subject 4302, the microbiological response of *S. pneumoniae* was unknown.

Table 13:
Subjects with a Poststudy Clinical Response of Relapse:
Intent-to-Treat Subjects (Study K90-71)

Subject	Investigator	Admission Pathogen	Clinical Response at Posttherapy	Microbiologic Response at Posttherapy
Treatment Group: Levofloxacin 500 mg IV/500 mg PO				
	Dunbar	*Haemophilus influenzae*	Cure	Eradicated[c]
	Dunbar	None identified	Improved	N/A
	Geckler	None identified	Improved	N/A
	Grunfeld	None identified	Improved	N/A
	Heuer	*Haemophilus parainfluenzae*	Cure	Eradicated
	Kohler	None identified	Cure	N/A
Treatment Group: Ceftriaxone IV/Cefuroxime PO				
	Geckler	*Streptococcus pneumoniae*	Cure	Eradicated
	Havlichek	*Acinetobacter calcoaceticus* *Chlamydia pneumoniae*	Improved	Eradicated Eradicated
	Heuer	*Haemophilus parainfluenzae*	Improved	Eradicated[c]
	Holloway	None identified	Cure	N/A
	Kohler	*Chlamydia pneumoniae*	Improved	Eradicated
	Player	*Chlamydia pneumoniae* *Streptococcus pneumoniae*	Cure	Eradicated Unknown

N/A = not applicable
[a] This subject was not microbiologically evaluable.
[b] This subject was not clinically or microbiologically evaluable.
[c] Poststudy microbiologic response was persisted for subjects ·
poststudy microbiologic response was unknown.

12.2.1.2. Clinical Response by Pathogen

Clinical success rates, i.e., percentages with clinical responses of cured or improved, for the two most prevalent respiratory pathogens in the levofloxacin group (*H. influenzae* and *S. pneumoniae*) were 100.0%; the clinical success rates for these two pathogens among ceftriaxone/cefuroxime-treated subjects were 79.2% and 93.9%, respectively. Clinical success rates of 100% were observed for the remaining prevalent pathogens isolated on respiratory culture from levofloxacin-treated subjects, with the exception of *H. parainfluenzae;* the clinical success rate for this pathogen was 87.5%. In the ceftriaxone/cefuroxime group, clinical success rates ranged from 72.7% (*H. parainfluenzae*) to 100% (*M. catarrhalis*) for the remaining prevalent pathogens isolated from respiratory cultures. In both treatment groups, 100% clinical success was observed against *S. pneumoniae* isolated in blood cultures. The most common pathogen (atypical or otherwise) for both treatment groups was *C. pneumoniae;* clinical success rates observed for this pathogen were 97.9% in the levofloxacin group and 92.6% in the ceftriaxone/cefuroxime group. Clinical success rates for the other atypical pathogens were 100.0% (*M. pneumoniae* and *L. pneumophila*) in the levofloxacin group, and 75.0% (*L. pneumophila*) and 100% (*M. pneumoniae*) in the ceftriaxone/cefuroxime group. The posttherapy clinical response rates by pathogen for the microbiologically evaluable and intent-to-treat groups were consistent with the results for the clinically evaluable group. In general, for each efficacy analysis group, poststudy clinical response rates of cure or improved by pathogen were similar to the respective posttherapy response rates.

Table 12.2.2
Clinical Response Rates For Subjects with Pathogens of Primary Interest: Sponsor's Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin				Ceftriaxone/Cefuroxime			
Method of Evaluation/ Pathogen[b]	N[c]	Cured	Improved	Failed	N	Cured	Improved	Failed
Respiratory Cultures								
Haemophilus influenzae	30	24 (80.0)	6 (20.0)	0 (0.0)	24	17 (70.8)	2 (8.3)	5 (20.8)
Streptococcus pneumoniae	30	23 (76.7)	7 (23.3)	0 (0.0)	33	24 (72.7)	7 (21.2)	2 (6.1)
Staphylococcus aureus	10	8 (80.0)	2 (20.0)	0 (0.0)	9	6 (66.7)	2 (22.2)	1 (11.1)
Haemophilus parainfluenzae	8	6 (75.0)	1 (12.5)	1 (12.5)	22	10 (45.5)	6 (27.3)	6 (27.3)
Moraxella (Branhamella) catarrhalis	7	4 (57.1)	3 (42.9)	0 (0.0)	7	3 (42.9)	4 (57.1)	0 (0.0)
Klebsiella pneumoniae	3	2 (66.7)	1 (33.3)	0 (0.0)	8	6 (75.0)	0 (0.0)	2 (25.0)
Blood Cultures								
Streptococcus pneumoniae	9	7 (77.8)	2 (22.2)	0 (0.0)	8	4 (50.0)	4 (50.0)	0 (0.0)
Serology/Other Evaluation Procedures								
Chlamydia pneumoniae	47	34 (72.3)	12 (25.5)	1 (2.1)	54	34 (63.0)	16 (29.6)	4 (7.4)
Mycoplasma pneumoniae	19	15 (78.9)	4 (21.1)	0 (0.0)	22	17 (77.3)	5 (22.7)	0 (0.0)
Legionella pneumophila	5	4 (80.0)	1 (20.0)	0 (0.0)	4	2 (50.0)	1 (25.0)	1 (25.0)

Numbers in parentheses are percentages for that category.
[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] The most prevalent pathogens (N≥5) are presented in this summary for each method of evaluation.
[c] Number of subjects who had that pathogen, alone or in combination with other pathogens.

12.2.1.3. Clinical Response by Severity of Infection

One hundred ninety (84.1%) of the 226 clinically evaluable subjects in the levofloxacin treatment group had mild/moderate infections as did 193 (83.9%) of the 230 clinically evaluable subjects in the ceftriaxone/cefuroxime group. The remaining subjects had severe infections. Similar proportions of subjects both within and between treatment groups with mild/moderate and severe infections had posttherapy clinical response ratings of cure (72.6% and 69.4%, respectively in the levofloxacin group; 69.4% and 67.6%, respectively, in the ceftriaxone/cefuroxime group) and improved (23.7% and 27.8%, respectively, in the levofloxacin group; 20.7% and 24.3%, respectively, in the ceftriaxone/cefuroxime group). Although the proportion of subjects who failed therapy was similar within treatment groups for the different severity of disease, a greater proportion of subjects in the ceftriaxone/cefuroxime group failed therapy (9.8% with mild/moderate infection, and 8.1% with severe infection) than in the levofloxacin group (3.7% and 2.8%, respectively).

Table 12.2.1.3
Clinical Response Five to Seven Days Posttherapy: Summarized by Severity of Infection: Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin				Ceftriaxone/Cefuroxime			
	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Severe	36	25 (69.4)	10 (27.8)	1 (2.8)	37	25 (67.6)	9 (24.3)	3 (8.1)
Mild/Moderate	190	138 (72.6)	45 (23.7)	7 (3.7)	193	134 (69.4)	40 (20.7)	19 (9.8)
Total	226	163 (72.1)	55 (24.3)	8 (3.5)	230	159 (69.1)	49 (21.3)	22 (9.6)

Numbers in parentheses are percentages for that category.
[a] A window of 1-10 days posttherapy was used for determination of evaluability.

12.2.1.4. Clinical Symptoms

The proportions of clinically evaluable subjects with resolution of clinical symptoms of pneumonia, based on the posttherapy assessment of subjects, are presented in Table 16. Levofloxacin treatment resulted in clearing of chills, pleuritic chest pain, and purulent sputum in at least 90.0% of clinically evaluable subjects; in the ceftriaxone/cefuroxime group, clearing of these symptoms was achieved in at least 85.2% of subjects. Shortness of breath resolved in 84.1% of levofloxacin-treated subjects compared with 67.8% of subjects in the ceftriaxone/cefuroxime group. Resolution of sputum occurred in 74.4% of levofloxacin-treated subjects and 70.2% of ceftriaxone/cefuroxime-treated subjects. Cough resolved in 58.4% and 56.6% of subjects in the levofloxacin and ceftriaxone/cefuroxime groups, respectively.

Table 12.2.1.4.A
Proportion of Subjects with Resolution of Clinically Symptoms of Pneumonia Based on Posttherapy Evaluation: Sponsor's Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin		Ceftriaxone/Cefuroxime	
Symptom	Resolved[a,b]	(%)	Resolved[a,b]	(%)
Chills	147/153	(96.1)	134/139	(96.4)
Pleuritic Chest Pain	126/140	(90.0)	109/128	(85.2)
Shortness of Breath	138/164	(84.1)	120/177	(67.8)
Cough Increase	128/219	(58.4)	128/226	(56.6)
Sputum Increase	151/203	(74.4)	139/198	(70.2)
Purulent Sputum	165/172	(95.9)	143/162	(88.3)

[a] Symptom present at admission and absent at posttherapy assessment.
[b] Denominator represents the number of subjects with that symptom at admission.

Improvement was evident in both the levofloxacin and ceftriaxone/cefuroxime treatment groups with at least 83.9% and 85.3% of subjects, respectively, showing resolution or improvement in each of the individual clinical signs of pneumonia at the posttherapy chest examination.

Table 12.2.1.4.B
Proportion of Subjects with Resolution or Improvement of Pneumonia Based on Posttherapy Chest Examination: Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin				Ceftriaxone/Cefuroxime			
Sign	Resolved[a,c]		Improved[b,c]		Resolved[a,c]		Improved[b,c]	
Diminished Breath Sounds	96/124	(76.6%)	9/124	(7.3%)	110/143	(76.9%)	12/143	(8.4%)
Rales	119/139	(85.6%)	11/139	(7.9%)	122/163	(74.8%)	27/163	(16.6%)
Egophony	50/51	(98.0%)	0/51	(0%)	50/53	(94.3%)	2/53	(3.8%)
Rhonchi	91/107	(85.0%)	7/107	(6.5%)	101/130	(77.7%)	11/130	(8.5%)
Wheezes	70/81	(86.4%)	6/81	(7.4%)	59/75	(78.7%)	7/75	(9.3%)

Numbers shown in parentheses are percentages for that category.

[a] Sign present at admission (mild, moderate, or severe) and absent (none) at posttherapy evaluation.
[b] Signs were graded 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 at admission.

Table 12.2.1.4.C
Proportion of Subjects with Resolution or Improvement (Posttherapy) in Abnormal Admission Radiographic (Chest X-ray) Findings: Clinically Evaluable Subjects (Study K90-071)

	Levofloxacin				Ceftriaxone/Cefuroxime			
Posttherapy Radiographic Findings	Resolved	(%)	Improved	(%)	Resolved	(%)	Improved	(%)
All Subjects:								
Infiltrate Present at Admission	128/218	(58.7)	84/218	(38.5)	125/218	(57.3)	74/218	(33.9)
Subjects with *C. pneumoniae*:								
Infiltrate Present at Admission	31/46	(67.4)	15/46	(32.6)	28/51	(54.9)	17/51	(33.3)

* Abnormal findings were graded as resolved, improved, no change, or worsened at the posttherapy evaluation. Data are presented for clinically evaluable subjects who had infiltrates at admission and who had radiographic findings reported posttherapy. Data for eight of 226 clinically evaluable subjects in the levofloxacin treatment group have been excluded: subjects [redacted] did not have radiographic findings reported at posttherapy. One of these subjects [redacted] was infected with *C. pneumoniae*, therefore, data are presented for 46 of 47 clinically evaluable subjects in the levofloxacin group who were infected with *C. pneumoniae*. Data for 12 of 230 clinically evaluable subjects in the ceftriaxone/cefuroxime treatment group have been excluded: subjects [redacted] did not have radiographic findings reported at posttherapy. Three of these subjects [redacted] were infected with *C. pneumoniae*, therefore, data are presented for 51 of 54 clinically evaluable subjects in the ceftriaxone/cefuroxime treatment group who were infected with *C. pneumoniae*.

Among clinically evaluable subjects in the levofloxacin and ceftriaxone/cefuroxime groups, 97.2% and 91.3%, respectively, showed resolution or improvement in abnormal admission radiographic findings at the posttherapy visit. For the most prevalent pathogen, *C. pneumoniae*, resolution or improvement of radiographic findings was noted for a greater proportion of subjects who received levofloxacin (100.0%) as compared with those who received ceftriaxone/cefuroxime (88.2%). Results were similar within treatment groups for all clinically evaluable subjects compared with the subset of subjects infected with *C. pneumoniae*.

12.2.2. Microbiologic Results

Microbiologic response was the secondary efficacy variable in this study. The analyses of microbiologic response, based primarily on the group of subjects evaluable for microbiologic efficacy, are presented in detail in this section, with results of other efficacy analysis groups provided in the Supporting Data section at the end of the text and briefly described here. The results from the other efficacy analysis groups were generally consistent with those from the microbiologically evaluable group.

12.2.2.1. *In Vitro* Susceptibility

Susceptibility to study medication was determined for all pathogens except *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. Among levofloxacin-treated subjects, 106 had pathogens isolated in respiratory cultures, 14 subjects had pathogens isolated in blood cultures, and 85 subjects had atypical pathogens identified from serologic or urinary antigen tests. For the ceftriaxone/cefuroxime group, 127 subjects had pathogens isolated in respiratory cultures, 10 had pathogens isolated in blood cultures, and 85 had atypical pathogens identified from serologic or urinary antigen tests. Among levofloxacin-treated subjects, there were 139 pathogens with known susceptibility and ceftriaxone/cefuroxime-treated subjects had 149 pathogens with known susceptibility to ceftriaxone and 149 pathogens with known susceptibility to cefuroxime. Of the pathogens with known susceptibility to levofloxacin, 100.0% were susceptible or moderately susceptible to levofloxacin. Of the 149 pathogens with known susceptibility to ceftriaxone, 148 (99.3%) were susceptible or moderately susceptible to ceftriaxone; of the 149 pathogens with known susceptibility to cefuroxime, 142 (95.3%) were susceptible or moderately susceptible to cefuroxime. The pathogens resistant to ceftriaxone and cefuroxime represent 0.7% and 4.7% of all isolates with known susceptibility from ceftriaxone/cefuroxime-treated subjects; none of the isolated pathogens were resistant to levofloxacin.

Table 12.3.1.A
In vitro Susceptibility of All Pathogens isolated at Admission: Modified Intent-to-Treat Subjects with an Admission Pathogen (Protocol K90-071)

	Levofloxacin		Ceftriaxone		Cefuroxime	
Susceptibility of Pathogen	N	(%)[b]	N	(%)[b]	N	(%)[b]
Susceptible	133	(95.7%)	109	(73.2%)	190	(67.2%)
Moderately Susceptible	6	(4.3%)	39	(26.2%)	12	(8.1%)
Resistant	0	(0.0%)	1	(0.7%)	7	(4.7%)
Unknown	14		26		26	
Total No. Pathogens	153		174		174	

[a] Susceptibility testing was not done for *C pneumoniae*, *M pneumoniae*, or *L pneumophila*; these pathogens are not included in this table.
[b] Percentages were based on numbers of pathogens with known susceptibilities. Admission pathogens were isolated from 166 levofloxacin-treated subjects and 181 ceftriaxone/cefuroxime-treated subjects.

The cross-susceptibility of pathogens isolated at admission to levofloxacin and ceftriaxone and levofloxacin and cefuroxime, respectively, was also investigated. One hundred ninety (68.8%) of 276 isolates with known susceptibility information for both levofloxacin and ceftriaxone were susceptible to both drugs; 276 (100.0%) isolates with known cross-susceptibilities were susceptible or moderately susceptible to levofloxacin and 271 (98.2%) isolates were susceptible or moderately susceptible to ceftriaxone. Five pathogens were levofloxacin-susceptible and ceftriaxone-resistant. Cross-susceptibility to both drugs was unknown for 26 isolates. When the cross-susceptibility of pathogens to levofloxacin and cefuroxime was considered, 230 (83.6%) of 275 isolates with known susceptibility information were susceptible to both drugs; 275 (100%) isolates with known cross-susceptibilities were susceptible or moderately susceptible to levofloxacin and 256 (93.1%) were susceptible or moderately susceptible to cefuroxime. Nineteen pathogens were levofloxacin-susceptible and cefuroxime-resistant. Cross-susceptibility to both drugs was unknown for 26 isolates.

Table 12.3.1.B
Cross-Susceptibility of Admission Pathogens to Levofloxacin and Ceftriaxone: Modified Intent-to-Treat Subjects with an Admission Pathogen (Protocol K90-071)

		Ceftriaxone				
		S	M	R	U	
Levofloxacin	S	190	74	5	24	293
	M	7	0	0	1	8
	R	0	0	0	0	0
	U	0	0	0	26	26
		197	74	5	51	327

S = Susceptible, M = Moderate, R = Resistant, U = Unknown.
* Susceptibility testing was not done for *C pneumoniae*, *M. pneumoniae*, or *L. pneumophila*; these pathogens are not included in this table.

Table 12.3.1.B
Cross-Susceptibility of Admission Pathogens to Levofloxacin and Cefuroxime: Modified Intent-to-Treat Subjects with an Admission Pathogen (Protocol K90-071)

		Cefuroxime				
		S	M	R	U	
Levofloxacin	S	230	19	19	25	293
	M	7	0	0	1	8
	R	0	0	0	0	0
	U	0	0	0	26	26
		237	19	19	52	327

S = Susceptible, M = Moderate, R = Resistant, U = Unknown.
* Susceptibility testing was not done for *C pneumoniae*, *M. pneumoniae*, or *L. pneumophila*; these pathogens are not included in this table.

12.2.2.2. Microbiologic Eradication Rates

12.2.2.2.1. Microbiologic Eradication Rates by Subject

Among microbiologically evaluable subjects in the levofloxacin treatment group, the eradication rate was 98.4% (including 96.1% presumed eradication and 2.3% documented eradication) compared with 87.5% (including 84.7% presumed eradication and 2.8% documented eradication) in the ceftriaxone/cefuroxime group, with a confidence interval of [-17.1, -4.7] for the difference (ceftriaxone/cefuroxime minus levofloxacin) in eradication rates. This confidence interval establishes that levofloxacin was at least therapeutically equivalent to ceftriaxone/cefuroxime in achieving microbiologic eradication. Two (1.6%) subjects in the levofloxacin treatment group and 18 (12.5%) subjects in the ceftriaxone/cefuroxime group had microbiologic persistence. Eradication rates were consistent regardless of sex, age, or race. Of the 128 microbiologically evaluable subjects in the levofloxacin group, 118 were treated with levofloxacin at q24h or q48h intervals throughout their entire course of therapy; the microbiologic eradication rate

for these subjects (99.2%) was similar to that for all microbiologically evaluable subjects . Among intent-to-treat subjects, levofloxacin treatment resulted in 88.0% eradication and 5.4% persistence; ceftriaxone/cefuroxime treatment resulted in 76.8% eradication and 12.7% persistence.

Table 12.3.2.1
Microbiologic Eradication Rates and Confidence Intervals by Study Center: Sponsor's Microbiologically Evaluable Patients (Protocol K90-071)

	Levofloxacin			Ceftriaxone/Cefuroxime			
	N	Eradicated[b,c]	Persisted[c]	N	Eradicated[b,c]	Persisted[c]	95% CI[d]
Alessi	4	4 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Baird	3	3 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Brankston	4	4 (100.0)	0 (0.0)	6	6 (100.0)	0 (0.0)	(. , .)
Budzak	3	3 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Bufford	3	3 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Dunbar	14	13 (92.9)	1 (7.1)	17	14 (82.4)	3 (17.6)	(-36.7, 15.7)
Ellis	1	1 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Ervin	0	0 –	0 –	1	1 (100.0)	0 (0.0)	(. , .)
File	7	7 (100.0)	0 (0.0)	3	2 (66.7)	1 (33.3)	(. , .)
Follett	4	4 (100.0)	0 (0.0)	5	4 (80.0)	1 (20.0)	(. , .)
Gardner	1	1 (100.0)	0 (0.0)	0	0 –	0 –	(. , .)
Geckler	10	9 (90.0)	1 (10.0)	3	3 (100.0)	0 (0.0)	(. , .)
Gombert	3	3 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Gomez	4	4 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Graham	0	0 –	0 –	1	1 (100.0)	0 (0.0)	(. , .)
Green J.	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Green S.	0	0 –	0 –	2	2 (100.0)	0 (0.0)	(. , .)
Grunfeld	2	2 (100.0)	0 (0.0)	2	1 (50.0)	1 (50.0)	(. , .)
Habib	5	5 (100.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	(. , .)
Havlichek	0	0 –	0 –	2	2 (100.0)	0 (0.0)	(. , .)
Heuer	9	9 (100.0)	0 (0.0)	17	9 (52.9)	8 (47.1)	(. , .)
Holloway	2	2 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Hunt	4	4 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Ironside	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Israelski	0	0 –	0 –	5	4 (80.0)	1 (20.0)	(. , .)
Joshi	1	1 (100.0)	0 (0.0)	4	2 (50.0)	2 (50.0)	(. , .)
Keller	0	0 –	0 –	3	3 (100.0)	0 (0.0)	(. , .)
Kohler	7	7 (100.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	(. , .)
Mandell	1	1 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Moyer	6	6 (100.0)	0 (0.0)	6	6 (100.0)	0 (0.0)	(. , .)
Padgett	0	0 –	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Parsons	2	2 (100.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	(. , .)
Payne	2	2 (100.0)	0 (0.0)	2	2 (100.0)	0 (0.0)	(. , .)
Player	14	14 (100.0)	0 (0.0)	8	8 (100.0)	0 (0.0)	(. , .)
Plouffe	4	4 (100.0)	0 (0.0)	3	3 (100.0)	0 (0.0)	(. , .)
Ruf	1	1 (100.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	(. , .)
Seggev	2	2 (100.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	(. , .)
Segreti	2	2 (100.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	(. , .)
Shankman	0	0 –	0 –	1	1 (100.0)	0 (0.0)	(. , .)
Combined[e]	144	113 (99.1)	1 (0.9)	127	112 (88.2)	15 (11.8)	(-17.2, -4.6)
Total	128	125 (98.4)	2 (1.6)	144	126 (87.5)	18 (12.5)	(-17.1, -4.7)

[a] A window of 1-10 days postherapy was used for determination of evaluability.
[b] Eradication of all pathogens isolated for a subject at admission.
[c] Numbers shown in parentheses are percentages for that category.
[d] Two-sided 95% confidence interval around the difference (ceftriaxone/cefuroxime minus levofloxacin) in microbiologic eradication rates was calculated for study centers enrolling 10 or more microbiologically evaluable subjects in each treatment group.
[e] Combined=centers that enrolled fewer than 10 microbiologically evaluable subjects in either treatment group: Alessi, Baird, Brankston, Budzak, Bufford, Ellis, Ervin, File, Follett, Gardner, Geckler, Gombert, Gomez, Graham, Green J., Green S., Grunfeld, Habib, Havlichek, Heuer, Holloway, Hunt, Ironside, Israelski, Joshi, Keller, Kohler, Mandell, Moyer, Padgett, Parsons, Payne, Player, Plouffe, Ruf, Seggev, Segreti, and Shankman. Investigator Declair did not enroll any microbiologically evaluable subjects.

12.2.2.2.2. Microbiologic Eradication Rates by Pathogen

The overall microbiologic eradication rates by pathogen in the levofloxacin and ceftriaxone/cefuroxime treatment groups in subjects evaluable for microbiologic efficacy were 98.4% and 90.4%, respectively. The microbiologic eradication rate was 100% for the most prevalent pathogens detected in respiratory culture for all microbiologically evaluable levofloxacin-treated subjects, with the exception of *H. parainfluenzae*, which had an eradication rate of 87.5%. In the ceftriaxone/cefuroxime group, eradication rates for these pathogens ranged from 71.4% to 100%. Levofloxacin eradicated 100% of *S.*

pneumoniae detected in blood cultures, as did treatment with ceftriaxone/cefuroxime. Among atypical pathogens detected by serology and urinary antigen assays for *Legionella*, levofloxacin treatment resulted in eradication rates of 97.9% to 100%, as compared with the 75.0% to 100% eradication rates observed in the ceftriaxone/cefuroxime group. The microbiologic eradication rates for *C. pneumoniae*, *H. influenzae*, *S. pneumoniae* (detected in respiratory specimens), *M. pneumoniae*, and *H. parainfluenzae*, the most prevalent pathogens, were 97.9%, 100%, 100%, 100%, and 87.5%, respectively, for all microbiologically evaluable subjects treated with levofloxacin as compared with 92.5%, 79.2%, 96.9%, 100%, and 71.4% among microbiologically evaluable subjects in the ceftriaxone/cefuroxime group. The most remarkable difference in eradication rates between groups was for *H. influenzae*; the 95% confidence interval for the difference in eradication rates was below zero for *H. influenzae*, suggesting that levofloxacin was atleast equivalent to, and possibly exhibits increased efficacy, as compared to ceftriaxone/cefuroxime. The eradication rate for these same pathogens was 100% in all cases among subjects who received levofloxacin at q24h or q48h intervals for their entire course of therapy. Microbiologic eradication rates posttherapy for clinically evaluable subjects were similar to those for microbiologically evaluable subjects. Posttherapy microbiologic eradication rates were somewhat lower for both treatment groups in the intent-to-treat population, as would be expected. For all efficacy analysis groups, microbiologic eradication rates poststudy were similar to or lower than the corresponding rates posttherapy; however, it was noted that a greater number of subjects had a response of "unknown" at the poststudy time point. One ceftriaxone/cefuroxime-treated subject (4502) with susceptibility data available at posttherapy had microbiologic persistence of a pathogen (*Pseudomonas aeruginosa*) that acquired resistance to ceftriaxone.

Table 12.2.2.2.2.
Microbiologic Eradication Rates Five to Seven Days Posttherapy [a] Summarized by Method of Evaluation, Pathogen, and Treatment Regimen: Microbiologically Evaluable Subjects (Study K90-071)

	Levofloxacin						
	q24h and q48h Regimen (N=116)		All Regimens[b] (N=126)		Ceftriaxone/ Cefuroxime (N=144)		
Method of Evaluation/Pathogen[c]	N	Eradicated[d]	N	Eradicated[d]	N	Eradicated[d]	95% CI[e]
Respiratory Cultures							
Haemophilus influenzae	28	28 (100.0)	30	30 (100.0)	24	19 (79.2)	(-39.2, -2.5)
Streptococcus pneumoniae	29	29 (100.0)	30	30 (100.0)	32	31 (96.9)	(-10.8, 4.6)
Staphylococcus aureus	9	9 (100.0)	10	10 (100.0)	9	9 (100.0)	(., .)
Haemophilus parainfluenzae	7	7 (100.0)	8	7 (87.5)	21	15 (71.4)	(., .)
Moraxella (Branhamella) catarrhalis	7	7 (100.0)	7	7 (100.0)	7	6 (85.7)	(., .)
Klebsiella pneumoniae	3	3 (100.0)	3	3 (100.0)	8	8 (100.0)	(., .)
Blood							
Streptococcus pneumoniae	8	8 (100.0)	9	9 (100.0)	8	8 (100.0)	(., .)
Serology							
Chlamydia pneumoniae	42	42 (100.0)	47	46 (97.9)	53	49 (92.5)	(-14.7, 3.9)
Mycoplasma pneumoniae	19	19 (100.0)	19	19 (100.0)	22	22 (100.0)	(-2.5, 2.5)
Legionella pneumophila	3	3 (100.0)	5	5 (100.0)	4	3 (75.0)	(., .)

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Includes 116 microbiologically evaluable subjects who received q24 and q48h levofloxacin dosing for the entire course of therapy and the 10 subjects who received one or more days of b.i.d. levofloxacin treatment.
[c] The most prevalent pathogens (N≥5) for either treatment group are presented in this summary for each method of evaluation.
[d] Numbers shown in parentheses are percentages for that category.
[e] Confidence intervals for the difference (ceftriaxone/cefuroxime minus levofloxacin) are given for all regimens only for pathogens with 10 or more admission isolates in each treatment group.

12.2.3. Microbiologic Eradication Rates by Severity of Infection

Eradication rates both by subject and by pathogen were 98.1% for subjects with mild/moderate infections and 100% for subjects with severe infections in the levofloxacin treatment group; for the ceftriaxone/cefuroxime group, these rates were 87.9% by subject and 90.2% by pathogen for subjects with mild/moderateinfections and 85.7% by subject and 90.9% by pathogen for subjects with severe infections. The data indicate that levofloxacin treatment, as assessed by subject or pathogen, was comparable in efficacy among subjects with severe infections and those with mild/moderate infections and produced eradication rates as high or higher than ceftriaxone/cefuroxime treatment.

Table 12.2.3.
Microbiologic Eradication Rates Five to Seven Days Posttherapy: Summarized by Severity of Infection: Microbiologically Evaluable Subjects (Study K90-071)

	Levofloxacin			Ceftriaxone/Cefuroxime		
	N	Eradicated[a]	Persisted[a]	N	Eradicated[a]	Persisted[a]
Severe						
Total Severe By Pathogen	34	34 (100.0)	0 (0.0)	55	50 (90.9)	5 (9.1)
Total Severe by Subject	21	21 (100.0)	0 (0.0)	28	24 (85.7)	4 (14.3)
Mild/Moderate						
Total Mild/Moderate By Pathogen	154	151 (98.1)	3 (1.9)	164	148 (90.2)	16 (9.8)
Total Mild/Moderate by Subject	107	105 (98.1)	2 (1.9)	116	102 (87.9)	14 (12.1)
Overall Total						
Total by Pathogen	188	185 (98.4)	3 (1.6)	219	198 (90.4)	21 (9.6)
Total by Subject	128	126 (98.4)	2 (1.6)	144	126 (87.5)	18 (12.5)

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Numbers shown in parentheses are percentages for that category.

12.2.4. Relationship Between Clinical and Microbiologic Response

As confirmatory information, a cross-tabulation of microbiologic response versus clinical response was provided for subjects evaluable for microbiologic efficacy. This summary was also provided by pathogen. treatment groups with respect to overall adverse event incidence rates, 95% confidence intervals are computed around the between-treatment overall difference in subject incidence rates. In addition, 95% confidence intervals are computed around the difference (ceftriaxone/cefuroxime minuslevofloxacin) in adverse events rates for each body system. Adverse events considered probably or definitely related to study drug are classified as drug-related. These adverse events are summarized by body system and primary term.

12.5. Superinfection

Three subjects treated with levofloxacin and four subjects in the cefuroxime/ceftriaxone treatment group developed superinfection. The organism causing the superinfection in two of the three levofloxacin-treated subjects was susceptible to levofloxacin; susceptibility of the pathogen to levofloxacin was unknown for the third subject. In the ceftriaxone/cefuroxime group, one subject had a superinfection due to organisms susceptible to both drugs, one subject's superinfection was caused by a pathogen resistant to both drugs, and two subjects had a superinfection caused by organisms for which susceptibility to ceftriaxone and cefuroxime was unknown.

Table 12.5
List of Subjects with Superinfections:
Sponsor's Modified Intent-to-Treat Cohort (Protocol K90-071)

Subject Number	Pathogen	Source	Susceptibility		
			Levofloxacin	Ceftriaxone	Cefuroxime
Levofloxacin					
	Haemophilus parainfluenzae	Respiratory/Sputum Culture	Susceptible	Susceptible	Susceptible
	Staphylococcus aureus (Methicillin-resistant)	Respiratory/Sputum Culture	Unknown	Unknown	Unknown
	Haemophilus parainfluenzae	Respiratory/Sputum Culture	Susceptible	Susceptible	Susceptible
Ceftriaxone/Cefuroxime					
	Staphylococcus aureus (Methicillin-resistant)	Respiratory/Sputum Culture	Resistant	Resistant	Resistant
	Streptococcus faecalis	Kidney/Urine	Unknown	Unknown	Unknown
	Pseudomonas aeruginosa	Respiratory/Sputum Culture	Susceptible	Unknown	Unknown
	Haemophilus parainfluenzae	Respiratory/Sputum Culture	Susceptible	Susceptible	Susceptible
	Moraxella (Branhamella) catarrhalis	Respiratory/Sputum Culture	Susceptible	Susceptible	Susceptible

12.6. Summary of Key Efficacy Results as per Sonsor

The clinical response rates are comparable among the analysis groups within treatment groups. Higher clinical response and microbiologic eradication rates were observed in the levofloxacin group than in the ceftriaxone/cefuroxime group. The clinical response rates in the levofloxacin group exceeded 90% for all analysis groups, as did the microbiologic eradication rate in the subjects evaluable for microbiologic efficacy; the microbiologic eradication rate for intent-to-treat subjects with an admission pathogen was 88%. Moreover, there was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency and reliability of these response measures. The clinical and microbiologic results clearly demonstrate that levofloxacin was at least equivalent to ceftriaxone/cefuroxime. The major clinical and microbiologic efficacy results are summarized in Table 12.6, on the following page.

Table 12.6
Summary of Key Efficacy Results as per Sponsor (Protocol K90-071)

Response/Group	Levofloxacin: Clinical Success or Microbiologic Eradication Rates (Posttherapy)[a]		Ceftriaxone/Cefuroxime: Clinical Success or Microbiologic Eradication Rates[a]		95% Confidence Interval[b]
Clinical and Microbiologic Response					
Clinical Response					
Intent-to-Treat	267/295	(90.5)	254/295	(86.1)	(-9.8, 0.9)
Clinically Evaluable	218/225	(96.5)	208/230	(90.4)	(-10.7, -1.3)
Microbiologically Evaluable	125/128	(97.7)	127/144	(88.2)	(-15.7, -3.2)
Microbiologic Response					
Microbiologically Evaluable	126/128	(98.4)	126/144	(87.5)	(-17.1, -4.7)
Intent-to-Treat[c]	146/155	(88.0)	139/181	(76.8)	(-19.4, -3.0)

Microbiologic Response Versus Clinical Response[d]

Microbiologic Response	Clinical Response: Levofloxacin N	Cured	Improved	Failed	Ceftriaxone/Cefuroxime N	Cured	Improved	Failed
Eradicated	126	93 (73.8)	32 (25.4)	1 (0.8)	126	91 (72.2)	32 (25.4)	3 (2.4
Persisted	2	0 (0.0)	0 (0.0)	2 (100.0)	18	3 (16.7)	1 (5.6)	14 (77.8
Total	128	93 (72.7)	32 (25.0)	3 (2.3)	144	94 (65.3)	33 (22.9)	17 (11.8

[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 (ceftriaxone/cefuroxime minus levofloxacin) in clinical success or microbiologic eradication rates.
[c] Subjects with admission pathogens.
[d] Based on microbiologically evaluable group.

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.

12.7. Sponsor's discussion of efficacy results

The objective of this study was to evaluate the safety and efficacy of levofloxacin versus ceftriaxone/cefuroxime in the treatment of community-acquired pneumonia in adults. Clinical response to treatment (evaluated by the investigator posttherapy as cured, improved, failed, or unable to evaluate and at the poststudy follow-up contact or visit (21 to 28 days posttherapy) as cured, improved, relapsed, or unable to evaluate) was assessed as the primary efficacy variable and was based on the group of subjects evaluable for clinical efficacy. Microbiologic response to treatment (eradication or persistence of pathogen(s) isolated at admission and of the subject's infection considering all pathogens isolated) was the secondary efficacy variable and was based on the group of subjects evaluable for microbiologic efficacy. Clinical and microbiologic results based on these analysis groups are supported by results from the intent-to-treat group. In all efficacy analysis groups examined, levofloxacin was both effective and safe in the treatment of community-acquired pneumonia. The results for the levofloxacin and ceftriaxone/cefuroxime groups that were obtained in this study are valid for comparison for several reasons. The two treatment groups were determined by randomization and were comparable with respect to demographics and other admission characteristics, premature discontinuation rate, concomitant medications, enrollment at study centers, reasons for exclusion, and clinical signs and symptoms at admission. Given the similar composition of the two groups, any differences or similarities in clinical response, microbiologic response, or adverse event profile can be attributed to the individual drugs. Levofloxacin treatment provided therapeutically equivalent clinical responses to those observed with ceftriaxone/cefuroxime. When the posttherapy clinical response categories "cured" and "improved" were combined into a single category of

"Clinical Success", levofloxacin treatment resulted in 96.5% clinical success for clinically evaluable subjects, while ceftriaxone/cefuroxime treatment resulted in 90.4% clinical success. The 95% confidence interval [-10.7, -1.31 for the difference (ceftriaxone/cefuroxime minus levofloxacin) in posttherapy success rates reflects the somewhat higher clinical success rate achieved with levofloxacin over ceftriaxone/cefuroxime and indicates that levofloxacin is at least equivalent to ceftriaxone/cefuroxime. The data indicate that levofloxacin treatment was comparable in efficacy among subjects with severe infections and those with mild/moderate infections. Additionally, the incidence of clinical relapse was <3.0%. In microbiologically evaluable subjects, levofloxacin therapy resulted in an overall eradication rate by subject of 98.4% versus 87.5% for ceftriaxone/cefuroxime with a 95% confidence interval of [-17.1, -4.7] for the difference (ceftriaxone/cefuroxime minus levofloxacin), establishing an advantage of levofloxacin therapy over ceftriaxone/cefuroxime therapy. In the microbiologically evaluable group, levofloxacin treatment resulted in 97.9% eradication of the most common pathogen (*C. pneumoniae*), 100% eradication of the second and third most common pathogens (*S. pneumoniae* and *H. influenzae*), and 100% of the fourth most common pathogen (*M. pneumoniae*) versus 79.2% to 96.9% eradication in the ceftriaxone/cefuroxime treatment group. There was 100% eradication of M. catarrhalis, 100% eradication of L. pneumophila, and 87.5% eradication of *H. parainfluenzae* in the levofloxacin treatment group versus 85.7%, 75.0% and 71.4% eradication, respectively, in the ceftriaxone/cefuroxime group.

Furthermore, good agreement between the clinical and microbiologic responses was observed. There was also general consistency of results across centers and across the efficacy analysis groups evaluated. The clinical and microbiologic results clearly demonstrate that levofloxacin is at least equivalent to ceftriaxone/cefuroxime. In medical practice, physicians almost always treat community-acquired pneumonia before any results of cultures and susceptibility testing are available. To this end, a new drug candidate must be evaluated as to its suitability as a reasonable empiric choice as well as its ultimate safety and efficacy. The distribution of pathogen types encountered should be evaluated on the basis of what is known about the disease and the pathogens encountered should be representative of what would be expected in the United States. In addition, it is important to know for what percentage of organisms the new drug candidate would have been entirely inappropriate, i.e., what percentage of organisms are resistant. In this study we identified the typical organisms, *H. influenzae*, *S. pneumoniae*, *M. (Branhamella) catarrhalis*, *K. pneumoniae*, *M. pneumoniae*, *L. pneumophila*, and *S. aureus*, that are historically associated with community-acquired pneumonia, as well as *C. pneumoniae* which is increasingly being recognized as a significant pathogen in respiratory tract infections worldwide. These eight organisms represent the most common pathogens and are consistent with what clinicians can be expected to encounter on a routine basis. It is noteworthy that none among all pathogens isolated at admission was ultimately identified as resistant to levofloxacin versus five for ceftriaxone and 19 for cefuroxime. In addition, all of the ceftriaxone/cefuroxime-resistant pathogens isolated at admission were fully susceptible to levofloxacin. From this standpoint it can be concluded that levofloxacin is a reasonable antimicrobial for the treatment of patients with community-acquired pneumonia.

13. Efficacy as per Medical Officer:

13.1. Patient Population:

Of the sponsor's intent-to-treat cohort, the medical officer considered 76% (446/590) clinically evaluable. Of the 446 clinically evaluable patients, the medical officer determined that 63% (282/446) of these were microbiologically evaluable. Of the clinically evaluable patients, 37% (164/446) were microbiologically unevaluable.

The clinically and microbiologically evaluable patient groups are further subdivided by treatment arm. In the subgroup of patients that were clinically evaluable, regardless of microbiologic evaluability, 49% (220/446) were treated with levofloxacin and 51% (226/446) were treated with ceftriaxone/cefuroxime. In the subgroup of FDA clinically AND microbiologically evaluable patients, 46% (130/282) were treated with levofloxacin and 54% (152/282) were treated with ceftriaxone/cefuroxime. The breakdown of the intent-to-treat cohort into evaluable and unevaluable subgroups is summarized in Tables 13.1.A and 13.1.B, on the following page. The reasons for both clinical and microbiologic nonevaluability are summarized in a series of tables under Section 13.1.2 of this review.

Table 13.1.A
FDA Clinically and Microbiologically Evaluable Patients: Subgroups of Sponsor's Intent-to-treat Cohort (Protocol K90-071)

Intent-to-treat Cohort
590 (100%)

Levofloxacin ALL DOSES 295/590 (50%)
Levofloxacin QD 278/590 (47%)
278/295 (94%)
Levofloxacin BID 17/590 (3%)
17/295 (6%)
Ceftriaxone/cefuroxime 295/590 (50%)

FDA Clinically Evaluable 446/590 (76%)	FDA Clinically Nonevaluable 144/590 (24%)
Levofloxacin ALL DOSES 220/446 (49%) Levofloxacin QD 207/446 (46%) 207/220 (94%) Levofloxacin BID 13/446 (3%) 13/220 (6%) Ceftriaxone/cefuroxime 226/446 (51%)	Levofloxacin ALL DOSES 75/144 (52%) Levofloxacin QD 71/144 (49%) 71/75 (95%) Levofloxacin BID 4/144 (3%) 4/75 (5%) Ceftriaxone/cefuroxime 71/144 (49%)

FDA Microbiologically Evaluable 282/446 (63%)	FDA Microbiologically Nonevaluable 164/446 (37%)	FDA Microbiologically Evaluable	FDA Microbiologically Nonevaluab 144/144 (100%)
Levofloxacin ALL DOSES 130/282 (46%) Levofloxacin QD 119/282 (42%) 119/130 (92%) Levofloxacin BID 11/282 (4%) 11/130 (8%) Ceftriaxone/cefuroxime 152/282 (54%)	Levofloxacin ALL DOSES 90/164 (55%) Levofloxacin QD 88/164 (54%) 88/90 (98%) Levofloxacin BID 2/164 (1%) 2/90 (2%) Ceftriaxone/cefuroxime 74/164 (45%)	0/144 (0%)	Levofloxacin ALL DOSES 75/144 (52%) Levofloxacin QD 71/144 (49%) 71/75 (95%) Levofloxacin BID 4/144 (3%) 4/75 (5%) Ceftriaxone/cefuroxime 71/144 (49%)

Because the protocol was amended to allow for twice daily dosing of levofloxacin in cases of severe pneumonia, the clinically and microbiologically evaluable patient groups were further subdivided by dose of assigned study medication. In the subgroup of 446 patients that were clinically evaluable, regardless of microbiologic evaluability, 51% (226/446) were treated with ceftriaxone/cefuroxime, 46% (207/446) were treated with levofloxacin 500 mg QD and 4% (13/446) were treated with levofloxacin 500 mg BID. In the subgroup of 282 FDA clinically AND microbiologically evaluable patients, 54% (152/282) were treated with ceftriaxone/cefuroxime, 46% (119/282) were treated with levofloxacin 500 mg QD and 4% (11/282) were treated with levofloxacin 500 mg BID. In the subgroup of 130 FDA clinically AND microbiologically evaluable patients treated with levofloxacin, 91% (119/130) were treated with levofloxacin 500 mg QD and 8% (11/130) were treated with levofloxacin 500 mg BID. The analysis of the FDA clinically evaluable subgroup by microbiologic evaluability and dose of study drug is summarized in Tables 13.1.B and 13.1.C, below.

Table 13.1.B
FDA Clinically and Microbiologically Evaluable Patients:
Subgroups of FDA Clinically Evaluable Cohort by Levofloxacin Dose
(Protocol K90-071)

<table>
<tr><td colspan="3">FDA Clinically Evaluable
All Patients
446/590 (76%)</td></tr>
<tr><td colspan="2">Levofloxacin QD/BID
220/446 (49%)</td><td rowspan="2">Ceftriaxone/cefuroxime
226/446 (51%)</td></tr>
<tr><td>Levofloxacin QD
207/446 (46%)
207/220 (94%)</td><td>Levofloxacin BID
13/446 (3%)
13/220 (6%)</td></tr>
</table>

Table 13.1.C
FDA Clinically and Microbiologically Evaluable Patients:
Subgroups of FDA Clinically Evaluable Cohort by
Microbiologic Evaluablility and Levofloxacin Dose (Protocol K90-071)

<table>
<tr><td colspan="6">FDA Clinically Evaluable
All Patients
446/590 (76%)</td></tr>
<tr><td colspan="3">FDA Clinically and
Microbiologically Evaluable
282/446 (63%)</td><td colspan="3">FDA Clinically Evaluable
Microbiologically Unevaluable
164/446 (37%)</td></tr>
<tr><td colspan="2">LEVO QD or BID</td><td>Ceftriaxone/
cefuroxime</td><td colspan="2">LEVO QD or BID</td><td>Ceftriaxone/
cefuroxime</td></tr>
<tr><td colspan="2">130/282 (46%)</td><td>152/282 (54%)</td><td colspan="2">90/164 (55%)</td><td>74/164 (45%)</td></tr>
<tr><td>LEVO QD</td><td>LEVO BID</td><td>Ceftriaxone/
cefuroxime</td><td>LEVO QD</td><td>LEVO BID</td><td>Ceftriaxone/
cefuroxime</td></tr>
<tr><td>9/282 (42%)
/130 (92%)</td><td>11/282 (4%)
11/130 (6%)</td><td>152/289 (54%)</td><td>88/164 (54%)
88/90 (98%)</td><td>2/164 (1%)
2/90 (2%)</td><td>74/164 (45%)</td></tr>
</table>

13.1.1. Demographics of FDA Clinically and Microbiologically Evaluable Cohorts

Of the 446 patients in the FDA clinically evaluable patient cohort, 246 (55%) were male and 200 (45%) were female. This is similar to the distribution found in the intent-to-treat cohort, as summarized in Table 12.1.2. In the cohort of 282 patients who were both clinically and microbiologically evaluable, there were 164 (58%) males and 118 (42%) females. The distribution among racial groups was similar for both cohorts, and this was similar to the distribution in the intent-to-treat cohort. Likewise, the age distribution in the clinically and clinically/ microbiologically evaluable cohorts was similar to that in the intent-to-treat cohort. The demographics of the FDA clinically evaluable and the FDA clinically and microbiologically evaluable patient subgroups are summarized in Table 3.1.1.A, below.

Table 13.1.1.A
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts (Protocol K90-071)

	FDA Clinically Evaluable Patients N (%)	FDA Clinically and Microbiologically Evaluable Patients N (%)
TOTAL	446	282/446 (63%)
Sex		
M	246/446 (55%)	164/282 (58%)
F	200/446 (45%)	118/282 (42%)
Race		
Caucasian	301/446 (67%)	193/282 (68%)
Black	137/446 (31%)	86/282 (30%)
Hispanic	6/446 (2%)	3/282 (1%)
Asian	0	0
Other	2/446 (<1%)	0
Age (yrs)		
≤45	201/446 (45%)	125/282 (44%)
46-64	133/446 (30%)	86/282 (30%)
≥65	112/446 (25%)	71/282 (25%)

When the FDA clinically and microbiologically evaluable patients were further subdivided by treatment arm, the treatment groups demonstrated the same distribution of demographic variables as did the intent-to-treated group. The demographics of the FDA clinically evaluable and the FDA clinically and microbiologically evaluable patient subgroups are summarized by treatment group in Table 3.1.1.B, below.

Table 13.1.1.B
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts:
Analysis by Treatment Group: Levofloxacin 500 mg QD vs. Ceftriaxone/cefuroxime
(Protocol K90-071)

	FDA Clinically Evaluable Patients N (%)			FDA Clinically and Microbiologically Evaluable Patients N (%)		
	ALL	LEVO* 500 mg QD	Ceftriaxone/ cefuroxime	ALL	LEVO 500 mg QD	Ceftriaxone/ cefuroxime
TOTAL	446	207/446 (46%)	226/446 (51%)	282/446 (63%)	119/282 (42%)	150/282 (54%)
Sex						
M	246/446 (55%)	112/207 (54%)	126/226 (56%)	164/282 (58%)	67/119 (56%)	91/152 (60%)
F	200/446 (45%)	95/207 (46%)	100/226 (44%)	118/282 (42%)	52/119 (44%)	61/152 (40%)
Race						
Caucasian	301/446 (66%)	142/207 (67%)	150/226 (66%)	193/282 (68%)	81/119 (68%)	105/152 (69%)
Black	137/446 (32%)	61/207 (31%)	72/226 (32%)	86/282 (30%)	37/119 (31%)	45/152 (30%)
Hispanic	6/446 (1.3%)	4/207 (2%)	2/226 (<1%)	3/282 (1%)	1/119 (<1%)	2/152 (1%)
Asian	0	0	0	0	0	0
Other	2/446 (<1%)	0	2/226 (<1%)	0	0	0
Age (yrs)						
≤45	201/446 (45%)	95/207 (47%)	101/226 (45%)	123/282 (45%)	55/119 (46%)	66/152 (43%)
46-64	133/446 (30%)	69/207 (32%)	62/226 (27%)	86/282 (30%)	36/119 (30%)	48/152 (32%)
≥65	112/446 (25%)	43/207 (19%)	63/226 (28%)	71/282 (25%)	28/119 (24%)	38/152 (25%)

* 14/446 (3%) of patients received levofloxacin 500 mg BID and are thus excluded from this table

13.1.2. Reasons for Nonevaluability

13.1.2.1. Reasons for Clinical Nonevaluability

Of the sponsor's intent-to-treat cohort, the medical officer considered 76% (446/590) clinically evaluable and 24% (144/590) clinically unevaluable. The three most common reasons for clinincal nonevaluability in the FDA clinically nonevaluable subgroup were (1) patient lost to follow-up, (2) insuffucient course of therapy, and (3) inappropriate clinical evaluation date. The reasons for clinical nonevaluability are summarized in the tables on the following page. Table 13.1.2.1.A contains a summary for the entire nonevaluable cohort, and Table 13.1.2.1.B lists the reasons for nonevaluability in cases in which the medical officer differed with the sponsor.

Table 13.1.2.1.A
Reasons for Clinical Nonevaluability:
ALL FDA Nonevaluable Patients (Protocol K90-071)

Reason for Nonevaluability	Total N	LEVO N	Ceftriaxone/ cefuroxime N	
Inappropriate clinical evaluation date	30	18	12	Includes patients with early EOT evaluation with no EOS evaluation
Clinical diagnosis unconfirmed	8	4	4	
Lost to follow-up	34	16	18	
Protocol violation	17	9	8	
HIV positive or AIDS patient	8	3	5	
Study Drug Therapy Insufficient course of therapy Multiple missed doses** Extended course of therapy	 32 4 1	 17 3 --	 15 1 1	** More than 2 missed doses
Effective concurrent antibiotics Prestudy antibiotic therapy**	8 3	4 1	4 2	** Prestudy Antibiotics with No Pathogen on Admission Culture
TOTAL Reasons **TOTAL Patients**	**145** **144**	**75** **75**	**70** **69**	

Of the 144 patients considered clinically nonevaluable by the medical officer, the medical officer differed with the sponsor's assessment in 19% (27/144) of the cases (i.e., the patient was considered clinically evaluable by the sponsor, but not by the medical officer). The reasons for clinical nonevaluability in this subgroup of patients are summarized in Table 13.1.2.1.B, below.

Table 13.1.2.1.B.
Reasons for Clinical Nonevaluability:
Patients Evaluable by Sponsor but Nonevaluable by FDA (Protocol K90-071)

Reason for Nonevaluability	Total N	LEVO N	Ceftriaxone/ cefuroxime N	
Insufficient course of therapy	2	--	2	
Multiple missed doses	4	3	1	Missed more than 2 doses
Prestudy antibiotic therapy	3	1	2	Prestudy antibiotics with no pathogen on admission culture
Concurrent antimicrobial	1	1	--	
Extended course of therapy	1	--	1	Unevaluable as clinical cure
Inappropriate clinical evaluation date	8	5	3	Early EOT visit with no EOS visit
Nosocomial infection	1	--	1	
AIDS or HIV seropositivity	8	3	5	
TOTAL Reasons **TOTAL Patients**	**28** **27**	**13** **13**	**15** **14**	

13.1.2.2. Reasons for Microbiologic Nonevaluability

Of the intent-to-treat cohort, 28% (164/590) were clinically, but not microbiologically, evaluable, and 24% (144/590) were neither clinically or microbiologically evaluable. Thus, of the intent-to-treat cohort, a total of 52% (308/590) were microbiologically unevaluable. The reasons for microbiologic nonevaluability are summarized in Table 13.1.2.2, below. The most common reasons for microbiologic nonevaluability were (1) no pathogen isolated on admission culture, (2) insufficient duration of therapy, (3) inappropriate bacteriologic culture, (4) lost to follow-up, and (5) residual sputum at the follow-up visit not cultured.

Table 13.1.2.2
Reasons for Microbiologic Nonevaluability:
All Admission Pathogens (Protocol K90-071)

	Clinically Evaluable/ Microbiologically Unevaluable			Clinically and Microbiologically Unevaluable		
	ALL	LEVO	Ceftriaxone/ cefuroxime	ALL	LEVO	Ceftriaxone/ cefuroxime
No Admission Pathogen	146	82	64	69	35	34
Clinical Diagnosis Unconfirmed	--	--	--	2	1	1
Drug Therapy						
Insufficient duration of therapy	--	--	--	20	10	10
Concurrent Antimicrobial Therapy	--	--	--	3	2	1
Multiple missed doses	--	--	--	2	1	1
Protocol Violation						
Inappropriate Bacteriologic Culture	--	--	--	17	10	7
Seizure Disorder	--	--	--	--	--	--
Other	1	0	1	8	4	4
AIDS or HIV seropositivity	--	--	--	2	0	2
Lost to Follow-up/ No End-of-study Evaluation	--	--	--	20	11	9
Residual Sputum at Posttherapy Visit not Cultured	17	8	9	1	1	0
Total: Microbiologically Nonevaluable Patients FDA Evaluable Patients: -All Microorganisms	164	90	74	144	75	69
Total: Microbiologically Nonevaluable Patients FDA Evaluable Patients: All Microorganisms	164			144		
	310					

13.2. Clinical Efficacy as per Medical Officer:

13.2.1. Clinical Cure Rates as per Medical Officer:

Using the medical officer's clinical evaluability criteria delineated in Section 10.2.1 of this review, a total of 446 clinically evaluable patients were selected from the intent-to-treat cohort: 220 levofloxacin-treated patients and 226 ceftriaxone/cefuroxime-treated patients. As discussed earlier in this review, the investigators were given the option of increasing the dosage of levofloxacin to 500 mg BID for cases of severe community-acquired pneumonia. Thus, in the levofloxacin arm, 207 patient received levofloxacin 500 mg QD, and 14 patients received levofloxacin 500 mg BID. The analysis of efficacy was conducted on the subgroup of patients who received levofloxacin 500 mg QD ONLY, as this was the dose and duration requested by the sponsor in the proposed labeling. Those patients who were treated with levofloxacin 500 mg BID are included in the tables for the purpose of completeness, but the total number of patients was too small to allow for any definitive conclusions to be drawn from this dosing group.

The overall cure rate was 62% (129/207) for the levofloxacin QD-treated cohort, and 46% (105/226) for the ceftriaxone/cefuroxime-treated cohort. The overall cure rates for the two treatment arms (including both doses of levofloxacin) were at least statistically equivalent in FDA's clinically evaluable patient group: the 95% confidence interval for the ceftriaxone/cefuroxime-treated arm minus levofloxacin-QD-treated arm was $_{226,207}(-25, -7)_{46\%,62\%}$, indicating superiority of levofloxacin treatment. Cure rates by investigator for levofloxacin-QD-treated patients are summarized in comparison to ceftriaxone/cefuroxime-treated patients in Table 13.2.1.A, below. Clinical cure rates are summarized by investigator and by levofloxacin dose (QD or BID) in Table 13.2.1.B, on the following page. Note that, in Table 13.2.1.A, the clinical cure rates are consistent across study sites for levofloxacin, but show greater variability across study sites in the ceftriaxone/cefuroxime-treated arm.

Table 13.2.1.A
Posttherapy Clinical Cure Rates By Investigator:
Levofloxacin 500 mg QD vs. Ceftriaxone/cefuroxime
FDA Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin 500 mg QD								Ceftriaxone/Cefuroxime							
Investigator	N	Cure		Improve		Fail			N	Cure		Improve		Fail		
Dunbar	17	11	(65)	6	(35)	0	(0)		30	16	(53)	9	(30)	5	(17)	
Heuer	17	10	(59)	4	(24)	3	(18)		17	4	(24)	4	(24)	9	(53)	
Kohler	16	10	(63)	6	(38)	0	(0)		18	7	(39)	9	(50)	2	(11)	
Player	18	12	(67)	6	(33)	0	(0)		16	4	(25)	12	(75)	0	(0)	
Other	139	86	(62)	46	(33)	7	(5)		145	74	(51)	48	(33)	23	(16)	
Total	207	129	(62)	68	(33)	10	(5)		226	105	(46)	82	(36)	39	(17)	

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

Table 13.2.1.B
Posttherapy Clinical Cure Rates By Investigator:
Levofloxacin 500 mg QD and Levofloxacin 500 mg BID
FDA Clinically Evaluable Subjects by Dose (Protocol K90-071)

	Levofloxacin 500 mg QD				Levofloxacin 500 mg BID			
Investigator	N	Cure	Improve	Fail	N	Cure	Improve	Fail
Dunbar	17	11 (65)	6 (35)	0 (0)	5	3 (60)	0 (0)	2 (40)
Geckler	11	7 (64)	3 (27)	1 (9)	--	-	-	-
Heuer	17	10 (59)	4 (24)	3 (18)	--	-	-	-
Kohler	16	10 (63)	6 (38)	0 (0)	--	-	-	-
Player	19	12 (63)	7 (37)	0 (0)	--	-	-	-
Other	131	81 (62)	44 (33)	6 (5)	9	6 (67)	2 (22)	1 (11)
Total	211**	131 (62)	70 (33)	10 (5)	14**	9 (64)	2 (14)	3 (21)

Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
Numbers shown in parentheses are percentages for that category.
**Of the 220 levofloxacin-treated patients who were clinically evaluable, 94% (211/220) received levofloxacin once a day and 6% (14/220) received levofloxacin twice a day.

13.2.2. Clinical Success Rates as per Medical Officer:

The clinical success rate is defined as the combined rate of patients clinically "cured" or "improved" at the follow-up evaluation. Using this definition, the overall clinical success rate was 95% (197/207) for the levofloxacin QD-treated cohort, and 83% (193/226) for the ceftriaxone/cefuroxime-treated cohort. The overall clinical success rates for the two treatment arms were at least statistically equivalent in FDA's clinically evaluable patient groups. The 95% confidence interval around the difference in clinical success rates for ceftriaxone/cefuroxime-treated arm minus levofloxacin-QD-treated arm was $_{226,207}(-18.6, -6.2)_{83\%,95\%}$, indicating superiority of levofloxacin treatment. Clinical success rates by investigator for levofloxacin-QD-treated patients are summarized in comparison to ceftriaxone/cefuroxime-treated patients in Table 13.2.2.A, on the following page. Clinical success rates are summarized by investigator and by levofloxacin dose (QD or BID) in Table 13.2.2.B, on the following page. Note that, in both Table 13.2.2.A and 13.2.2.B, the clinical success rates are consistent across study sites for levofloxacin, but show greater variability across study sites in the ceftriaxone/cefuroxime-treated arm.

Table 13.2.2.A
Posttherapy Clinical Success Rates By Investigator:
Levofloxacin 500 mg QD vs. Ceftriaxone/Cefuroxime
FDA Clinically Evaluable Subjects (Protocol K90-071)

Investigator	Levofloxacin 500 mg QD		Ceftriaxone/Cefuroxime		95% Confidence Interval[b]
	N	Success[a]	N	Success[a]	
Dunbar	17	17 (100)	30	25 (83)	(-34.6, 1.3)
Heuer	17	14 (82)	17	8 (47)	(-71.0, 0.4)
Kohler	16	16 (100)	18	16 (89)	(-31.5, 9.3)
Player	18	18 (100)	16	16 (100)	N/A
Other	139	132 (95)	145	122 (84)	(-18.5, -3.2)
Total	207	197 (95)	226	187 (83)	(-18.6, -6.2)

Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[a]Clinical success is defined as either clinical cure or clinical improvement. Numbers shown in parentheses are percentages for that category.

Table 13.2.2.B
Posttherapy Clinical Success Rates By Investigator:
Levofloxacin 500 mg QD and Levofloxacin 500 mg BID
FDA Clinically Evaluable Subjects (Protocol K90-071)

Investigator	Levofloxacin 500 mg QD		Levofloxacin 500 mg BID	
	N	Success[a]	N	Success[a]
Dunbar	17	17/17 (100)	5	3/5 (60)
Geckler	11	10/11 (91)	--	--
Heuer	17	14/17 (82)	--	--
Kohler	16	16/16 (100)	--	--
Player	19	19/19 (100)	--	--
Other	131	125/131 (95)	9	8/9 (89)
Total	211**	201/211 (95)	14**	11/14 (79)

Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
[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 (ceftriaxone/cefuroxime minus levofloxacin) in clinical success rate.
**Of the 220 levofloxacin-treated patients who were clinically evaluable, 94% (211/220) received levofloxacin once a day and 6% (14/220) received levofloxacin twice a day.

13.2.3. Clinical Cure Rates by Pathogen:

Using the medical officer's clinical and microbiologic evaluability criteria delineated in Sections 10.2.1 and 10.2.2 of this review, a total of 282/590 (63%) patients were both clinically and microbiologically evaluable. It is this subgroup on which the following analysis is based.

Clinical cure rates by pathogen for levofloxacin-QD-treated patients are summarized in comparison to ceftriaxone/cefuroxime-treated patients in Table 13.2.3.A, below. Clinical success rates are summarized by pathogen and by levofloxacin dose (QD or BID) in Table 13.2.3.B, on the following page.

Table 13.2.3.A
Poststudy Clinical Cure Rates for Subjects with Pathogens of Primary Interest:
Levofloxacin 500 mg QD vs. Ceftriaxone/cefuroxime
All FDA Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin 500 mg QD								Ceftriaxone/Cefuroxime							
Pathogen	N*	Cure		Improve		Fail			N*	Cure		Improve		Fail		
Routine Bacterial Pathogens																
Haemophilus influenzae	27	22	(81)	5	(19)	0	(0)		24	10	(42)	5	(21)	9	(38)	
Haemophilus parainfluenzae	9	5	(56)	4	(44)	0	(0)		20	7	(35)	6	(30)	7	(35)	
Klebsiella pneumoniae	1	1	(100)	0	(0)	0	(0)		7	2	(29)	0	(0)	5	(71)	
Moraxella catarrhalis	7	4	(57)	2	(29)	1	(14)		6	4	(67)	1	(17)	1	(17)	
Staphylococcus aureus	7	7	(100)	0	(0)	0	(0)		7	6	(86)	1	(14)	0	(0)	
Streptococcus pneumoniae	29	20	(69)	8	(28)	1	(3)		34	22	(65)	7	(21)	5	(15)	
Other Pathogens																
Chlamydia pneumoniae	58	35	(60)	21	(36)	2	(3)		91	44	(48)	34	(37)	13	(14)	
Legionella pneumophila	3	3	(100)	0	(0)	0	(0)		2	0	(0)	0	(0)	2	(100)	
Mycoplasma pneumoniae	21	12	(57)	8	(38)	1	(5)		20	12	(60)	7	(35)	1	(5)	

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

Table 13.2.3.B
Poststudy Clinical Cure Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects by Levofloxacin Dose (Protocol K90-071)

Pathogen	Levofloxacin 500 mg QD				Levofloxacin 500 mg BID			
	N*	Cure	Improve	Fail	N*	Cure	Improve	Fail
Routine Bacterial Pathogens								
Haemophilus influenzae	27	22 (81)	5 (19)	0 (0)	2	1 (50)	1 (50)	0 (0)
Haemophilus parainfluenzae	9	5 (56)	4 (44)	0 (0)	1	0 (0)	0 (0)	1 (100)
Klebsiella pneumoniae	1	1 (100)	0 (0)	0 (0)	--	-	-	-
Moraxella catarrhalis	7	4 (57)	2 (29)	1 (14)	--	-	-	-
Staphylococcus aureus	7	7 (100)	0 (0)	0 (0)	1	1(100)	0 (0)	0 (0)
Streptococcus pneumoniae	29	20 (69)	8 (28)	1 (3)	2	1 (50)	1 (50)	0 (0)
Other Pathogens								
Chlamydia pneumoniae	59	36 (61)	21 (36)	2 (3)	7	5 (71)	0	2 (29)
Legionella pneumophila	3	3 (100)	0 (0)	0 (0)	2	1	0	1
Mycoplasma pneumoniae	21	12 (57)	8 (38)	1 (5)	--	--	--	--

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

13.2.4. Clinical Success Rates by Pathogen:

Clinical success rate is defined as the combined rate of patients clinically "cured" or "improved" at follow-up assessment. Clinical success rates by pathogen for levofloxacin-QD-treated patients are summarized in comparison to ceftriaxone/cefuroxime-treated patients in Table 13.2.4.A, below. Clinical success rates are summarized by pathogen and by levofloxacin dose (QD or BID) in Table 13.2.4.B, on the following page.

Table 13.2.4.A
Poststudy Clinical Success Rates by Pathogen
Levofloxacin 500 mg QD vs. Ceftriaxone/Cefuroxime
All FDA Clinically Evaluable Subjects (Protocol K90-071)

Pathogen	Levofloxacin 500 mg QD			Ceftriaxone/Cefuroxime			95% Confidence Interval*
	N*	Clinical Success		N	Clinical Success		
Routine Bacterial Pathogens							
Haemophilus influenzae	27	27	(100)	24	15	(62)	(-57, -19)
Haemophilus parainfluenzae	9	9	(100)	20	13	(65)	- - -
Klebsiella pneumoniae	1	1	(100)	7	2	(29)	- - -
Moraxella catarrhalis	7	6	(86)	6	5	(83)	- - -
Staphylococcus aureus	7	7	(100)	7	7	(100)	- - -
Streptococcus pneumoniae	29	28	(97)	34	29	(85)	(-26, 2)
Other Pathogens							
Chlamydia pneumoniae	59	57	(97)	91	78	(86)	(-19, -3)
Legionella pneumophila	3	3	(100)	2	0	(0)	- - -
Mycoplasma pneumoniae	21	20	(95)	20	19	(95)	(-13, 13)

*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 success rate.

Note: Two patients with admission *C. pneumoniae* IgM titers equal to 1:16 were left out of the levofloxacin (QD) treatment group because they also had evidence of preexisting IgG on admission serologies. They were left out of the analysis because they were clinical cured/improved and, therefore, would falsely increase the clinical cure, clinical improved, clinical success, and overall success rates when they represented background seroprevalence and not acute infection.

Table 13.2.4.B
Poststudy Clinical Cure Rates by Pathogen
Levofloxacin 500 mg QD and Levofloxacin 500 mg BID
FDA Clinically Evaluable Subjects (Protocol K90-071)

Pathogen	Levofloxacin 500 mg QD			Levofloxacin 500 mg BID	
	N*	Clinical Success		N*	Clinical Success
Routine Bacterial Pathogens					
Haemophilus influenzae	27	27	(100)	2	2 (50)
Haemophilus parainfluenzae	9	9	(100)	1	0 (0)
Klebsiella pneumoniae	1	1	(100)	--	-
Moraxella catarrhalis	7	6	(86)	--	-
Staphylococcus aureus	7	7	(100)	1	1(100)
Streptococcus pneumoniae	29	28	(97)	2	2 (100)
Other Pathogens					
Chlamydia pneumoniae	59	57	(97)	7	5 (71)
Legionella pneumophila	3	3	(100)	2	1 (50)
Mycoplasma pneumoniae	21	20	(95)	--	--

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

13.2.5. Clinical Response Rates and Clinical Success Rates by Severity of Infection.

The clinical response rates and clinical success rates analyzed by severity of infection in Tables 13.2.5.A and 13.2.5.B, below. The 95% confidence intervals around the difference in **clinical cure rates** was $_{191,\ 174}(-29,-9)_{45\%,\ 64\%}$ for patients with mild-moderate infections and $_{35,\ 33}(-25,\ 23)_{54\%,\ 55\%}$ for patients with severe infections. The 95% confidence intervals around the difference in **clinical success rates** was $_{191,\ 174}(-29,-9)_{82\%,\ 95\%}$ for patients with mild-moderate infections and $_{35,\ 33}(-24,\ 2)_{86\%,\ 97\%}$ for patients with severe infections. Thus, by two parameters of clinical response, levofloxacin is statistically superior to the comparison regimen in the treatment of mild-moderate infections and statistically equivalent to ceftriaxone/cefuroxime in the treatment of severe infections.

Table 13.2.5.A
Clinical Response Rates by Severity of Infection:
FDA Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin				Ceftriaxone/Cefuroxime			
Severity	N	Cure	Improve	Fail	N	Cure	Improve	Fail
Mild/Moderate	174	111 (64)	54 (31)	9 (5)	191	86 (45)	71 (37)	34 (18)
Severe	33	18 (55)	14 (42)	1 (3)	35	19 (54)	11 (31)	5 (14)

Numbers shown in parentheses are percentages for that category

Table 13.2.5.B
Clinical Cure Rates by Severity of Infection:
FDA Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin 500 mg QD		Ceftriaxone/Cefuroxime		95% Confidence Interval
Severity	N	Clinical Cure	N	Clinical Cure	
Mild/Moderate	174	165 (64)	191	157 (45)	(-29, -9)
Severe	33	32 (55)	35	30 (54)	(-25, 23)

Numbers shown in parentheses are percentages for that category

Table 13.2.5.C
Clinical Success Rates by Severity of Infection:
FDA Clinically Evaluable Subjects (Protocol K90-071)

	Levofloxacin 500 mg QD			Ceftriaxone/Cefuroxime			95% Confidence Interval
Severity	N	Clinical Success	Fail	N	Clinical Success	Fail	
Mild/Moderate	174	165 (95)	9 (5)	191	157 (82)	34 (18)	(-19, -7)
Severe	33	32 (97)	1 (3)	35	30 (86)	5 (14)	(-24, 2)

Numbers shown in parentheses are percentages for that category

13.3 Microbiologic Response as per Medical Officer

The overall eradication rates in the levofloxacin-QD-treated patients are summarized by pathogen in Table 13.3.A, below, and 13.3.B, on the following page. The overall eradication rates are all in the range of 90-100%, with the exception of *M. catarrhalis* (86%, 6/7), although this is calculated on a limited number of isolates and is not outside of the range that would support inclusion of this organism in the labeling. *Legionella pneumophilia* had an eradication rate of 100% (3/3), although this too is calculated on a limited number of isolates. Of note, these estimates are limited by the small number of isolates for each organism. All of the confidence interval either overlap zero or lie entirely within the negative range, indicating statistical equivalence or superiority, respectively, of levofloxacin in comparison to ceftriaxone/cefuroxime.

Table 13.3.A
Microbiologic Eradication Rates by Pathogen Category and Pathogen: All FDA Microbiologically Evaluable Subjects (Protocol K90-071)

Pathogen Category/Pathogen	Levofloxacin 500 mg QD		Ceftriaxone/ Cefuroxime		95% Confidence Interval[b]
	N	Eradicated[a]	N	Eradicated[a]	
Pathogen Category					
Gram-positive aerobic pathogens	55	52 (95)	63	58 (92)	(-13.2, 8.2)
Gram-negative aerobic pathogens	54	53 (98)	79	53 (67)	(-43.6, -18.5)
Other	70	68 (97)	91	83 (91)	(-14.2, 2.3)
Total by pathogen	179	173 (97)	233	194 (83)	(-19.4, -7.4)
Total by subject	119	114 (96)	152	123 (81)	(-22.8, -6.9)
Routine Bacterial Pathogens					
Haemophilus influenzae	27	27 (100)	20	14 (70)	(-54.4, -5.6)
Haemophilus parainfluenzae	9	9 (100)	19	12 (63)	N/A
Klebsiella pneumoniae	1	1 (100)	7	3 (43)	N/A
Moraxella catarrhalis	7	6 (86)	6	5 (83)	N/A
Staphylococcus aureus	7	7 (100)	7	7 (100)	N/A
Streptococcus pneumoniae	26	25 (96)	31	26 (84)	(-27, 3)
Other Pathogens					
Chlamydia pneumoniae	58	56 (97)	90	78 (87)	(-18, -2)
Legionella pneumophila	3	3 (100)	2	0 (0)	N/A
Mycoplasma pneumoniae	21	20 (95)	20	19 (95)	(-18.3, 17.8)

[a]Numbers shown in parentheses are percentages for that category.
[b]A two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

Table 13.3.B
Microbiologic Eradication Rates by Pathogen Category and Pathogen:
Levofloxacin 500 mg QD, and Levofloxacin 500 mg BID
FDA Microbiologically Evaluable Subjects by Dose (Protocol K90-071)

Pathogen Category/Pathogen	Levofloxacin 500 mg QD		Levofloxacin 500 mg BID	
	N	Eradicated[a]	N	Eradicated[a]
Pathogen Category				
Gram-positive aerobic pathogens	55	52 (95)	3	3/3 (100)
Gram-negative aerobic pathogens	54	53 (98)	3	2/3 (67)
Other	70	68 (97)	N/A	N/A
Total by pathogen	179	173 (97)	15	12/15 (73)
Total by subject	119	114 (96)	12	9/12 (75)
Routine Bacterial Pathogens				
Haemophilus influenzae	27	27 (100)	2	2/2 (100)
Haemophilus parainfluenzae	9	9 (100)	1	0/1 (0)
Klebsiella pneumoniae	1	1 (100)	---	--- ---
Moraxella catarrhalis	7	6 (86)	---	--- ---
Staphylococcus aureus	7	7 (100)	1	1/1 (100)
Streptococcus pneumoniae	26	25 (96)	2	2/2 (100)
Other Pathogens				
Chlamydia pneumoniae	58	56 (97)	7	5/7 (71)
Legionella pneumophila	3	3 (100)	2	1/2 (50)
Mycoplasma pneumoniae	21	20 (95)	---	--- ---

[a]Numbers shown in parentheses are percentages for that category.
[b]A two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in microbiologic eradication rate was calculated for pathogens with 10 or more admission isolates in each treatment group.

13.4. Overall Success Rates:

The overall success rates for clinically and microbiologically evaluable patients are summarized in Table 13.4.A, below. The overall success rates are shown by pathogen Table 13.4.B, on the following page. There is some variability from one center to the other in overall success rates, but the 95% confidence intervals (for each center) all overlap zero or lie within the negative range, indicating, at minimum, statistical equivalence of the two regimens. The 95% confidence interval around the difference in overall success rates was $_{152,\ 118}(-23.5,\ -7.4)_{80\%,\ 96\%}$, indicating superiority of levofloxacin over competitor in the treatment of community-acquired pneumonia.

Table 13.4.A
Overall Success Rates[a] and Confidence Intervals By Pathogen:
Levofloxacin 500 mg QD vs. Ceftriaxone/Cefuroxime
FDA Microbiologically Evaluable Subjects (Protocol K90-071)

Investigator	Levofloxacin 500 mg QD		Ceftriaxone/Cefuroxime		95% Confidence Interval[c]
	N	Overall Success[b]	N	Overall Success[b]	
Dunbar	12	12 (100)	23	19 (83)	(-39.2, 4.4)
Heuer	11	9 (82)	17	8 (47)	(-75.1, 5.6)
Other	95	92 (97)	112	95 (85)	(-20.5, -3.5)
Total	118	113 (96)	152	122 (80)	(-23.5, -7.4)

Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other". [a]Overall success is defined as either 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 (ceftriaxone/cefuroxime minus levofloxacin) in overall success rate.

There is some variability in overall success rates of levofloxacin against the pathogens of community-acquired pneumonia, with a range from 78-100%. However, the 95% confidence intervals (for pathogens with greater than 10 isolates per treatment arm) all overlap zero or lie within the negative range, indicating, at minimum, statistical equivalence of the two regimens. The 95% confidence interval around the difference in overall success rates was $_{152,\ 118}(-23.5, -7.4)_{80\%,\ 96\%}$, indicating superiority of levofloxacin over competitor in the treatment of community-acquired pneumonia.

Table 13.4.B
Overall Success Rates[a] and Confidence Intervals by Pathogen:
Levofloxacin 500 mg QD vs. Ceftriaxone/Cefuroxime
FDA Microbiologically Evaluable Subjects (Protocol K90-071)

Investigator	Levofloxacin 500 mg QD		Ceftriaxone/Cefuroxime		95% Confidence Interval[c]
	N	Overall Success[b]	N	Overall Success[b]	
Routine Bacterial Pathogens					
Haemophilus influenzae	27	27 (100)	20	14 (70)	(-50, -10)
Haemophilus parainfluenzae	9	7 (78)	19	14 (74)	----
Klebsiella pneumoniae	1	1 (100)	7	2 (29)	----
Moraxella catarrhalis	7	6 (86)	6	5 (83)	----
Staphylococcus aureus	7	7 (100)	7	7 (100)	----
treptococcus pneumoniae	26	25 (96)	31	26 (84)	(-27, 3)
Other Pathogens					
Chlamydia pneumoniae	58	56 (97)	90	78 (87)	(-18, -2)
Legionella pneumophila	3	3 (100)	2	0 (0)	----
Mycoplasma pneumoniae	21	19 (95)	20	19 (95)	(-13, 13)
Total	119	114 (96)	152	122 (80)	(-23, -9)

[a]Overall success is defined as either 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 (ceftriaxone/cefuroxime minus levofloxacin) in overall success rate. 95% confidence intervals are presented for pathogens with 10 or more microbiologically evaluable patients in each treatment group.

14. Safety Results as per Sponsor

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any postadmission safety data were available. Five hundred eighty-four of the 590 (99.0%) subjects enrolled were evaluated for safety. Of the 584 subjects, 291 received levofloxacin and 293 received ceftriaxone/cefuroxime. Six subjects (four in the levofloxacin treatment group and two in the ceftriaxone/cefuroxime group) were lost to follow-up with no safety data available and were therefore excluded from the safety analysis. Therapy discontinuation/completion information for these six subjects was unknown.

Table 14.1

Subjects Excluded from Safety Analysis and Reasons for Exclusion

Subject Number	Age	Sex	Investigator	Reasons for Exclusion
Levofloxacin				
	34	M	Grunfeld	Lost to follow-up, no available data
	42	F	Kohler	Lost to follow-up, no available data
	30	M	Kohler	Lost to follow-up, no available data
	71	F	Padgett	Lost to follow-up, no available data
Ceftriaxone/Cefuroxime				
	66	F	Gomes	Lost to follow-up, no available data
	22	M	Kohler	Lost to follow-up, no available data

14.2. Overview of Safety Data

The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal (GI) system, central and peripheral nervous system, body as a whole, and in the category of psychiatric disorders, and consisted primarily of headache, diarrhea, nausea, and insomnia. The nature and frequency of adverse events were generally comparable across the two treatment groups, except for a higher incidence of headache and diarrhea in the ceftriaxone/cefuroxime group (10.6%, and 11.3%, respectively) than in the levofloxacin group (6.5% and 5.8%, respectively) and small differences between treatments in some other GI events; also, as noted below, there was a higher incidence of chest pain among levofloxacin-treated subjects than in ceftriaxone/cefuroxime-treated subjects. The incidence of disorders of the female reproductive system was greater in the levofloxacin group (4.6%) than in the ceftriaxone/cefuroxime group (1.5%); adverse events reported by levofloxacin-treated subjects in this body system consisted primarily of vaginitis. The incidence of central and peripheral nervous system adverse events was greater in the ceftriaxone/cefuroxime group than in the levofloxacin group (14.7% and 10.7%, respectively); the difference was due primarily to the difference in the incidence of headache between the two groups, as noted earlier. The body system with the highest reported incidence of adverse events for both treatment groups was the gastrointestinal system; a similar proportion of subjects in the two treatment groups experienced adverse events of this system (22.3% for levofloxacin and 25.9% for ceftriaxone/cefuroxime). While the overall incidence of adverse events classified under the "body as a whole" system was similar between the two treatment groups, chest pain occurred in 11 (3.8%) of levofloxacin-treated subjects; none of the ceftriaxone/cefuroxime-treated subjects reported chest pain. Similarly, heart rate and rhythm disorders occurred more frequently among levofloxacin-treated subjects while disorders of the urinary system occurred more frequently among ceftriaxone/cefuroxime-treated

frequency of adverse events was generally comparable across the two treatment groups. However, a higher percentage of levofloxacin-treated subjects (4.6%) compared with ceftriaxone/cefuroxime-treated subjects (1.5%) reported adverse events of the female reproductive system; adverse events in this body system consisted primarily of vaginitis. A higher percentage of ceftriaxone/cefuroxime-treated subjects (14.7%) compared with levofloxacin-treated subjects (10.7%) reported central and peripheral nervous system adverse events. For both treatment groups, adverse events in this body system consisted primarily of headache.

Table 14.3.1.A
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol K90-071)

Body System	Levofloxacin (N=291) N	(%)	Ceftriaxone/ Cefuroxime (N=293) N	(%)	95% Confidence Interval[a]
Gastrointestinal System Disorders	65	(22.3)	76	(25.9)	(-3.5, 10.7)
Central & Peripheral Nervous System Disorders	31	(10.7)	43	(14.7)	(-1.5, 9.5)
Body as a Whole--General Disorders	30	(10.3)	24	(8.2)	(-7.0, 2.8)
Psychiatric Disorders	23	(7.9)	29	(9.9)	(-2.8, 6.8)
Respiratory System Disorders	21	(7.2)	22	(7.5)	(-4.1, 4.7)
Skin and Appendages Disorders	18	(6.2)	13	(4.4)	(-5.5, 2.1)
Metabolic and Nutritional Disorders	11	(3.8)	8	(2.7)	(-4.1, 2.0)
Resistance Mechanism Disorders	8	(2.7)	6	(2.0)	(-3.4, 2.0)
Cardiovascular Disorders, General	6	(2.1)	6	(2.0)	(-2.5, 2.5)
Reproductive Disorders, Female[b]	6	(4.6)	2	(1.5)	(-7.6, 1.5)
Heart Rate and Rhythm Disorders	5	(1.7)	0	(0.0)	(-3.4, -0.1)
Musculo-Skeletal System Disorders	4	(1.4)	5	(1.7)	(-1.8, 2.5)
Autonomic Nervous System Disorders	4	(1.4)	6	(2.0)	(-1.6, 2.9)
Neoplasms	4	(1.4)	2	(0.7)	(-2.5, 1.1)
Application Site Disorders	4	(1.4)	4	(1.4)	(-2.1, 2.0)
Vision Disorders	3	(1.0)	1	(0.3)	(-2.2, 0.8)
Special Senses Other, Disorders	3	(1.0)	0	(0.0)	(-2.4, 0.3)
Myo-, Endo-, Pericardial & Valve Disorders	3	(1.0)	2	(0.7)	(-2.0, 1.3)
Endocrine Disorders	1	(0.3)	0	(0.0)	(-1.2, 0.5)
Vascular (Extracardiac) Disorders	1	(0.3)	4	(1.4)	(-0.6, 2.7)
White Cell and RES Disorders[c]	1	(0.3)	0	(0.0)	(-1.2, 0.5)
Platelet, Bleeding & Clotting Disorders	1	(0.3)	1	(0.3)	(-1.1, 1.1)
Reproductive Disorders, Male[d]	1	(0.8)	0	(0.0)	(-2.2, 0.9)
Hearing and Vestibular Disorders	0	(0.0)	3	(1.0)	(-0.3, 2.3)
Liver and Biliary System Disorders	0	(0.0)	3	(1.0)	(-0.3, 2.3)
Red Blood Cell Disorders	0	(0.0)	3	(1.0)	(-0.3, 2.3)
Urinary System Disorders	0	(0.0)	5	(1.7)	(0.1, 3.4)
Total With Adverse Events (%)	146	(50.2)	146	(49.8)	(-8.6, 7.9)

[a] Two-sided 95% confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in incidence of adverse events.
[b] Percentages calculated from a total number of women evaluable for safety in each treatment group. The total number of women who received levofloxacin was 131 and the total number of women who received ceftriaxone/cefuroxime was 131.
[c] RES = reticulendothelial system
[d] Percentages calculated from a total number of men evaluable for safety in each treatment group. The total numb

Adverse events (primary terms) reported for at least 2.0% of subjects in either treatment group are presented in the table below. Although similar percentages of levofloxacin-treated and ceftriaxone/cefuroxime-treated subjects reported gastrointestinal adverse events overall, the incidence of specific gastrointestinal complaints showed small differences between treatments; some adverse events (e.g., flatulence) were more common in the levofloxacin group (2.1% versus 0%), while others (e.g., diarrhea, dyspepsia, and abdominal pain)

had a higher incidence in the ceftriaxone/cefuroxime group (5.8%, 3.1%, and 1.7%, respectively, among levofloxacin-treated subjects and 11.3%, 4.1%, and 3.8%, respectively, among ceftriaxone/cefuroxime-treated subjects). Headache and insomnia were also among the most common adverse events with levofloxacin-treated subjects showing a lower incidence of headache (6.5%) compared with ceftriaxone/cefuroxime-treated subjects (10.6%); insomnia was reported by 4.5% and 5.5% of subjects in the levofloxacin and ceftriaxone/cefuroxime treatment groups, respectively. The two treatment groups were generally comparable with respect to the type and incidence of other adverse events with the exception of chest pain, which was reported by 11 (3.8%) of levofloxacin-treated subjects as compared with none of the ceftriaxone/cefuroxime-treated subjects.

Table 14.3.1.B
Incidence of Frequently Reported Adverse Events (≥2%)
Summarized by Primary Term: Subjects Evaluable for Safety

	Levofloxacin (N=291)		Ceftriaxone/ Cefuroxime (N=293)	
Body System/Primary Term	N	(%)	N	(%)
All Body Systems	146	(50.2)	146	(49.8)
Skin and Appendages Disorders				
Rash	2	(0.7)	6	(2.0)
Central & Peripheral Nervous System Disorders				
Headache	19	(6.5)	31	(10.6)
Dizziness	5	(1.7)	10	(3.4)
Psychiatric Disorders				
Insomnia	13	(4.5)	16	(5.5)
Gastrointestinal System Disorders				
Nausea	20	(6.9)	22	(7.5)
Diarrhea	17	(5.8)	33	(11.3)
Constipation	12	(4.1)	10	(3.4)
Vomiting	11	(3.8)	10	(3.4)
Dyspepsia	9	(3.1)	12	(4.1)
Flatulence	6	(2.1)	0	(0.0)
Abdominal Pain	5	(1.7)	11	(3.8)
Respiratory System Disorders				
Dyspnea	6	(2.1)	4	(1.4)
Rhinitis	3	(1.0)	6	(2.0)
Reproductive Disorders, Female[a]				
Vaginitis	4	(3.1)	2	(1.5)
Body As A Whole - General Disorders				
Chest Pain	11	(3.8)	0	(0.0)
Back Pain	6	(2.1)	6	(2.0)
Pain	6	(2.1)	4	(1.4)
Fatigue	2	(0.7)	6	(2.0)

[a] Primary term reported by ≥2.0% of subjects in either treatment group.
[b] Percentages calculated from a total number of women evaluable for safety in each treatment group. The total number of women who received levofloxacin was 131 and the total number of women who received ceftriaxone/cefuroxime was 131.

The majority of adverse events were assessed as mild in severity. Twenty subjects in each of the levofloxacin and ceftriaxone/cefuroxime treatment groups reported one or more adverse events of marked severity. In the levofloxacin group, the most common marked adverse events included respiratory disorders (dyspnea, hypoxia, pneumonia, or respiratory insufficiency) in five subjects, and cardiac events in four subjects (myocardial infarction, atrial fibrillation, ventricular fibrillation, or cardiac failure). In the ceftriaxone/cefuroxime group, the most common marked adverse events were respiratory disorders (respiratory insufficiency, bronchitis, coughing, increased sputum, pleural

14. Safety Results as per Sponsor

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any postadmission safety data were available. Five hundred eighty-four of the 590 (99.0%) subjects enrolled were evaluated for safety. Of the 584 subjects, 291 received levofloxacin and 293 received ceftriaxone/cefuroxime. Six subjects (four in the levofloxacin treatment group and two in the ceftriaxone/cefuroxime group) were lost to follow-up with no safety data available and were therefore excluded from the safety analysis. Therapy discontinuation/completion information for these six subjects was unknown.

Table 14.1

Subjects Excluded from Safety Analysis and Reasons for Exclusion

Subject Number	Age	Sex	Investigator	Reasons for Exclusion
Levofloxacin				
	34	M	Grunfeld	Lost to follow-up, no available data
	42	F	Kohler	Lost to follow-up, no available data
	30	M	Kohler	Lost to follow-up, no available data
	71	F	Padgett	Lost to follow-up, no available data
Ceftriaxone/Cefuroxime				
	66	F	Gomez	Lost to follow-up, no available data
	22	M	Kohler	Lost to follow-up, no available data

14.2. Overview of Safety Data

The most frequently reported adverse events in both treatment groups occurred in the gastrointestinal (GI) system, central and peripheral nervous system, body as a whole, and in the category of psychiatric disorders, and consisted primarily of headache, diarrhea, nausea, and insomnia. The nature and frequency of adverse events were generally comparable across the two treatment groups, except for a higher incidence of headache and diarrhea in the ceftriaxone/cefuroxime group (10.6%, and 11.3%, respectively) than in the levofloxacin group (6.5% and 5.8%, respectively) and small differences between treatments in some other GI events; also, as noted below, there was a higher incidence of chest pain among levofloxacin-treated subjects than in ceftriaxone/cefuroxime-treated subjects. The incidence of disorders of the female reproductive system was greater in the levofloxacin group (4.6%) than in the ceftriaxone/cefuroxime group (1.5%); adverse events reported by levofloxacin-treated subjects in this body system consisted primarily of vaginitis. The incidence of central and peripheral nervous system adverse events was greater in the ceftriaxone/cefuroxime group than in the levofloxacin group (14.7% and 10.7%, respectively); the difference was due primarily to the difference in the incidence of headache between the two groups, as noted earlier. The body system with the highest reported incidence of adverse events for both treatment groups was the gastrointestinal system; a similar proportion of subjects in the two treatment groups experienced adverse events of this system (22.3% for levofloxacin and 25.9% for ceftriaxone/cefuroxime). While the overall incidence of adverse events classified under the "body as a whole" system was similar between the two treatment groups, chest pain occurred in 11 (3.8%) of levofloxacin-treated subjects; none of the ceftriaxone/cefuroxime-treated subjects reported chest pain. Similarly, heart rate and rhythm disorders occurred more frequently among levofloxacin-treated subjects while disorders of the urinary system occurred more frequently among ceftriaxone/cefuroxime-treated

subjects. Similar proportions of subjects (approximately 7%) in the two treatment groups had adverse events considered marked in severity. Seventeen (5.8%) levofloxacin-treated subjects and 25 (8.5%) ceftriaxone/cefuroxime-treated subjects had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug. Two subjects in the ceftriaxone/cefuroxime group, but none in the levofloxacin group, had marked drug-related adverse events (diarrhea and nausea, and tongue edema).

Twenty-five subjects discontinued study drug due to adverse events, 13 subjects in the levofloxacin treatment group and 12 subjects in the ceftriaxone/cefuroxime treatment group. In the levofloxacin group, all of the adverse events leading to discontinuation emerged within the first five days of therapy with the exception of one late occurring event on Day 12 (diarrhea); these adverse events included primarily gastrointestinal complaints (e.g., diarrhea, nausea, vomiting, and abdominal pain) or central and peripheral nervous system-related symptoms (e.g., convulsions, stupor, tremor, speech disorder, and dizziness). Treatment-limiting adverse events in the ceftriaxone/cefuroxime group consisted of gastrointestinal complaints in four subjects; the remaining complaints were scattered across various body systems. Twenty-three subjects in the levofloxacin treatment group and 24 subjects in the ceftriaxone/cefuroxime treatment group reported serious or potentially serious adverse events, the majority of which were unrelated or remotely related to the study drug and, in many cases, appeared to be related to the subject's underlying physical condition. Two levofloxacin-treated subjects and eight ceftriaxone/cefuroxime-treated subjects died up to approximately four weeks after completing study therapy. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs were comparable across treatment groups.

14.3. Treatment-Emergent Adverse Events

14.3.1. Summary of All Adverse Events

One hundred forty-six (50.2%) of 291 subjects evaluable for safety in the levofloxacin treatment group and 146 (49.8%) of 293 subjects evaluable for safety in the ceftriaxone/cefuroxime treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. All body systems had confidence intervals that included zero, indicating no statistically significant differences in frequency, with two exceptions: heart rate and rhythm disorders, and urinary system disorders. Five levofloxacin-treated subjects experienced adverse events classified as heart rate and rhythm disorders (atrial fibrillation, ventricular fibrillation, palpitation, and tachycardia) as compared with none of the ceftriaxone/cefuroxime-treated subjects, while five ceftriaxone/cefuroxime-treated subjects experienced urinary system disorders (micturition frequency, oliguria, abnormal renal function, incontinence, and abnormal urine) as compared with none of the levofloxacin-treated subjects. The body system with the highest reported incidence of adverse events for both treatment groups (22.3% for levofloxacin and 25.9% for ceftriaxone/cefuroxime) was the gastrointestinal system. The body system with the second highest reported incidence of adverse events for both treatment groups was the central and peripheral nervous system. The incidence of adverse events in this body system was approximately one-half that observed for the gastrointestinal system. The

frequency of adverse events was generally comparable across the two treatment groups. However, a higher percentage of levofloxacin-treated subjects (4.6%) compared with ceftriaxone/cefuroxime-treated subjects (1.5%) reported adverse events of the female reproductive system; adverse events in this body system consisted primarily of vaginitis. A higher percentage of ceftriaxone/cefuroxime-treated subjects (14.7%) compared with levofloxacin-treated subjects (10.7%) reported central and peripheral nervous system adverse events. For both treatment groups, adverse events in this body system consisted primarily of headache.

Table 14.3.1.A
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol K90-071)

Body System	Levofloxacin (N=291) N	(%)	Ceftriaxone/ Cefuroxime (N=293) N	(%)	95% Confidence Interval[a]
Gastrointestinal System Disorders	65	(22.3)	76	(25.9)	(-3.5, 10.7)
Central & Peripheral Nervous System Disorders	31	(10.7)	43	(14.7)	(-1.5, 9.5)
Body as a Whole--General Disorders	30	(10.3)	24	(8.2)	(-7.0, 2.8)
Psychiatric Disorders	23	(7.9)	29	(9.9)	(-2.8, 6.8)
Respiratory System Disorders	21	(7.2)	22	(7.5)	(-4.1, 4.7)
Skin and Appendages Disorders	18	(6.2)	13	(4.4)	(-5.5, 2.1)
Metabolic and Nutritional Disorders	11	(3.8)	8	(2.7)	(-4.1, 2.0)
Resistance Mechanism Disorders	8	(2.7)	6	(2.0)	(-3.4, 2.0)
Cardiovascular Disorders, General	6	(2.1)	6	(2.0)	(-2.5, 2.5)
Reproductive Disorders, Female[b]	6	(4.5)	2	(1.5)	(-7.5, 1.5)
Heart Rate and Rhythm Disorders	5	(1.7)	0	(0.0)	(-3.4, -0.1)
Musculo-Skeletal System Disorders	4	(1.4)	5	(1.7)	(-1.8, 2.5)
Autonomic Nervous System Disorders	4	(1.4)	6	(2.0)	(-1.5, 2.9)
Neoplasms	4	(1.4)	2	(0.7)	(-2.5, 1.1)
Application Site Disorders	4	(1.4)	4	(1.4)	(-2.1, 2.0)
Vision Disorders	3	(1.0)	1	(0.3)	(-2.2, 0.8)
Special Senses Other, Disorders	3	(1.0)	0	(0.0)	(-2.4, 0.3)
Myo-, Endo-, Pericardial & Valve Disorders	3	(1.0)	2	(0.7)	(-2.0, 1.3)
Endocrine Disorders	1	(0.3)	0	(0.0)	(-1.2, 0.5)
Vascular (Extracardiac) Disorders	1	(0.3)	4	(1.4)	(-0.5, 2.7)
White Cell and RES Disorders[c]	1	(0.3)	0	(0.0)	(-1.2, 0.5)
Platelet, Bleeding & Clotting Disorders	1	(0.3)	1	(0.3)	(-1.1, 1.1)
Reproductive Disorders, Male[d]	1	(0.5)	0	(0.0)	(-2.2, 0.9)
Hearing and Vestibular Disorders	0	(0.0)	3	(1.0)	(-0.3, 2.3)
Liver and Biliary System Disorders	0	(0.0)	3	(1.0)	(-0.3, 2.3)
Red Blood Cell Disorders	0	(0.0)	3	(1.0)	(-0.3, 2.3)
Urinary System Disorders	0	(0.0)	5	(1.7)	(0.1, 3.4)
Total With Adverse Events (%)	146	(50.2)	146	(49.8)	(-8.6, 7.9)

[a] Two-sided 95% confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in incidence of adverse events.
[b] Percentages calculated from a total number of women evaluable for safety in each treatment group. The total number of women who received levofloxacin was 131 and the total number of women who received ceftriaxone/cefuroxime was 131.
[c] RES = reticulendothelial system
[d] Percentages calculated from a total number of men evaluable for safety in each treatment group. The total numb

Adverse events (primary terms) reported for at least 2.0% of subjects in either treatment group are presented in the table below. Although similar percentages of levofloxacin-treated and ceftriaxone/cefuroxime-treated subjects reported gastrointestinal adverse events overall, the incidence of specific gastrointestinal complaints showed small differences between treatments; some adverse events (e.g., flatulence) were more common in the levofloxacin group (2.1% versus 0%), while others (e.g., diarrhea, dyspepsia, and abdominal pain)

had a higher incidence in the ceftriaxone/cefuroxime group (5.8%, 3.1%, and 1.7%, respectively, among levofloxacin-treated subjects and 11.3%, 4.1%, and 3.8%, respectively, among ceftriaxone/cefuroxime-treated subjects). Headache and insomnia were also among the most common adverse events with levofloxacin-treated subjects showing a lower incidence of headache (6.5%) compared with ceftriaxone/cefuroxime-treated subjects (10.6%); insomnia was reported by 4.5% and 5.5% of subjects in the levofloxacin and ceftriaxone/cefuroxime treatment groups, respectively. The two treatment groups were generally comparable with respect to the type and incidence of other adverse events with the exception of chest pain, which was reported by 11 (3.8%) of levofloxacin-treated subjects as compared with none of the ceftriaxone/cefuroxime-treated subjects.

Table 14.3.1.B
Incidence of Frequently Reported Adverse Events (≥2%)
Summarized by Primary Term: Subjects Evaluable for Safety

	Levofloxacin (N=291)		Ceftriaxone/ Cefuroxime (N=293)	
Body System/Primary Term	**N**	**(%)**	**N**	**(%)**
All Body Systems	146	(50.2)	146	(49.8)
Skin and Appendages Disorders				
Rash	2	(0.7)	6	(2.0)
Central & Peripheral Nervous System Disorders				
Headache	19	(6.5)	31	(10.6)
Dizziness	5	(1.7)	10	(3.4)
Psychiatric Disorders				
Insomnia	13	(4.5)	16	(5.5)
Gastrointestinal System Disorders				
Nausea	20	(6.9)	22	(7.5)
Diarrhea	17	(5.8)	33	(11.3)
Constipation	12	(4.1)	10	(3.4)
Vomiting	11	(3.8)	10	(3.4)
Dyspepsia	9	(3.1)	12	(4.1)
Flatulence	6	(2.1)	0	(0.0)
Abdominal Pain	5	(1.7)	11	(3.8)
Respiratory System Disorders				
Dyspnea	6	(2.1)	4	(1.4)
Rhinitis	3	(1.0)	6	(2.0)
Reproductive Disorders, Female[a]				
Vaginitis	4	(3.1)	2	(1.5)
Body As A Whole - General Disorders				
Chest Pain	11	(3.8)	0	(0.0)
Back Pain	6	(2.1)	6	(2.0)
Pain	6	(2.1)	4	(1.4)
Fatigue	2	(0.7)	6	(2.0)

[a] Primary term reported by ≥2.0% of subjects in either treatment group.
[b] Percentages calculated from a total number of women evaluable for safety in each treatment group. The total number of women who received levofloxacin was 131 and the total number of women who received ceftriaxone/cefuroxime was 131.

The majority of adverse events were assessed as mild in severity. Twenty subjects in each of the levofloxacin and ceftriaxone/cefuroxime treatment groups reported one or more adverse events of marked severity. In the levofloxacin group, the most common marked adverse events included respiratory disorders (dyspnea, hypoxia, pneumonia, or respiratory insufficiency) in five subjects, and cardiac events in four subjects (myocardial infarction, atrial fibrillation, ventricular fibrillation, or cardiac failure). In the ceftriaxone/cefuroxime group, the most common marked adverse events were respiratory disorders (respiratory insufficiency, bronchitis, coughing, increased sputum, pleural

effusion, dyspnea, or asthma) which occurred in eight subjects and general disorders of the body as a whole (back pain, fever, asthenia, and fatigue) which occurred in four subjects. Most of the marked adverse events were considered by the investigator as unrelated or remotely related to the study drug. Two subjects had marked drug-related (probably or definitely related to study drug) adverse events; both were in the ceftriaxone/cefuroxime treatment group (diarrhea and nausea, and tongue edema). Ten of the 40 subjects with marked adverse events discontinued study drug treatment prematurely due to adverse events (six subjects in the levofloxacin treatment group and four subjects in the ceftriaxone/cefuroxime treatment group). The marked adverse event(s) listed in Table 14.3.1.c,on the following page, was the reason given for discontinuation in all but one ([redacted]) of these 10 subjects. Of the nine subjects, the marked adverse event which led to discontinuation of therapy was considered serious or potentially serious in two levofloxacin-treated subjects ([redacted]) and one ceftriaxone/cefuroxime-treated subject ([redacted]). Eighteen subjects who did not discontinue the study prematurely (nine in the levofloxacin treatment group and nine in the ceftriaxone/cefuroxime treatment group) had marked adverse events that were considered serious or potentially serious. Seventeen (5.8%) subjects in the levofloxacin treatment group and 25 (8.5%) subjects in the ceftriaxone/cefuroxime 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 nausea (1.7%), diarrhea (1.4%), and injection site pain (1.0%). Drug-related adverse events reported by ≥1.0% of ceftriaxone/cefuroxime-treated subjects were diarrhea (3.8%), nausea (2.0%), dyspepsia (1.0%), and vomiting (1.0%). In general, the profile of adverse events in these different subgroups was comparable to that observed in the study population as a whole. However, the overall incidence of adverse events was somewhat higher among women than men in both treatment groups (54.2% and 46.9%, respectively for levofloxacin-treated women and men; 52.7% and 47.5%, respectively for ceftriaxone/cefuroxime-treated women and men). These sex-related differences were primarily due to differences in the incidence of adverse events in the skin and subcutaneous and gastrointestinal body systems. In addition, the overall incidence of adverse events increased with age category in both treatment groups. These results are summarized in Table 14.3.1.C, on the following page.

Table 14.3.1.C
Subjects with Adverse Events of Marked Severity:
Subjects Evaluable for Safety (Protocol K90-071)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship to Study Drug*
Levofloxacin				
	53	F	Dyspnea	None
	47	M	Sepsis†	None
			Myocardial infarction†	None
	48	M	Convulsions†	None
	52	M	Hyperglycaemia†	None
	60	M	Pulmonary carcinoma†	None
	47	F	Pruritus	Remote
	72	M	Cardiac failure	None
	50	F	Infection fungal	Possible
	36	F	Dyspnea†	None
			Hypoxia†	None
	65	F	Somnolence	Remote
			Speech disorder	Remote
			Stupor	Remote
			Tremor	Remote
	61	F	Pneumonia†	None
	34	M	Carcinoma†	None
	40	M	Pancreatitis†	None
	70	M	Pituitary neoplasm, benign	None
			Stupor	None
	57	F	Sweating increased	Possible
	76	F	Syncope†	Possible
	74	F	Fibrillation atrial†	None
	58	M	Malaise	Possible
	66	M	Respiratory insufficiency†	None
			Fibrillation ventricular†	None
	58	F	Dyspnea	Remote
Ceftriaxone/Cefuroxime				
	82	F	Back pain	None
			Hypoglycaemia†	None
	72	M	Hepatic failure†	Remote
	96	F	Respiratory insufficiency†	None
			Fever†	None
	67	F	Diarrhea	Definite
			Nausea	Definite
	76	F	Bronchitis†	None
			Respiratory insufficiency†	None
	39	F	Dyspnea	None
			Somnolence	None
	38	M	Headache	None
	73	F	Tongue edema	Definite
	75	F	Respiratory insufficiency†	None
	60	M	Asthenia†	None
			Leukemia†	None
			Pancytopenia†	None
	76	F	Coughing	None
	67	F	Renal function abnormal†	None
			Dyspnea†	None
			Sputum increased†	None
	62	F	Fatigue	Remote
	42	M	Hyperglycaemia†	Remote
	81	F	Asthma	Remote
	42	M	Intestinal perforation†	None
	72	F	Myocardial infarction‡†	None
	44	M	Pleural effusion	None
	65	F	Phlebitis	None
	34	F	Headache	None

* Based on investigator's assessment.
‡ ECG and cardiac enzyme analysis showed myocardial infarction occurred 48 to 72 hours earlier (reported in RWJPRI clinical data base with incorrect date). This event was not considered treatment-emergent as it occurred prior to the study. On-study events for this subject included arrhythmia, cardiac arrest, and respiratory insufficiency, all of which were considered serious or potentially serious (see Table 30).
* Subject discontinued therapy due to this adverse event(s) (see Table 29).
† Serious or potentially serious adverse event (see Table 30).
** Subject also had a markedly abnormal laboratory value (see Table 34).

14.4. Discontinuations Due to Adverse Events

Twenty-five subjects discontinued the study drug prematurely due to adverse events, including 13 subjects in the levofloxacin treatment group and 12 in the ceftriaxone/cefuroxime treatment group. One additional levofloxacin-treated subject ([redacted] from Dr. Maggiacomo's site discontinued study therapy due to an adverse event (vomiting). In the levofloxacin group, all of the adverse events leading to discontinuation emerged within the first five days of therapy with the

exception of one case of mild diarrhea, which occurred on Day 12 (subject [redacted]; these adverse events included primarily gastrointestinal complaints (e.g., diarrhea, nausea, vomiting, and abdominal pain) or central and peripheral nervous system-related symptoms (e.g., convulsions, stupor, tremor, speech disorder, dizziness). Treatment-limiting adverse events in the ceftriaxone/cefuroxime group consisted of gastrointestinal complaints in four subjects, with remaining events being distributed among several body systems. The treatment-limiting adverse event was considered serious or potentially serious in three levofloxacin-treated subjects ([redacted]-convulsions, [redacted]-asthenia, dehydration, nausea, and vomiting, and 4406-syncope) and two ceftriaxone/cefuroxime-treated subjects [redacted] gastroenteritis and [redacted]-myocardial infarction).

Table 14.4.A
Subjects who Discontinued due to Adverse Events:
Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Event (Primary Term)	Study Day Of Onset*	Severity	Relationship to Study Drug†	Duration of Therapy (Days)
Levofloxacin							
	53	F	Dyspnea	1	Marked	None	1
	48	M	Convulsions‡	1	Marked	None	1
	60	F	Diarrhea	12	Mild	Probable	12
	72	M	Cardiac failure	4	Marked	None	4
	69	F	Vomiting	3	Moderate	Probable	3
	62	F	Injection site pain	1	Moderate	Definite	1
			Injection site reaction	1	Moderate	Definite	
			Pruritus	1	Moderate	Definite	
	65	F	Somnolence	3	Marked	Remote	2
			Speech disorder	3	Marked	Remote	
			Stupor	3	Marked	Remote	
			Tremor	3	Marked	Remote	
	44	M	Diarrhea	5	Moderate	Possible	5
	72	M	Abdominal pain	2	Moderate	Probable	2
	70	M	Asthenia‡	2	Moderate	None	3
			Dehydration‡	2	Moderate	Possible	
			Nausea‡	2	Moderate	Possible	
			Vomiting‡	2	Unknown	Possible	
	78	F	Asthenia	2	Moderate	Definite	2
			Dizziness	2	Moderate	Definite	
			Rigors	2	Moderate	Definite	
			Vomiting	2	Moderate	Definite	
	25	M	WBC abnormal	5	Moderate	None	4
	76	F	Syncope‡	3	Marked	Possible	2
Ceftriaxone/Cefuroxime							
	58	F	Gastroenteritis‡	3	Moderate	None	2
	68	M	Rash	5	Mild	Possible	5
	79	M	Sputum increased	7	Moderate	Possible	7
	67	F	Diarrhea	3	Marked	Definite	12
			Nausea	3	Marked	Definite	
			Diarrhea	10	Marked	Definite	
	39	F	Dyspnea	2	Marked	None	2
			Somnolence	3	Marked	None	
	73	F	Tongue edema	1	Marked	Definite	1
	39	F	Headache	1	Moderate	Possible	5
			Insomnia	1	Mild	Possible	
	64	F	Abdominal pain	5	Moderate	Possible	5
			Diarrhea	5	Moderate	Possible	
	70	F	Diarrhea	5	Moderate	Probable	12
			Tongue disorder	5	Moderate	Probable	
	62	M	Rash	3	Moderate	Probable	4
	72	F	Myocardial infarction‡	2**	Marked	None	1
	67	F	Phlebitis	3	Mild	Possible	2

* Relative to start of therapy (Day 1).

† Based on investigator's assessment.

‡ ECG and cardiac enzyme analysis showed myocardial infarction occurred 48 to 72 hours earlier (reported in the individual study report data base with incorrect date). This event was not considered treatment-emergent as it occurred prior to the study. On Day 2, this subject experienced arrhythmia, cardiac arrest, and respiratory insufficiency; none of these events is listed in the individual study report data base nor given as the reason for discontinuation, but all were reported in the RWJPRI serious adverse event reporting database. Study drug was discontinued and the subject died on the same day.

† Serious or potentially serious adverse event (see Table 30).

** Subject also had a markedly abnormal laboratory value (see Table 34).

14.5. Serious or Potentially Serious Adverse Events, Including Death

Twenty-three subjects in the levofloxacin treatment group and 24 subjects in the ceftriaxone/cefuroxime treatment group (including one subject in each treatment group from Dr. Maggiacomo's site) reported a serious or potentially serious adverse event during or up to approximately four weeks after completing study therapy, including two deaths in the levofloxacin group and eight deaths in the ceftriaxone/cefuroxime group[1]. Of the 47 subjects with serious or potentially serious adverse events, five withdrew from the study because of the adverse event. In all but six cases (levofloxacin-treated subjects [redacted] [hyperkalemia and gastroenteritis], [redacted] [esophagitis], [redacted] [malaise, nausea, vomiting], [redacted] [dehydration, nausea, vomiting], and [redacted] [syncope], and ceftriaxone/cefuroxime-treated subject [redacted] [dehydration, dyspepsia, nausea, vomiting]), the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug and, in many cases, appeared to be related to the subject's underlying physical condition. These results are summarized in Table 14.5.A. and Table 14.5.B, on the following pages.

[1] Reports of the serious or potentially serious events for 15 of these 47 subjects were not collected on the case report form and do not appear in the individual study report data base but do appear in the RWJPRI serious adverse event reporting data base and are in the pooled data base for the NDA Integrated Safety Summary.

Table 14.5.A
Subjects with Serious Adverse Events:
Levofloxacin-treated Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Events (Primary Term)	Study Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
Levofloxacin							
	47	M	Cardiac failure[d]	46 (PT 33)	Unknown	None	13
			Sepsis	46 (PT 33)	Marked	None	
			Myocardial infarction	47 (PT 34)	Marked	None	
	48	M	Convulsions	1	Marked	None	1
	52	M	Hyperglycaemia	5	Marked	None	10
	75	M	Pneumonia[d]	31 (PT 21)	Unknown	Remote	10
	60	M	Pulmonary carcinoma	4	Marked	None	10
	73	F	Hyperkalaemia	17 (PT 6)	Moderate	Possible	11
			Gastroenteritis	19 (PT 8)	Moderate	Possible	
	50	F	Pleurisy[d]	16 (PT 6)	Unknown	None	10
			Pulmonary infiltration[d]	42 (PT 32)	Unknown	None	
	59	F	Neuroma[d]	17 (PT 14)	Unknown	Remote	3
	53	M	Pancreatitis	16 (PT 2)	Marked	None	14
			Vomiting	16 (PT 2)	Marked	None	
			Abdominal pain	16 (PT 2)	Marked	None	
	31	M	Dyspnea	36 (PT 26)	Mild	None	10
			Cardiomyopathy	41 (PT 31)	Moderate	None	
	36	F	Dyspnea	3	Marked	None	3
			Hypoxia	3	Marked	None	
	30	M	Back pain	15 (PT 1)	Mild	None	14
	67	M	Esophagitis	6	Moderate	Possible	8
	61	F	Pneumonia	2	Marked	None	11
	83	F	Malaise	5	Moderate	Possible	14
			Nausea	5	Moderate	Possible	
			Vomiting	5	Moderate	Possible	
	34	M	Carcinoma	24 (PT 17)	Marked	None	7
	40	M	GI hemorrhage	18 (PT 4)	Moderate	None	14
			Pancreatitis	18 (PT 4)	Marked	None	
			Hypoglycaemia[d]	37 (PT 23)	Unknown	Remote	
			Alcohol intolerance[d]	37 (PT 23)	Unknown	Remote	
	70	M	Asthenia	2	Moderate	None	3
			Dehydration	2	Moderate	Possible	
			Nausea	2	Moderate	Possible	
			Vomiting[e]	2	Unknown	Possible	
	76	F	Syncope[f,*]	3 (PT 1)	Marked	Possible	2
			Dehydration[e]	7 (PT 5)	Unknown	Remote	
			Postural hypotension[e]	7 (PT 5)	Unknown	Remote	
	74	F	Fibrillation atrial	2	Marked	None	8
	73	F	Paresis[d]	20 (PT 7)	Unknown	Remote	13
			Speech disorder[d]	20 (PT 7)	Unknown	Remote	
			Stupor[d]	20 (PT 7)	Unknown	Remote	
	56	M	Respiratory insufficiency	2 (PT 1)	Marked	None	1
			Fibrillation ventricular	9 (PT 8)	Marked	None	
			Acute renal failure[e]	Unknown	Unknown	Remote	
	50	M	Skin neoplasm malignant	2	Moderate	None	14
			Angina pectoris aggravated	29 (PT 15)	Moderate	None	
			Dyspnea	29 (PT 15)	Moderate	None	

[a] Relative to start of therapy (Day 1). Note: PT refers to the number of days posttherapy relative to last day of study drug administration.
[b] Based on investigator's assessment.
[c] An IND Safety Report was filed with the FDA for this subject.
[d] This serious adverse event was reported 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 is therefore reflected in the pooled safety database 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 pooled safety data base for the NDA Integrated Safety Summary.
[f] This serious adverse event, which appears as non-serious in the individual study report database, was captured as serious in the RWJPRI serious adverse event reporting data base; it is therefore reflected as serious in the pooled safety data base for the NDA Integrated Safety Summary.
[g] This subject was enrolled by Dr. Maggiacomo and is therefore not included in the individual study report data base. The serious or potentially serious adverse event reported for this subject is included here for completeness in serious adverse event reporting.
[*] Subject discontinued due to this adverse event.
[**] Subject also had markedly abnormal laboratory value (see Table 34).
[†] Subject died as a result of the serious adverse event(s). An IND Safety Report was submitted to FDA for Subject [redacted].

Table 14.5.B
Subjects with Serious Adverse Events:
Ceftriaxone/cefuroxime-treated Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Events (Primary Term)	Study Day of Onset[a]	Severity	Relationship to Study Drug[b]	Duration of Therapy (Days)
Ceftriaxone/Cefuroxime							
	36	M	Anemia	15 (PT 4)	Moderate	None	11
	66	M	Heart disorder[d]	18 (PT 11)	Unknown	Unknown	7
			Dyspnea[d]	17 (PT 10)	Unknown	Unknown	
	82	F	Hypoglycemia	25 (PT 11)	Marked	None	14
			Urinary tract infection[e]	25 (PT 11)	Unknown	None	
	54	F	Bone disorder[d]	44 (PT 29)	Unknown	None	15
			Dyspnea[d]	44 (PT 29)	Unknown	None	
	72	M	Hepatic failure	12 (PT 1)	Marked	Remote	11
	58	F	Gastroenteritis	3 (PT 1)	Moderate	None	2
	72	F	Respiratory failure[d]	19 (PT9)	Unknown	Remote	10
	96	F	Respiratory insufficiency	7	Marked	None	8
			Fever	8	Marked	None	
	70	M	Pneumocystis carinii[d]	23 (PT 10)	Unknown	None	13
			Sepsis[d]	23 (PT 10)	Unknown	None	
	66	M	Aggressive reaction	8	Mild	None	9
			Dementia	8	Mild	None	
			Depression	8	Mild	None	
	71	F	Dyspnea[e]	1	Unknown	Unknown	1
	76	F	Bronchitis	18 (PT 3)	Marked	None	15
			Respiratory insufficiency	18 (PT 3)	Marked	None	
	67	M	Pulmonary carcinoma[e]	9 (PT 1)	Unknown	Remote	8
	96	M	Cerebrovascular disorder	9 (PT 4)	Unknown	Remote	5
			Sepsis	9 (PT 4)	Unknown	Remote	
	75	F	Respiratory insufficiency	2	Marked	None	2
	61	F	Pulmonary carcinoma[g]	0[g]	Unknown	Remote	15
	80	M	Asthenia	13 (PT 5)	Marked	None	8
			Leukemia	13 (PT 5)	Marked	None	
			Pancytopenia	13 (PT 5)	Marked	None	
			Hemorrhage[e]	24 (PT 16)	Unknown	None	
			Cardiac failure[e]	24 (PT 16)	Unknown	None	
	67	F	Renal function abnormal	4	Marked	None	14
			Dyspnea	7	Marked	None	
			Sputum increased	15 (PT 1)	Marked	None	
			Respiratory insufficiency[d]	37 (PT 23)	Unknown	Remote	
	35	F	Dehydration	4	Moderate	Probable	14
			Dyspepsia	4	Moderate	Probable	
			Nausea	4	Moderate	Probable	
			Vomiting	4	Moderate	Probable	
	42	M	Hyperglycemia	3	Marked	Remote	13
			Diabetes mellitus[d]	35 (PT 22)	Unknown	None	
			Ketosis[d]	35 (PT 22)	Unknown	None	
	76	M	Cerebrovascular disorder[d]	30 (PT 19)	Unknown	Remote	11
	42	M	Intestinal perforation	5	Marked	None	5
	72	F	Arrhythmia[e]	2 (PT 1)	Unknown	Remote	1
			Cardiac arrest[e]	2 (PT 1)	Unknown	Remote	
			Respiratory insufficiency[e]	2 (PT 1)	Unknown	Remote	
			Myocardial infarction[e]	2[h]	Marked	None	
	72	M	Colon carcinoma	5 (PT 2)	Moderate	None	3

[a] Relative to start of therapy (Day 1). Note: PT refers to the number of days posttherapy relative to last day of study drug administration.
[b] Based on investigator's assessment.
[c] An IND Safety Report was filed with the FDA for this subject.
[d] This serious adverse event was reported 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 is therefore reflected in the pooled safety database 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 pooled safety data base for the NDA Integrated Safety Summary.
[f] This subject was enrolled by Dr. Maggiacomo and is therefore not included in the individual study report data base. The serious or potentially serious adverse event reported for this subject (which occured after the posttherapy visit) is included here for completeness in serious adverse event reporting.
[g] This event was thought to be preexisting.
[h] ECG and cardiac enzyme analysis showed myocardial infarction occurred 48 to 72 hours earlier (reported in the individual study report data base with incorrect date). This event was not considered treatment-emergent as it occurred prior to the study. On Day 2, this subject experienced arrhythmia, cardiac arrest, and respiratory insufficiency; none of these events is listed in the individual study report data base nor given as the reason for discontinuation, but all were reported in the RWJPRI serious adverse event reporting database. Study drug was discontinued and the subject died on the same day.
[i] Subject discontinued due to this adverse event.
[j] Subject also had markedly abnormal laboratory value (see Table 34).
[k] Subject died as a result of the serious adverse event(s).

14.6. Dosage Reductions and Concomitant Therapies

Twenty-five subjects had study drug therapy stopped prematurely due to adverse events and 47 subjects reported serious or potentially serious adverse events. Several of these treatment-limiting adverse events and serious or potentially serious adverse events required treatment with concomitant therapies, as described in the individual narrative descriptions. Other subjects who required concurrent therapy due to drug-related adverse events are shown in Table 14.6, below; in the majority of cases, the event requiring therapy was related to the gastrointestinal system (e.g., nausea, diarrhea, dyspepsia). One subject in the ceftriaxone/cefuroxime group [redacted] required an adjustment of study medication due to an adverse event (anorexia). On Study Day 4, this subject's dose of ceftriaxone sodium was reduced from 2 g i.v. q24h to 1 g i.v. q24h, with resolution of the anorexia on the following day.

Table 14.6
Subjects who Required Concomitant Therapy for Adverse Events: Subjects Evaluable for Safety

Subject Number	Age	Sex	Adverse Events (Primary Term)	Study Day of Onset*	Severity	Concomitant Therapy
Levofloxacin						
	41	F	Nausea	3	Mild	Trimethobenzamide
			Rash	6	Mild	Diphenhydramine HCl
	63	M	Dyspepsia	3	Moderate	Cimetidine
	78	M	Diarrhea	2	Mild	Loperamide
	64	F	Nausea	1	Mild	Phenobarbital/hyoscyamine sulfate/ atropine sulfate/scopolamine hydrobromide
			Insomnia	2	Moderate	Diphenhydramine HCl
	40	F	Headache	2	Mild	Propoxyphene napsylate with acetaminophen
Ceftriaxone/Cefuroxime						
	45	M	Nausea	3	Mild	Prochlorperazine
	35	F	Diarrhea	1	Moderate	Loperamide
	35	F	Diarrhea	3	Mild	Loperamide
	31	F	Nausea	1	Moderate	Prochlorperazine
			Vomiting	1	Moderate	Compazine
	65	F	Vaginitis	8	Moderate	Clotrimazole
	69	M	Stomatitis, ulcerative	12	Mild	Nystatin

* Includes events considered by the investigator to be probably or definitely related to study drug, except for those resulting in study drug discontinuation or considered serious or potentially serious as discussed in Sections IV.I.3.b. and IV.I.3.c.
* Relative to start of therapy (Day 1)

14.6. Clinical Laboratory Tests

14.6.1. Overall Changes

A summary of the means and mean changes from admission to posttherapy for selected laboratory analytes (blood chemistry and hematology) by treatment group is presented in Table 14.6.1. on the following page. No summaries are provided for basophils, monocytes, bicarbonate, or urinalysis analytes. There were no clinically significant mean changes from admission for any laboratory analyte in the levofloxacin-treated or ceftriaxone/cefuroxime-treated group, with comparable results in both groups. Statistically significant differences ($p<0.05$) were

observed for uric acid and platelet count. The differences between the treatment groups in the cumulative distribution functions for uric acid reflected slightly larger mean increases in uric acid in levofloxacin-treated subjects. Most subjects in both treatment groups showed an increase from admission to posttherapy in platelet count; the increases of levofloxacin-treated subjects tended to be larger than those found for ceftriaxone/cefuroxime-treated subjects.

Table 14.6.1
Means and Mean Changes from Admission to Posttherapy for Laboratory Analytes: Subjects Evaluable for Safety with Data Available at Admission and Posttherapy

	Levofloxacin							Ceftriaxone/Cefuroxime						
		Admission		Posttherapy		Change			Admission		Posttherapy		Change	
Laboratory Test	N	Mean	(SD)	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	Mean	(SD)
Blood Chemistry														
Glucose (mg/dL)	236	117.0	(54.59)	107.4	(52.91)	-9.5	(48.08)	232	121.8	(62.33)	108.4	(55.78)	-13.4	(55.71)
Calcium (mg/dL)	253	8.5	(0.64)	8.9	(0.47)	0.3	(0.53)	238	8.5	(0.57)	8.9	(0.55)	0.3	(0.64)
Sodium (mEq/L)	253	136.8	(3.51)	138.5	(2.95)	1.6	(3.51)	238	136.9	(3.56)	138.7	(3.07)	1.8	(3.72)
Potassium (mEq/L)	242	4.1	(0.49)	4.3	(0.42)	0.2	(0.52)	232	4.1	(0.51)	4.3	(0.46)	0.2	(0.54)
Chloride (mEq/L)	253	101.0	(4.93)	103.0	(3.64)	2.0	(4.89)	238	100.7	(4.71)	103.3	(4.27)	2.7	(5.23)
Phosphorus, Inorg. (mg/dL)	234	3.2	(0.76)	3.8	(0.72)	0.6	(0.94)	228	3.2	(0.77)	3.7	(0.65)	0.5	(0.88)
Blood Urea Nitrogen (mg/dL)	254	13.5	(7.36)	13.8	(6.76)	0.2	(6.23)	238	14.6	(8.41)	14.2	(6.54)	-0.4	(8.10)
Lactic Dehydrogenase (U/L)	243	201.3	(95.62)	171.7	(54.07)	-29.6	(81.76)	231	204.7	(66.84)	185.6	(74.14)	-19.0	(80.27)
Total Protein (g/dL)	254	7.0	(0.85)	7.2	(0.70)	0.2	(0.76)	238	7.0	(0.77)	7.2	(0.70)	0.1	(0.76)
Albumin (g/dL)	245	3.4	(0.62)	3.7	(0.52)	0.3	(0.49)	233	3.4	(0.58)	3.7	(0.50)	0.3	(0.51)
Uric Acid (mg/dL)	254	5.1	(1.81)	5.7	(1.58)	0.6	(1.24)	238	5.2	(1.84)	5.4	(1.61)	0.2	(1.51)
Creatinine (mg/dL)	254	1.1	(0.25)	1.1	(0.22)	-0.0	(0.17)	238	1.2	(0.30)	1.1	(0.26)	-0.0	(0.23)
Alkaline Phosphatase (U/L)	247	80.9	(33.96)	76.8	(42.63)	-2.1	(38.52)	234	85.6	(62.14)	83.3	(58.41)	-2.3	(28.85)
SGOT (U/L)	254	28.2	(34.53)	23.2	(13.27)	-5.0	(33.51)	238	27.1	(27.40)	25.1	(15.94)	-2.0	(28.03)
SGPT (U/L)	254	24.5	(33.26)	22.1	(15.14)	-2.4	(31.99)	238	24.3	(19.29)	28.2	(28.55)	4.0	(25.67)
Total Bilirubin (mg/dL)	239	0.5	(0.43)	0.5	(0.27)	-0.1	(0.38)	230	0.7	(0.41)	0.5	(0.20)	-0.2	(0.38)
Hematology														
Hemoglobin (g/dL)	237	13.5	(1.76)	13.5	(1.62)	0.1	(1.07)	226	13.5	(1.78)	13.5	(1.58)	0.1	(1.05)
Hematocrit (%)	225	40.0	(5.03)	40.5	(4.62)	0.5	(3.51)	214	40.2	(5.10)	40.5	(4.93)	0.5	(3.69)
WBC (x 10^3/µL)	238	11.9	(5.20)	7.5	(3.33)	-4.3	(5.91)	226	12.3	(5.97)	7.7	(3.53)	-4.5	(5.59)
RBC (x 10^6/µL)	237	4.5	(0.56)	4.5	(0.51)	0.1	(0.37)	226	4.5	(0.55)	4.5	(0.57)	0.1	(0.37)
Neutrophils (x 10^3/µL)	238	9.4	(5.79)	4.9	(2.67)	-4.5	(5.56)	226	9.9	(5.83)	5.1	(3.39)	-4.8	(5.41)
Lymphocytes (x 10^3/µL)	238	1.6	(0.89)	2.0	(0.83)	0.4	(0.87)	226	1.5	(0.69)	2.0	(0.79)	0.5	(0.77)
Eosinophils (x 10^3/µL)	238	0.1	(0.19)	0.2	(0.20)	0.0	(0.18)	225	0.1	(0.14)	0.2	(0.16)	0.1	(0.16)
Platelet Count (x 10^3/µL)	229	227.9	(105.00)	346.2	(119.50)	68.2	(115.50)	222	269.3	(93.50)	326.5	(121.00)	37.2	(110.00)

N=Number of subjects with admission and posttherapy results.

14.6.2. Individual Subject Changes

The sponsor examined the percentage of subjects with low or high values (relative to the sponsor's reference range) at admission and posttherapy and number of subjects having changes from admission to posttherapy for selected blood chemistry and hematology laboratory tests. The distribution of subjects with low, normal, or high values was comparable in the treatment groups at both pretherapy and posttherapy time points, and showed little change from pretherapy to posttherapy.

14.6.3. Marked Abnormalities

The laboratory values were classified as markedly abnormal according to standard criteria developed by RWJPRI, which take into account the postadmission value of the analyte and the change or percentage change from admission. The incidence of markedly abnormal test results for individual analytes within a given

treatment group for subjects who had admission data available was low (≤4.7%) and comparable across the two treatment groups, with the exception of SGPT and SGOT, which were elevated in a greater proportion of ceftriaxone/cefuroxime-treated subjects than levofloxacin-treated subjects.

Table 14.6.3.A
Incidence of Treatment-emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

	Levofloxacin		Ceftriaxone/Cefuroxime	
	Proportion*	%	Proportion*	%
Blood Chemistry				
Elevated Glucose	3/255	1.2	3/248	1.2
Decreased Glucose	11/255	4.3	8/248	3.2
Elevated Potassium	0/260	0.0	1/251	0.4
Decreased Potassium	0/260	0.0	1/251	0.4
Elevated Phosphorous	3/254	1.2	0/246	0.0
Decreased Phosphorous	4/254	1.6	2/246	0.8
Elevated BUN	1/269	0.4	0/257	0.0
Elevated LDH	0/261	0.0	2/251	0.8
Decreased Albumin	0/262	0.0	1/251	0.4
Elevated Uric Acid	0/269	0.0	1/257	0.4
Elevated Alkaline Phosphatase	1/265	0.4	1/254	0.4
Elevated SGOT	1/269	0.4	9/257	3.5
Elevated SGPT	2/269	0.7	12/257	4.7
Elevated Bilirubin	1/258	0.4	0/247	0.0
Hematology				
Decreased Neutrophils	1/253	0.4	0/243	0.0
Decreased Lymphocytes	7/253	2.8	11/243	4.5
Decreased Platelet Count	0/244	0.0	1/240	0.4

* Numerator = number of subjects with a treatment-emergent markedly abnormal test value and denominator = number of subjects evaluable (i.e., admission and postadmission data available) for that analyte. Subjects with posttherapy laboratory results obtained more than 30 days PT are not included in this analysis.

Seventy-five subjects (34 in the levofloxacin group and 41 in the ceftriaxone/cefuroxime group) had a total of 99 markedly abnormal test results after therapy start. Four subjects in the levofloxacin treatment group and 15 subjects in the ceftriaxone/cefuroxime treatment group had markedly abnormal liver function tests (elevations in SGOT, SGPT, or alkaline phosphatase). Seven subjects in the levofloxacin group and 11 in the ceftriaxone/cefuroxime group had lymphopenia, which was classified as mild (lymphocyte count 0.59-0.99 x 10^3 /μL) for seven of those subjects (three levofloxacin-treated subjects and four ceftriaxone/cefuroxime-treated subjects). Twenty-five subjects had abnormal glucose levels: 14 levofloxacin-treated subjects and 11 ceftriaxone/cefuroxime-treated subjects. Of these, three levofloxacin-treated subjects and three ceftriaxone/cefuroxime-treated subjects had hyperglycemia; the hyperglycemia was considered mild (201-250 mg/dL) in one [redacted] levofloxacin-treated subject and one [redacted] ceftriaxone/cefuroxime-treated subject. Eleven levofloxacin-treated subjects and eight ceftriaxone/cefuroxime-treated subjects had hypoglycemia, including six levofloxacin-treated subjects and six ceftriaxone/ cefuroxime-treated subjects whose hypoglycemia was classified as mild (serum glucose values of 60-69 mg/dL). Four levofloxacin-treated subjects and two ceftriaxone/cefuroxime-treated subjects had hypophosphatemia (serum phosphorus

level <2.0 mg/dL). As further described below, some abnormalities were related to the underlying disease state of the subject.

Table 14.6.3.B
Subjects with Treatment-emergent Markedly Abnormal Laboratory Values: Levofloxacin-treated Subjects Evaluable for Safety

Subject Number	Age	Sex	Laboratory Test[a] (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[b]	Follow-up Value (Therapy Day)[b]	Duration of Therapy (Days)
Levofloxacin								
	36	F	SGOT (>75 IU/L)	54.00	140.00	14 (PT 7)	–	7
	58	M	Glucose (<70 or >200 mg/dL)	87.00	54.00	33(PT 23)	–	10
	75	M	Lymphocytes (<1.0x10^3/µg)	2.73	0.92	4	1.06 (PT 5)	10
	31	F	Glucose (<70 or >200 mg/dL)	99.00	59.00	13 (PT 3)	–	10
	55	M	Lymphocytes (<1.0x10^3/µg)	0.89	0.43	3	1.30 (8)	14
	26	M	SGPT (>75 IU/L)	23.00	92.00	14 (PT 7)	–	7
	54	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	2.80	1.50	2	3.70 (PT 5)	15
	35	M	Glucose (<70 or >200 mg/dL)	175.00	65.00	4	193.00 (PT 7)	10
	35	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.10	7.30	15 (PT 5)	–	10
	45	M	Lymphocytes (<1.0x10^3/µg)	1.66	0.97	4	1.55 (PT 5)	14
	28	F	Lymphocytes (<1.0x10^3/µg)	1.84	0.75	4	1.80 (PT 7)	10
	51	M	Neutrophils (<1.0x10^3/µg)	8.44	0.90	20 (PT 6)	--	14
	67	M	SGPT (>75 IU/L)	19.00	81.00	6	–	8
	61	F	Lymphocytes (<1.0x10^3/µg)	0.31	0.14	2	0.80 (4)	11
	35	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.10	6.70	4	–	unknown
	77	M	Blood Urea Nitrogen (>40 mg/dL)	25.00	52.00	4	25.00 (PT 4)	9
	24	M	Glucose (<70 or >200 mg/dL)	107.00	44.00	15 (PT 5)	–	10
	52	F	Glucose (<70 or >200 mg/dL)	132.00	380.00	16 (PT 6)	–	10
	36	M	Glucose (<70 or >200 mg/dL)	81.00	53.00	22 (PT 8)	--	14
	23	F	Glucose (<70 or >200 mg/dL)	107.00	66.00	19 (PT 9)	--	10
	78	F	Glucose (<70 or >200 mg/dL)	86.00	201.00	17(PT 15)	--	2
	32	M	Glucose (<70 or >200 mg/dL)	110.00	65.00	17 (PT 5)	–	12
	44	M	Glucose (<70 or >200 mg/dL)	98.00	65.00	15 (PT 5)	--	10
	28	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.40	9.10	5	–	5
	74	F	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	2.80	1.80	2	3.90 (7)	8
	73	F	Glucose (<70 or >200 mg/dL)	93.00	59.00	8	–	13
					42.00	14 (PT 1)		
					56.00	18 (PT 5)		
			Lymphocytes (<1.0x10^3/µg)	1.31	0.42	4		
					0.67	8		
					0.14	14 (PT 1)	1.01 (PT 5)	
	56	M	Lymphocytes (<1.0x10^3/µg)	1.26	0.53	3 (PT 2)	–	1
	25	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.50	1.40	3	4.20 (PT 6)	10
	51	F	Glucose (<70 or >200 mg/dL)	109.00	69.00	3	153.00 (PT 13)	12
	40	M	Alkaline Phosphatase (>250 IU/L)	91.00	501.00	8 (PT 7)	–	1
	31	F	Total Bilirubin (>1.5 mg/dL)	0.80	1.60	15 (PT 5)	–	10
	34	M	Glucose (<70 or >200 mg/dL)	128.00	64.00	19 (PT 5)	–	14
	47	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	2.90	1.80	3	3.50 (PT 7)	13
	69	F	Glucose (<70 or >200 mg/dL)	119.00	287.00	4		14
					321.00	21 (PT 7)	–	
Ceftriaxone/Cefuroxime								
	69	M	Lymphocytes (<1.0x10^3/µg)	1.85	0.83	7	1.62 (PT 8)	10
	71	M	Lymphocytes (<1.0x10^3/µg)	1.59	0.65	18 (PT 4)	–	14
	70	M	Lactic Dehydrogenase (>600 IU/L)	438.00	695.00	20 (PT 7)	–	13
	87	F	Uric Acid (>10.0 mg/dL)	6.60	12.00	16 (PT 8)	--	8
	39	F	Glucose (<70 or >200 mg/dL)	145.00	61.00	3 (PT 1)	–	2
	67	M	Lymphocytes (<1.0x10^3/µg)	0.43	0.08	8	–	8
	33	M	Potassium (<3.0 or >6.0 mEq/L)	3.20	6.10	16 (PT 6)	–	10
			SGPT (>75 IU/L)	14.00	81.00	3	24.00 (PT 6)	
	50	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.10	1.80	2	–	2

[a] Only range given in table. For complete criteria see Attachment 32a.
[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.
* Subject discontinued due to adverse event. (See Table 29)
† Subject also had a serious or potentially serious adverse event (see Table 30).

Table 14.6.3.C
Subjects with Treatment-emergent Markedly Abnormal Laboratory Values:
Ceftriaxone/cefuroxime-treated Subjects Evaluable for Safety

Subject Number	Age	Sex	Laboratory Test[a] (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day[b]	Follow-up Value (Therapy Day)[b]	Duration of Therapy (Days)
Ceftriaxone/Cefuroxime (continued)								
	28	M	SGPT (>75 IU/L)	34.00	80.00	15 (PT 3)	–	12
	20	M	Glucose (<70 or >200 mg/dL)	94.00	59.00	19 (PT 5)	--	14
	49	F	SGOT (>75 IU/L)	17.00	89.00	2	–	12
			SGPT (>75 IU/L)	17.00	76.00	2	–	
	75	F	Glucose (<70 or >200 mg/dL)	102.00	55.00	3 (PT 1)	–	2
	46	F	Glucose (<70 or >200 mg/dL)	212.00	69.00	16	–	23
	39	F	Glucose (<70 or >200 mg/dL)	121.00	60.00	22 (PT 7)	–	15
	30	M	SGPT (>75 IU/L)	23.00	77.00	16 (PT 4)	–	12
	74	M	Glucose (<70 or >200 mg/dL)	133.00	464.00	24 (PT 9)	–	15
	53	M	SGOT (>75 IU/L)	27.00	80.00	4	30.00 (PT 8)	16
			SGPT (>75 IU/L)	15.00	173.00	4	30.00 (PT 8)	
	44	M	SGPT (>75 IU/L)	26.00	77.00	18 (PT 11)	–	7
	79	M	Glucose (<70 or >200 mg/dL)	172.00	69.00	22 (PT 8)	–	14
	58	M	Lactic Dehydrogenase (>600 IU/L)	542.00	663.00	2	–	2
	38	M	Albumin (<2.0 g/dL)	2.70	1.70	5	–	8
			Lymphocytes (<1.0x10^3/µg)	2.26	0.32	5	–	
	67	F	Lymphocytes (<1.0x10^3/µg)	0.91	0.20	4	–	14
	40	F	Lymphocytes (<1.0x10^3/µg)	0.59	0.29	14 (PT 8)	–	6
	45	F	SGOT (>75 IU/L)	29.00	83.00	2	18.00 (PT 5)	10
	42	M	Lymphocytes (<1.0x10^3/µg)	1.34	0.72	11 (PT 1)	–	10
	42	M	SGOT (>75 IU/L)	36.00	76.00	19 (PT 6)	–	13
			Glucose (<70 or >200 mg/dL)	169.00	340.00	19 (PT 6)	–	
					515.00	33 (PT 20)		
	36	F	Glucose (<70 or >200 mg/dL)	103.00	61.00	3	–	14
					66.00	22 (PT 8)		
	33	M	Lymphocytes (<1.0x10^3/µg)	1.49	0.57	3	–	unknown
	42	M	Platelet Count (<75 x 10^3/µL)	95.00	27.00	2	100.0 (PT 2)	5
	22	M	SGOT (>75 IU/L)	33.00	120.00	8		10
					126.00	13 (PT 3)	–	
			SGPT (>75 IU/L)	27.00	205.00	8		
					244.00	13 (PT 3)	–	
	48	M	Potassium (<3.0 or >6.0 mEq/L)	4.30	2.90	5	–	unknown
			SGOT (>75 IU/L)	14.00	76.00	5	–	
	39	F	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.10	1.80	3	4.5 (7)	8
	20	M	SGPT (>75 IU/L)	27.00	76.00	19 (PT 5)	–	14
	76	M	SGOT (>75 IU/L)	15.00	84.00	4	20.00 (PT 3)	7
			SGPT (>75 IU/L)	14.00	79.00	4	42.00 (PT 3)	
	34	M	SGOT (>75 IU/L)	15.00	223.00	4	54.00 (7)	7
			SGPT (>75 IU/L)	16.00	388.00	4		
					272.00	7		
					79.00	12 (PT 5)	23.00 (PT 31)	
	79	M	Alkaline Phosphatase (>250 IU/L)	60.00	281.00	5	–	5
			SGOT (>75 IU/L)	15.00	95.00	5	–	
			SGPT (>75 IU/L)	14.00	188.00	5	–	
			Glucose (<70 or >200 mg/dL)	112.00	207.00	3	120.00 (5)	
	44	M	SGPT (>75 IU/L)	13.00	168.00	8	21.00 (PT 8)	22
	69	M	Lymphocytes (<1.0x10^3/µg)	2.15	0.60	3	–	17
	69	M	Lymphocytes (<1.0x10^3/µg)	0.85	0.56	3	1.27 (PT 5)	14
	32	M	Glucose (<70 or >200 mg/dL)	97.00	63.00	19 (PT 10)	--	9
	67	F	Lymphocytes (<1.0x10^3/µg)	0.44	0.18	3 (PT 1)	–	2

[a] Only range given in table. For complete criteria see Attachment 32a.
[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.
* Subject discontinued due to adverse event. (See Table 29)
† Subject also had a serious or potentially serious adverse event (see Table 30).

15. Medical Officer's Conclusions from Study K90-071:

15.1. Clinical and Microbiologic Efficacy

15.1.1. Protocol K90-071 was an active-controlled study comparing levofloxacin to ceftriaxone/cefuroxime in the treatment of community-acquired pneumonia.

15.1.2. Protocol K90-071 has significant flaws in the protocol design including:

15.1.2.1. The protocol was a completely unblinded study. This is particularly significant in light of the fact that all of the endpoints are clinical and, thus, subjective and subject to bias by both (1) observer/expectation bias from the investigator and (2) reporting/recall bias in the patient reporting the symptoms[2].

15.1.2.2. The window for clinical evaluation at the End-of-therapy was inappropriate. In this protocol, the window for EOT evaluation was changed to span from Post-therapy day 1-10. This is not in keeping with either (1) the IDSA guidelines, which recommend follow-up on posttherapy day 5-7 or (2) DAIDP consultants, which recommend that follow-up evaluations for this indication be conducted no earlier than day 7 posttherapy.

15.1.2.3. Post-study clinical evaluation was conducted at 21-28 days post-therapy and was within an appropriate time frame for late follow-up, but was not conducted on all patients. Patients without clinical symptoms at the posttherapy evaluation and without X-ray evidence of pneumonia at the posttherapy evaluation were not brought back for late follow-up.

15.1.3. Protocol K90-071 has significant flaws in the protocol implementation including:

15.1.3.1. Omission of culture of persistent pulmonary secretions at the follow-up visits (both EOT and EOS), with overuse of the designation of "presumed eradication" in cases where documentation of microbiologic outcome was possible.

15.1.3.2. Changes in drug dosage and duration were made during the course of the study

15.1.3.3. Additional antimicrobial coverage for atypical pneumonias (doxycycline) was added to the cephalosporin-treatment arm during the course of the study.

15.1.3.4. Changes in the days of the post-therapy follow-up evaluation were made during the course of the study

15.1.4. Clinical Outcome

In protocol K90-071, the **clinical cure rate** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 62% (129/207) for levofloxacin-treated patients and 46% (105/226) for cephalosporin-treated patients. The 95% confidence interval around the difference in clinical cure rates was $_{226,207}(-25,-7)_{46\%,62\%}$, indicating at minimum statistical equivalence of the two treatments arms, if not outright superiority of levofloxacin.

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[2] Sackett DL. Bias in Clinical Research. J Chronic Dis 32:51-63, 1979.

In protocol K90-071, the **clinical success (cured or improved) rate** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 95% (197/207) for levofloxacin-treated patients and 83% (193/226) for cephalosporin-treated patients. The 95% confidence interval around the difference in clinical success rates was $_{226,207}(-18.6, -6.2)_{83\%,95\%}$, indicating, at minimum, statistical equivalence of the two treatments arms, if not outright superiority of levofloxacin.

In protocol K90-071, the **overall success rate (clinically cured or improved plus microbiologically eradicated)** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 96% (113/118) for levofloxacin-treated patients and 80% (122/152) for cephalosporin-treated patients. The 95% confidence interval around the difference in clinical success rates was $_{152,118}$ $(-23.5, -7.4)_{80\%,96\%}$, indicating superiority of levofloxacin treatment in this indication.

15.1.5. Microbiologic Outcome

15.1.5.1. Bacterial Pathogens

15.1.5.1.1. *Haemophilus influenzae*

The **total number of microbiologically evaluable isolates** of *Haemophilus influenzae* patients was 51: 27 in levofloxacin-treated patients and 24 in ceftriaxone/cefuroxime-treated patients. The **clinical cure rate** for patients with *Haemophilus influenzae* in levofloxacin-treated patients was 81% (22/27) and in ceftriaxone/cefuroxime-treated patients was 42% (10/24). The **clinical success rate** for patients with *Haemophilus influenzae* in levofloxacin-treated patients was 100% (27/27) and in ceftriaxone/cefuroxime-treated patients was 66% (15/24). The **eradication rate** of *Haemophilus influenzae* in levofloxacin-treated patients was 100% (27/27) and in ceftriaxone/cefuroxime-treated patients was 70% (14/20). In addition, the confidence intervals for the difference in eradication rates between levofloxacin and ceftriaxone/cefuroxime-treated patients was (-54.4 to -5.6), indicating at the statistical superiority of levofloxacin. Thus, the total number of isolates is adequate, and the absolute and relative eradication rates all support the inclusion of this organism in the labeling.

15.1.5.1.2. *Haemophilus parainfluenzae*

The **total number of microbiologically evaluable isolates** of *Haemophilus parainfluenzae* patients was 28: 9 in levofloxacin-treated patients and 19 in ceftriaxone/cefuroxime-treated patients. The **clinical cure rate** for patients with *Haemophilus parainfluenzae* in levofloxacin-treated patients was 56% (5/9) and in ceftriaxone/cefuroxime-treated patients was 35% (7/20). The **clinical success rate** for patients with *Haemophilus parainfluenzae* in levofloxacin-treated patients was 100% (9/9) and in ceftriaxone/cefuroxime-treated patients was 65% (13/20). The **eradication rate** of *Haemophilus parainfluenzae* in levofloxacin-treated patients was 100% (9/9) and in ceftriaxone/cefuroxime-treated patients was 63% (12/19). Thus, the total number of isolates is borderline for levofloxacin, and the absolute and relative eradication rates support the inclusion of this organism in the labeling.

15.1.5.1.3. *Streptococcus pneumoniae*

The total number of microbiologically evaluable isolates of *Streptococcus pneumoniae* patients was 77: 35 in levofloxacin-treated patients and 42 in ceftriaxone/cefuroxime-treated patients. **The clinical cure rate** for patients with *Streptococcus pneumoniae* in levofloxacin-treated patients was 79% (30/38) and in ceftriaxone/cefuroxime-treated patients was 65% (28/43). **The clinical success rate** for patients with *Streptococcus pneumoniae* in levofloxacin-treated patients was 97% (37/38) and in ceftriaxone/cefuroxime-treated patients was 88% (38/43). **The eradication rate** of *Streptococcus pneumoniae* in levofloxacin-treated patients was 97% (34/35) and in ceftriaxone/cefuroxime-treated patients was 90% (38/42). In addition, the confidence intervals for the difference in eradication rates between levofloxacin and ceftriaxone/cefuroxime-treated patients was (-19.7, 6.4), indicating statistical equivalence of the two reatment arms. Thus, the total number of isolates is adequate, and the absolute and relative eradication rates all support the inclusion of this organism in the labeling. However, the issues surrounding the resistance of this organism to the quinolone antibiotics need to be considered, since the use of this antibiotic in general medical practice for the treatment of comminity-acquired pneumonia will, in many cases, be empiric.

15.1.5.1.4. *Klebsiella pneumoniae*

The **total number of microbiologically evaluable isolates** of *Klebsiella pneumoniae* was 8: 1 in levofloxacin-treated patients and 7 in ceftriaxone/cefuroxime-treated patients. Thus, the total number of isolates is inadequate to support the inclusion of this organism in the labeling. **See recommendations section.**

15.1.5.1.5. *Moraxella catarrhalis*

The **total number of microbiologically evaluable isolates** of *Moraxella catarrhalis* was 13: 7 in levofloxacin-treated patients and 6 in ceftriaxone/cefuroxime-treated patients. **The clinical cure rate** for patients with *Moraxella catarrhalis* in levofloxacin-treated patients was 57% (4/7) and in ceftriaxone/cefuroxime-treated patients was 67% (4/6). The **clinical success rate** for patients with *Moraxella catarrhalis* in levofloxacin-treated patients was 86% (6/7) and in ceftriaxone/cefuroxime-treated patients was 83% (5/6). **The eradication rate** of *Moraxella catarrhalis* in levofloxacin-treated patients was 86% (6/7) and in ceftriaxone/cefuroxime-treated patients was 83% (5/6). Thus, the total number of isolates is inadequate, although the absolute and relative eradication rates in would support the inclusion of this organism in the labeling.

15.1.5.1.6. *Staphylococcus aureus*

The **total number of microbiologically evaluable isolates** of *Staphylococcus aureus* was 14: 7 in levofloxacin-treated patients and 7 in ceftriaxone/cefuroxime-treated patients. **The clinical cure rate** for patients with *Staphylococcus aureus* in levofloxacin-treated patients was 100% (7/7) and in ceftriaxone/cefuroxime-treated patients was 86% (6/7). The **clinical success rate** for patients with *Staphylococcus aureus* in levofloxacin-treated patients was 100% (7/7) and in

ceftriaxone/cefuroxime-treated patients was 100% (7/7). The **eradication rate** of *Staphylococcus aureus* in levofloxacin-treated patients was 100% (7/7) and in ceftriaxone/cefuroxime-treated patients was 100% (7/7). Thus, the total number of isolates is inadequate, although the absolute and relative eradication rates in would support the inclusion of this organism in the labeling.

15.1.5.2. Atypical Pathogens

15.1.5.2.1. *Legionella pneumophilia*

The **total number of microbiologically evaluable cases** of *Legionella pneumophilia* patients was 5: 3 in levofloxacin-treated patients and 2 in ceftriaxone/cefuroxime-treated patients. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, 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. There were no cases defined by isolation of the organism from culture of respiratory secretions. The **clinical cure rate** for patients with *Legionella pneumophilia* in levofloxacin-treated patients was 100% (3/3) and in ceftriaxone/cefuroxime-treated patients was 0%. The **clinical success rate** for patients with *Legionella pneumophilia* in levofloxacin-treated patients was 100% (3/3) and in ceftriaxone/cefuroxime-treated patients was 0%. The **eradication rate** of *Legionella pneumophilia* in levofloxacin-treated patients was 100% (3/3) and in ceftriaxone/cefuroxime-treated patients was 0%. Thus, the total number of isolates is inadequate, although the absolute and relative eradication rates would support the inclusion of this organism in the labeling.

15.1.5.2.2. *Chlamydia pneumoniae*

The **total number of microbiologically evaluable patients** with *Chlamydia pneumoniae* was 147: 58 in levofloxacin-treated patients and 90 in ceftriaxone/cefuroxime-treated patients. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, allowed for both culture and serologic methods in the diagnosis of *Chlamydia pneumoniae* infection, the microbiologically evaluable patient cohort was composed entirely of cases diagnosed by serologic methods. There were no cases defined by isolation of the organism from culture of respiratory secretions. The **clinical cure rate** for patients with *Chlamydia pneumoniae* in levofloxacin-treated patients was 61% (36/59) and in ceftriaxone/cefuroxime-treated patients was 48% (44/91). The **clinical success rate** for patients with *Chlamydia pneumoniae* in levofloxacin-treated patients was 97% (57/59) and in ceftriaxone/cefuroxime-treated patients was 86% (78/91). The **eradication rate** of *Chlamydia pneumoniae* in levofloxacin-treated patients was 97% (56/58) and in ceftriaxone/cefuroxime-treated patients was 87% (78/90). The 95% confidence interval for the difference in eradication rates between levofloxacin and ceftriaxone/cefuroxime-treated patients was (-18, -2), indicating statistical superiority of levofloxacin. Thus, the total number of isolates is adequate, and the absolute and relative eradication rates would support the inclusion of this organism in the labeling.

15.1.5.2.3. *Mycoplasma pneumoniae*

The **total number of microbiologically evaluable cases** of *Mycoplasma pneumoniae* was 41: 20 in levofloxacin-treated patients **and** 21 in ceftriaxone/cefuroxime-treated patients. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, allowed for both culture and serologic methods in the diagnosis of *Mycoplasma pneumoniae* infection, the microbiologically evaluable patient cohort was composed entirely of cases diagnosed by serologic methods. There were no cases defined by isolation of the organism from culture of respiratory secretions. The **clinical cure rate** for patients with *Mycoplasma pneumoniae* in levofloxacin-treated patients was 57% (12/21) and in ceftriaxone/cefuroxime-treated patients was 60% (12/20). The **clinical success rate** for patients with *Mycoplasma pneumoniae* in levofloxacin-treated patients was 95% (20/21) and in ceftriaxone/cefuroxime-treated patients was 95% (19/20). The **eradication rate** of *Mycoplasma pneumoniae* in levofloxacin-treated patients was 95% (20/21) and in ceftriaxone/cefuroxime-treated patients was 95% (19/20). Thus, the total number of isolates is adequate, and the absolute and relative eradication rates would support the inclusion of this organism in the labeling.

Recommendations:

Recommendations for the use of levofloxacin in the treatment of community-acquired pneumonia based on the results of Protocol K90-071 are discussed in conjunction with the results of Protocol M92-075 following Section 15, "Conclusions", of the Medical Officer's Review of Protocol M92-075 and Section 16, "Combined Analysis of Protocols 90-071 and 92-075", which follows the Medical Officer's Review of Protocol M92-075.

Medical Officer's Review of NDA 20-634
Levaquin ® (levofloxacin) Tablets
Medical Officer's Review of NDA 20-635
Levaquin ® (levofloxacin) Injection

Indication: Community-Acquired Pneumonia due to Typical and Atypical Pathogens

Protocol: M92-075

Study Title: A multicenter, noncomparative, open-label study to evaluate the safety and efficacy of oral levofloxacin (500 mg PO or IV QD for 7-14 days) in the treatment of community acquired pneumonia in adults

Study dates: DATE STUDY INITIATED: September 30, 1993
DATE STUDY COMPLETED: July 20, 1994

1. Study Objective:

The objective of this study was to evaluate the safety and efficacy of levofloxacin 500 mg administered intravenously or orally once daily for 7 to 14 days in the treatment of community-acquired pneumonia due to susceptible organisms in adult inpatients and outpatients.

2. Protocol design:

This was a noncomparative multicenter study designed to evaluate the safety and efficacy of levofloxacin in the treatment of community-acquired pneumonia. This study was conducted in the United States. Approximately 245 subjects were to have been enrolled to ensure microbiologically evaluable data from a minimum of 80 subjects.

2.1. Study Procedures:

2.1.1. Baseline Evaluation:

For subjects meeting the entry criteria, admission (baseline) evaluations included a pertinent medical history, chest X-ray, and physical examination (including chest examination and vital sign measurements); specimen of respiratory secretions (expectorated or suctioned sputum, transtracheal aspirates, bronchial brushings, washings, biopsies, or pleural fluid) for Gram stain, culture, and susceptibility testing, as well as a direct fluorescent antibody (DFA) test for *L. pneumophila* (optional) and a DNA probe test for *Legionella* sp. (optional); blood samples for serology testing and cultures (at least two separate specimens for hospitalized subjects only); a urinary antigen test for *L. pneumophila*; samples for hematology, blood chemistry, and urinalysis; and a pregnancy test for women of childbearing potential. Between Days 2 and 4 of study drug administration, subjects were to be examined for overall clinical progress. Subjects were allowed to remain in the study in the absence of recovery of an admission pathogen, or if the pathogen(s) isolated at admission were

resistant to the study drug, as long as in the opinion of the investigator, there had been no deterioration in clinical status. Two blood cultures were to be obtained for subjects who were bacteremic at admission. Hematology, blood chemistry, and urinalysis laboratory evaluations were to be performed at this time and every five days thereafter for hospitalized subjects.

2.1.2. Efficacy evaluations:

Efficacy evaluations included assessments of clinical signs and symptoms, clinical response rates (assessed as cured, improved, failed, or unable to evaluate at posttherapy and as cured, improved, relapse, or unable to evaluate at poststudy), and microbiologic eradication rates by pathogen (assessed as eradicated, persisted, persisted with acquisition of resistance, or unknown) and by infection (assessed as eradicated, persisted, or unknown). Clinical symptoms were to be recorded as present or absent while on therapy (Days 2 to 4), at the posttherapy (Posttherapy Days 5-7) visit, and by a poststudy follow-up telephone contact or visit (Posttherapy Days 21-28). Clinical signs of lower respiratory tract infection obtained from a chest examination were to be graded as none, mild, moderate, or severe, and clinical response was to be assessed by the investigator posttherapy (Posttherapy Days 5-7) and poststudy (Posttherapy Days 21-28) for subjects who had a poststudy visit. **A poststudy visit, which included a chest examination and a chest X-ray, was required for subjects with a significant persistent infiltrate on chest X-ray at the posttherapy evaluation and subjects with persistent symptoms or relapse at the poststudy telephone contact.** Safety evaluations included the incidence of treatment-emergent adverse events; laboratory tests of hematology, blood chemistry, and urinalysis; and physical examinations including vital sign measurements.

2.1.3. Protocol Amendments:

Protocol 92-075 was amended twice during the course of the study. The amendments are discussed in detail under Sections 2.1.3.1 and 2.1.3.2, below. Fewer than 10% of the subjects were enrolled in the study before the first protocol amendment was issued. Approximately half of the subjects were enrolled between November 2, 1993, and March 11, 1994, the date the second amendment was issued, with the remaining subjects (approximately 40%) enrolled after both protocol amendments had been issued.

2.1.3.1. Protocol Amendment #1 dated November 2, 1993:

The **study protocol was amended on November 2, 1993,** to clarify provisions for enrollment of subjects who received prior antimicrobial therapy. **Fewer than 10% of the subjects were enrolled in the study before the first protocol amendment was issued.** In addition, procedures for the diagnosis and evaluation of infections due to atypical pathogens (*C. pneumoniae, L. pneumophila,* and *M. pneumoniae*) were specified; these included a urinary antigen detection test for *L. pneumophila*, cultures for atypical pathogens to have been performed by local laboratories, addition of repeat serologies for atypical pathogens posttherapy, and DFA and DNA probe tests (both optional) for *L. pneumophila*. Susceptibility data for *C. pneumoniae* were added, and MIC and inhibition zone criteria for susceptibility of *H. influenzae* were specified. The amendment also included provisions for twice-daily dosing of subjects based on severity of infection, and for increasing the dosing interval for subjects with creatinine clearances of

20 to 50 mL/minute. The amendment specified the clinical picture consistent with pneumonia. Several changes or clarifications of study procedures and the timing of procedures were also made:

(i) poststudy visit scheduled three to four weeks after completion of therapy;
(ii) admission blood cultures required for hospitalized subjects only;
(iii) culture and Gram stain of respiratory secretions to have been performed, if possible, at the posttherapy evaluation;
(iv) poststudy chest X-ray not required for subjects evaluated solely for the purpose of obtaining convalescent serologies.

2.1.3.2. Protocol Amendment #2 dated March 11, 1994:

The **second amendment to the protocol on March 11, 1994**, included clarification of provisions for enrollment of subjects failing previous antimicrobial therapy and the exclusion criteria regarding subjects with seizure disorders or unstable psychiatric conditions. **Approximately half of the subjects were enrolled between November 2, 1993, and March 11, 1994, the date the second amendment was issued, with the remaining subjects (approximately 40%) enrolled after both protocol amendments had been issued.** This amendment also excluded from enrollment subjects with pulmonary infections known to have been resistant to levofloxacin. In addition, the definition of clinical response of "improved" was modified to clarify that subjects who required additional nonstudy antimicrobials (for the treatment of the initial pneumonia) could not have been considered clinically improved; the definition of "unable to evaluate" was also clarified. The amendment specified that clinical failures could have been considered evaluable if they had taken more than 48 hours of levofloxacin therapy, that subjects with resistant pathogens could have been included in the efficacy analyses, and that subjects who did not complete a posttherapy evaluation between one and 10 days posttherapy were not evaluable for efficacy.

3. Diagnostic criteria:

3.1. **Clinical:** The diagnosis was based on clinical signs and symptoms of a lower respiratory tract infection, including at least two of the following: fever (oral temperature of 38°C/100.4°F or greater or rectal temperature of 39°C/102.2°F or greater), cough, purulent sputum (<10 epithelial cells and >25 WBC per low power field), chest pain, shortness of breath, or evidence of pulmonary consolidation on physical examination(rales on auscultation, dullness to percussion, or egophony).

3.2. **Radiographic:** A chest X-ray infiltrate compatible with acute infection also was required.

3.3. **Microbiologic:** Culture of purulent sputum (<10 epithelial cells and >25 WBC per low power field).

4. Inclusion and exclusion criteria:

4.1. Inclusion criteria:

4.1.1. As per Original Protocol dated July 21, 1993:

Subject must have been at least 18 years old with clinical signs and symptoms of a lower respiratory tract infection and an initial chest X-ray

compatible with acute pneumonia.

4.1.2. As per Protocol Amendment #1 dated November 2, 1993:

Unchanged from original protocol

4.1.3. As per Protocol Amendment #2 dated March 11, 1994:

Unchanged from original protocol

4.1.4. As per Study Summary:

1. Subject must have been at least 18 years old with clinical signs and symptoms of a lower respiratory tract infection and an initial chest X-ray compatible with acute pneumonia.
2. Subjects who received previous antimicrobial therapy could have been enrolled if their therapy duration was 24 hours or less, or, if previous therapy duration was greater than 24 hours, the subject did not improve or stabilize on that therapy.
3. Women were required to have been 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.

4.2. Exclusion criteria:

4.2.1. As per Original Protocol dated July 21, 1993:

1. previous allergic or serious adverse reaction to any member of the quinolone class of antimicrobials
2. diagnosis of cystic fibrosis, tuberculosis, or an infection due to fungus, parasite, virus, mycobacteria, or other organism resistant to levofloxacin
3. severe renal failure (creatinine clearance <20 mL/min)
4. presence of neutropenia
5. high probability of death during the course of study
6. history of seizure disorder or major psychiatric disorder
7. pregnant women or nursing mothers

4.2.2. As per Protocol Amendment #1 dated November 2, 1993:

Unchanged from original protocol

4.2.3. As per Protocol Amendment #2 dated March 11, 1994:

1. previous allergic or serious adverse reaction to any member of the quinolone class of antimicrobials
2. diagnosis of cystic fibrosis, or an infection due to fungus, parasite, virus, mycobacteria, or other organism resistant to levofloxacin
3. severe renal failure (creatinine clearance <20 mL/min)
4. presence of neutropenia
5. high probability of death during the course of study
6. **presence of seizure disorder**
7. **unstable psychiatric conditions**
8. pregnant women or nursing mothers

4.2.4. As per NDA Study Summary:

1. Subjects with a history of allergic or serious adverse reaction to levofloxacin, or any other member of the quinolone class of antimicrobial drugs, were excluded from the study.
2. Subjects were excluded if they required additional systemic antibiotic therapy in combination with levofloxacin, unless they had developed

bacterial pneumonia while receiving an antifungal or antiviral agent.

3. Subjects with a diagnosis of cystic fibrosis or a pulmonary infection that was acquired in a hospital or due to a fungus, parasite, virus, mycobacteria, or other organism known to be resistant to levofloxacin were not eligible for treatment under this protocol.
4. Subjects who used any investigational agent within 30 days before study entry and those who received previous treatment under this protocol also were excluded.
5. Subjects with a high probability of death during the course of the study were not eligible for enrollment. Also excluded were subjects with neutropenia, empyema, or human immunodeficiency virus (HIV) infection and CD4 counts of less than 200.
6. Women who were pregnant or nursing
7. Subjects with severe renal failure (calculated creatinine clearance less than 20 mL/min)
8. Subjects with seizure disorder
9. Subjects with unstable psychiatric conditions were not eligible for treatment under this protocol.

5. Medications:

5.1. Dosage and Administration of Study Drug:

5.1.1. As per Original Protocol dated July 21, 1993:

The following regimens were to have been utilized:

Levofloxacin 500 mg IV or PO q24h.

- Intravenous levofloxacin was to have been administered by slow infusion over one (1) hour. Total therapy duration for levofloxacin was to have been 7 to 14 days. If, in the opinion of the investigator, a subject requires more than 14 days of therapy, the PRI medical monitor should have been contacted. Duration of levofloxacin IV therapy was to have been a minimum of three days. The subject may then receive levofloxacin 500 mg PO q24h for the remainder of therapy, if clinically indicated.
- For those subjects who have pathogens isolated with an MIC greater than 1.0 mcg/mL but less than or equal to 4.0 mcg/mL (or zone size greater than or equal to 13 mm but less than 18 mm for levofloxacin disks) and/or who are not clinically improving, the dosage may have been increased to 500 mg q12h.
- Dosage of levofloxacin should have been adjusted for subjects with a calculated creatinine clearance less than or equal to 50 mL/min. These subjects should receive an initial (loading) dose of 500 mg of levofloxacin. Subsequent dosing should have been adjusted as follows: For subjects with a creatinine clearance less than or equal to 50 mL/min, the levofloxacin dosage and dosing interval were to have been 500 mg every 48 hours

5.1.2. As per Protocol Amendment #1 dated November 2, 1993:

The following regimens were to have been utilized:

Levofloxacin 500 mg i.v. or p.o. q24h

- Intravenous levofloxacin was to have been administered by slow infusion over one (1) hour. Total therapy duration for levofloxacin was to have been 7 to 14 days. If, in the opinion of the investigator, a subject requires more than 14 days of therapy, the PRI medical monitor should have been contacted. Duration of levofloxacin i.v. therapy was to have been a minimum of three days. The subject may then receive levofloxacin 500 mg p.o. q24h for the remainder of therapy, if clinically indicated.
- For subjects assigned to levofloxacin therapy who, at enrollment, have hypotension

(diastolic blood pressure <60 mmHg) in the absence of volume depletion, altered mental status, who require intubation, mechanical ventilation, or have a baseline respiratory rate >28 per minute, the dosage may have been increased to 500 mg i.v. or p.o. q12h.

- Dosage of levofloxacin should have been adjusted for subjects with a calculated creatinine clearance less than or equal to 50 mL/min. These subjects should receive an initial (loading) dose of 500 mg of levofloxacin. Subsequent dosing should have been adjusted as follows: For subjects with a creatinine clearance less than or equal to 50 mL/min, the levofloxacin dosage and dosing interval were to have been 500 mg every 48 hours. Subjects with a creatinine clearance of 20-50 mL/min and who were receiving levofloxacin every 12 hours should have had their dosing interval adjusted to 24 hours.

5.1.3. As per Protocol Amendment #2 dated March 11, 1994:

Levofloxacin dosage and administration were unchanged from those specified by Protocol Amendment #1 dated November 2, 1993.

5.1.4. As per study report from NDA submission:

Inpatient or outpatient subjects were assigned to receive 500 mg of levofloxacin intravenously or orally once daily for 7 to 14 days. Subjects assigned to intravenous levofloxacin treatment were administered the intravenous formulation for a minimum of three days, with oral levofloxacin administered for the remainder of the treatment period. Levofloxacin dosage was to have been reduced for subjects with creatinine clearances of 20 to 50 mL/min. Investigators were given the option of increasing the levofloxacin dosage to 500 mg twice daily for subjects with severe community-acquired pneumonia, defined as those with hypotension in the absence of volume depletion, subjects with altered mental status, subjects with baseline respiration rates greater than 28 breaths per minute, or subjects who required intubation or mechanical ventilation. Levofloxacin regimens of 500 mg q24h were administered either intravenously (i.v.) or orally (p.o.). Subjects administered the oral dosage regimen received one 500-mg levofloxacin tablet once daily. Subjects who received the i.v. dosage regimen were administered a 100-mL solution containing 500 mg of levofloxacin in D5W once daily as a one-hour i.v. infusion.

The duration of levofloxacin therapy was seven to 14 days, as clinically indicated. If, in the opinion of the investigator, a subject required a longer duration of therapy, the subject could have been continued on the same levofloxacin dosage regimen without any break in dosing. The investigator was to contact RWJPRI for approval to extend therapy in these cases. The minimum duration of i.v. levofloxacin therapy specified by the protocol was three days. Subjects could receive levofloxacin 500 mg p.o. q24h for the remainder of therapy, if clinically indicated. Levofloxacin dosage could have been increased, at the discretion of the investigator, to 500 mg i.v. or p.o. q12h for subjects with hypotension (diastolic blood pressure <60 mm Hg) in the absence of volume depletion; subjects with altered mental status; and subjects who required intubation, mechanical ventilation or who had a baseline respiratory rate >28 breaths per minute. Levofloxacin dosage was to have been reduced for subjects with calculated creatinine clearance values of 20 to 50 mL/min. These subjects were to receive an initial (loading) dose of 500 mg of levofloxacin followed by

levofloxacin 500 mg i.v. or p.o. q48h. Subjects who had creatinine clearances of 20 to 50 mL/min and who were receiving levofloxacin 500 mg q12h were to have their dosage interval adjusted to q24h.

5.2. Concomitant use of medications and other antimicrobial agents:
The use of other medications during the study was to have been kept to a minimum. Administration of nonstudy systemic antimicrobials was to be prohibited and aluminum-magnesium based antacids (e.g., Maalox •) and mineral supplements or vitamins with iron or minerals were to be strongly discouraged because these agents may decrease the bioavailability of levofloxacin. However, if administration of an antacid was necessary, it was to have been administered at least two hours before or after levofloxacin administration. If the administration of any other medication was required, it was to be reported on the subject's CRF.

6. Efficacy Criteria per Sponsor:
Efficacy evaluations included evaluations of clinical signs and symptoms, clinical response ratings (assessed as cured, improved, failed, or unable to evaluate at posttherapy and as cured, improved, relapse, or unable to evaluate at poststudy), and microbiologic eradication rates by pathogen with acquisition of resistance, or unknown) and by infection (assessed as eradicated, persisted, or unknown). Microbiologic response posttherapy in the group of subjects evaluable for microbiologic efficacy represented the primary efficacy variable in this study. Clinical response in the groups of subjects evaluable for clinical and microbiologic efficacy was a secondary efficacy variable. Safety evaluations included the incidence of treatment-emergent adverse events; laboratory tests of hematology, blood chemistry, and urinalysis; and physical examinations including vital signs.

7. Schedule and procedures for Efficacy and Safety Evaluations
7.1. Clinical Efficacy Evaluation:
7.1.1. Clinical Signs and Symptoms

Clinical symptoms of a lower respiratory tract infection, including chills, cough, purulent sputum, pleuritic chest pain, or shortness of breath, were to be indicated by the investigator as present or absent at admission, during therapy (Days 2-4), at the posttherapy (Posttherapy Days 5-7) visit, and during the poststudy follow-up (Posttherapy Days 21-28) telephone contact or visit. Clinical signs of acute lower respiratory tract infection obtained from a chest examination (diminished breath sounds, rales, egophony, rhonchi, or wheezes) were to be assessed during therapy (Days 2-4) and graded by the investigator at the posttherapy visit (Posttherapy Days 5-7) as none, mild, moderate, or severe. In addition, the investigator was to examine the chest X-ray for presence or absence of acute infiltrates or other pulmonary abnormalities (Posttherapy Days 5-7). For subjects with a significant persistent infiltrate or persistent symptoms at the posttherapy evaluation or possible relapse at the follow-up telephone contact, the chest examination and chest X-ray were to be repeated at a poststudy visit (Posttherapy Days 21-28).

7.1.2. Clinical Response Rating

7.1.2.1. Clinical Response Rating at the posttherapy visit:

At the posttherapy visit, five to seven days after the end of therapy or at the time of early withdrawal, the investigator was to assess clinical response as cured, improved, failure, or unable to evaluate. The definitions for these assessments were as follows:

Clinical Cure: Resolution of signs and symptoms associated with active infection and improvement in or resolution of chest X-ray findings.

Clinically Improved: Incomplete resolution of signs, symptoms, and chest X-ray findings and no additional antimicrobial therapy required. Subjects who were lost to follow-up but who had "clinical improvement" listed as the reason for a change in levofloxacin dosage or route of administration were assigned posttherapy clinical response ratings of Clinically Improved.

Clinical Failure: No response to therapy.

Unable to evaluate: Unable to evaluate because subject lost to follow-up.

7.1.2.2. Clinical Response Rating at the poststudy visit:

At the poststudy visit (Posttherapy Days 21-28), which was required for subjects with a significant persistent infiltrate on chest X-ray at the posttherapy evaluation and subjects with persistent symptoms or relapse at the poststudy telephone contact, the investigator was to assess clinical response as cured, improved, relapse, or unable to evaluate by comparing poststudy and posttherapy symptoms, signs from chest examination, and chest X-ray findings (if performed). The definitions for these assessments were as follows:

Clinical Cure: Resolution of signs and symptoms associated with active infection and improvement in or resolution of chest X-ray findings.

Clinically Improved: Continued incomplete resolution of signs and symptoms with no deterioration or relapse since the posttherapy evaluation and no additional antimicrobial therapy required.

Clinical Relapse: Resolution or improvement of signs and symptoms at the posttherapy evaluation (Posttherapy Clinical Response of Cure or Improved) followed by reappearance or worsening of signs and symptoms of infection.

Unable to Evaluate: Not able to evaluate because subject lost to follow-up and did not return for poststudy evaluation.

7.2. Microbiologic Efficacy Evaluation:

7.2.1. Specimen Collection

7.2.1.1. Respiratory Secretions

Specimens were to be obtained from respiratory secretions, including deep expectorated or suctioned sputum, transtracheal aspirates, pleural fluid, bronchial brushings, biopsies, or washings. At admission (within 48 hours before therapy start), respiratory secretions were to be collected for routine culture, Gram stain, and susceptibility tests. Specimens also were to have been cultured for *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*, if the local laboratory had the capability to perform these cultures. A direct fluorescent antibody test (DFA) of sputum or bronchoalveolar lavage fluid for *L. pneumophila* and a DNA probe test for detection of infection caused by *Legionella* sp. also were to have been performed, if the hospital microbiology laboratory was capable of performing these tests. Additional specimens were to be obtained at the posttherapy visit (five to seven days after the end of therapy) and, if indicated, at the poststudy visit for culture and Gram stain.

7.2.1.2. Blood Culture

At least two separate specimens for blood cultures were to be obtained from each hospitalized subject within 48 hours before therapy was started. Cultures were to be repeated during therapy (Days 2-4) and at the posttherapy visit (Posttherapy Days 5-7), if at least one of the admission blood cultures was positive.

7.2.1.3. Serology

7.2.1.3.1. Blood Samples for Serology

Blood samples were to be obtained from each subject at admission (within 48 hours before therapy start) for serologic studies of *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. These evaluations were to be repeated at the posttherapy (Posttherapy Days 5-7) and poststudy (Posttherapy Days 21-28) visits.

7.2.1.3.1. Urine Antigen Testing

Urine specimens were to be obtained at admission (within 48 hours before therapy start). A urinary antigen detection test for *L. pneumophila* was to be performed for all subjects.

7.2.1.4. Susceptibility Testing:

Susceptibility to levofloxacin was to be determined for all aerobic pathogens, excluding *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*. The MIC susceptibility was the primary susceptibility criterion. If the MIC values were not available, discs were used to determine susceptibility. Disc susceptibility testing was to be performed for all aerobic pathogens, excluding *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*, in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) methods using 5-μg levofloxacin discs provided by RWJPRI.

7.2.1.5. Diagnosis of Infection Due to Atypical Pathogens

Diagnosis of infection due to *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* was to be made on the basis of the clinical, radiologic, serologic, and other diagnostic criteria, as described in the following case definitions:

7.2.1.5.1. *Legionella* case definition:

Clinical and radiologic evidence of pneumonia in association with one or more of the following: (i) a single IGM ELISA titer ≥1:256 or a fourfold increase or decrease in titer from admission to poststudy; (ii) a single IGG ELISA titer ≥1:256 or a fourfold increase or decrease in titer from admission to poststudy; (iii) a positive DFA on sputum, bronchial lavage, or tracheal aspirate; (iv) a positive culture for *L. pneumophila* from respiratory secretions; or (v) a positive urine antigen test.

7.2.1.5.2. *Chlamydia pneumoniae* case definition:

Respiratory signs and symptoms compatible with *C. pneumoniae* infection in association with one or more of the following: (i) a single microimmunofluorescence IgM titer >1:32 or a fourfold increase or decrease in titer from admission to poststudy; (ii) a single microimmunofluorescence IGG titer >1:512; (iii) a positive admission sputum or nasopharyngeal culture; or (iv) a positive culture from pleural fluid or other pertinent respiratory tissue or fluid.

7.2.1.5.3. *Mycoplasma* case definition:

Clinical and radiologic evidence of pneumonia in association with one or more of the following: (I) a single IgM ELISA titer ≥1:16 or a four-fold increase or decrease in titer from admission to poststudy; (ii) a single IgG ELISA titer ≥1:128 or a fourfold increase or decrease in titer from admission to poststudy; or (iii) a positive culture from sputum or other respiratory fluid or material.

The criteria described above for diagnosis of *C. pneumoniae* and *Mycoplasma* infections using a single IgG titer have been modified from those specified in the protocol. The protocol stated that a single IgG titer >1:64 or a fourfold increase or decrease in the IGG titer from admission to poststudy were diagnostic for *C. pneumoniae*; the modified criterion described above in the case definition was used for diagnosis of *C. pneumoniae* infections using a single IgG titer. For *Mycoplasma*, the protocol contained an error indicating that a single IgG ELISA titer >1:28 (rather than the correct titer of >1:128) was diagnostic for infection.

7.3. Efficacy Criteria

7.3.1. Efficacy Criteria for Microbiologic Response

The primary efficacy variable was microbiologic response. Microbiologic response at posttherapy and poststudy was evaluated by RWJPRI in terms of pathogen and infection eradication rates. Microbiologic response also was to be assessed for blood pathogens (bacteremia) and for atypical pathogens, including *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*. A culture or nonculture evaluation was to be considered valid if the subject was not receiving any effective concomitant antimicrobial agent. In addition, valid posttherapy cultures were required to have been obtained at least one day posttherapy.

7.3.1.1 Microbiologic Response: Sputum Culture

The microbiologic response for pathogens isolated at admission was determined by evaluating the posttherapy and poststudy culture results. Results were categorized as follows:

Eradicated: Eradication of the admission pathogen as evidenced by no isolation of the pathogen in the posttherapy/early termination or poststudy culture. If clinical improvement occurs such that no sputum was produced and invasive procedures for culture were contraindicated, then the pathogen was presumed eradicated.

Persisted: Persistence of the admission pathogen as evidenced by isolation of the pathogen in the posttherapy/early termination or poststudy culture. If a subject was discontinued due to clinical failure or resistant pathogen, or was considered a clinical failure upon completion of therapy, or persistence of the admission pathogen was not confirmed by valid 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 termination or poststudy culture with documented acquisition of resistance.

Unknown: No posttherapy/early termination or poststudy culture results available due to lost-to-follow-up, lost culture, or culture not done when specimen was available. If culture was performed on last day of therapy and subject was not a clinical failure or culture done while subject was receiving effective antimicrobial agent for reasons other than clinical failure, the response was unknown.

The overall 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 culture results for at least one admission pathogen isolated at admission with no pathogen persisting.

7.3.1.2 Microbiologic Response: Blood Pathogens

The microbiologic response for blood pathogens was based on posttherapy blood culture results of subjects with confirmed bacteremia at admission. Bacteremia was defined as at least one positive blood culture obtained at admission. Microbiologic response for each admission pathogen was determined for subjects with posttherapy blood culture results as follows:

Blood Culture #1	Blood Culture #2	Clinical Response	Microbiologic Response
Negative	Negative	All**	Eradicated
Negative	Unknown	Cure/improved	Eradicated
Negative	Unknown	Failure	Persisted
Positive	Positive	All	Persisted
Positive	Negative	All	Persisted
Positive	Unknown	All	Persisted

** "All" includes clinical response of cured, improved and fail

7.3.1.3. Microbiologic Response: Atypical Pathogens

The microbiologic response for *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* was based on clinical response, and was determined as follows:

Clinical Response	Microbiologic Response
Cured/improved	Eradicated
Failure	Persisted
Unknown/unable to evaluate	Unknown

7.3.1.4. Superinfection

A superinfection was defined as a new infection, which was found at any site during therapy, which was caused by a new pathogen (not recognized as the original causative agent), and which was documented by culture results. A superinfection was to have been associated with clinical signs and symptoms of infection and required antimicrobial therapy.

7.3.2. Efficacy criteria for Clinical Response:

Clinical response, a **secondary efficacy variable**, was to be assessed by the investigator as cured, improved, failed, or unable to evaluate at the posttherapy visit (Posttherapy Days 5-7) and as cured, improved, relapse, or unable to evaluate at the poststudy contact or visit (Posttherapy Days 21-28). The clinical cure rate was to be evaluated by determining the percentage of subjects who were cured, and the clinical success rate was based on the percentage of subjects who were cured or improved.

7.4. Safety Evaluations

7.4.1. Treatment-Emergent Adverse Events

Adverse events were defined as treatment-emergent signs and symptoms, i.e., events that were not present at baseline or events that represented an increase in severity or frequency of a sign or symptom already present at admission. Each subject was to be assessed at each visit during therapy and at the posttherapy visit (Posttherapy Days 5-7) for possible adverse events that might have occurred throughout the study period. The investigator was to record all treatment-emergent adverse events on the CRFs and graded their severity as mild, moderate, or marked. The

investigator also was to assess the relationship of the adverse event to trial treatment using the following ratings: none, remote, possible, probable, or definite. Other information to be recorded on the subject's CRF included: the date of onset of the event, control measures taken (i.e., dose reductions, discontinuation of study drug, or administration of remedial therapy), the outcome (resolved, persisted, or unknown), and the date of resolution of the event. Serious adverse events were defined as those events that presented a significant threat to the well-being of the subject. Serious adverse events included any event that was fatal, life-threatening, permanently or significantly disabling, required hospitalization or prolonged hospitalization, resulted in long-term outpatient treatment (greater than six months), or was a congenital anomaly, cancer, or overdose. Investigators were instructed to report all serious adverse events immediately to RWJPRI. A 5 mL venous blood sample for determination of levofloxacin plasma concentration was to be obtained at the time of a serious adverse event. However, due to practical limitations, these blood samples were not consistently obtained as planned.

7.4.2. Clinical Laboratory Tests

The following standard clinical laboratory evaluations were to be performed before dosing (admission) and at the posttherapy visit (Posttherapy Days 5-7). Additional determinations were to be made for hospitalized subjects during therapy (Days 2-4) and every five days thereafter while hospitalized. Although not required by protocol, additional determinations were to be made for some subjects at the poststudy visit. A central laboratory (SciCor Inc., Indianapolis, IN) was used. Local laboratories could be used for prothrombin time and partial thromboplastin time determinations.

Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, red blood cell (RBC) count, and platelet count. Prothrombin time and partial thromboplastin time were obtained for subjects receiving concurrent treatment with anticoagulants.

Blood Chemistry: glucose, blood urea nitrogen (BUN), total bilirubin, total protein, albumin, uric acid, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), creatinine, calcium, sodium, potassium, chloride, inorganic phosphorus, and bicarbonate.

Urinalysis: pH, specific gravity, and microscopic examination for red blood cells, white blood cells, and nonamorphous crystals.

7.4.3. Physical Examinations and Vital Signs

Physical examinations, including vital sign measurements, were to be performed at admission and again at the posttherapy visit or upon early withdrawal. Additional physical examinations were to be performed at a poststudy visit for subjects with a significant persistent infiltrate at the posttherapy evaluation and for subjects with persistent symptoms or relapse at the follow-up telephone contact. Any physical examination abnormalities were to be noted on the CRFs. Vital sign measurements included oral temperature, respiration rate, pulse rate, and blood pressure. Weight and height were to be obtained at admission only.

8. Discontinuation from study:

Subjects could have been 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, including physical examination and vital signs, culture, Gram stain, and susceptibility testing of respiratory secretions and/or blood specimens if indicated, chest X-ray, and clinical laboratory tests, were to have been performed. The investigator was to record the reason for premature discontinuation on the subject's CRF.

9. Evaluability Criteria:

9.1. Evaluability criteria as per Sponsor:

9.1.1. Evaluability criteria as outlined in Statistical Methods Section of Original Study Protocol:

9.1.1.1. Safety Evaluability Criteria as per Sponsor:

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

9.1.1.2. Clinical Evaluability Criteria as per Sponsor:

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

a. Not evaluable for safety.

b. Clinical diagnosis unconfirmed:
   - A subject must have been diagnosed as having community-acquired pneumonia as described in the protocol.

c. Insufficient course of therapy.
   - A subject did not take at least 5 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.

d. Effective concomitant therapy.
   - A subject received an effective systemic antimicrobial between time of admission culture through test-of-cure culture. (Subjects who received previous antimicrobial therapy could have been 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.

e. Posttherapy clinical evaluation was not on days 1-10 posttherapy.
   - If a subject was discontinued due to a clinical failure or considered a clinical failure upon the completion of therapy and the test-of-cure evaluation was performed on the last day of therapy, the subject was not considered unevaluable for this reason.

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

g. 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.

The hierarchy given above (a-g) was used as a guide to assign a primary reason for being unevaluable for clinical efficacy; final classification

rested with the RWJPRI medical monitor. If a subject had more than one reason for being unevaluable, the higher reason was assigned.

9.1.1.3. Microbiologic Evaluability Criteria as per Sponsor:
A subject was to be evaluable for microbiologic efficacy if all criteria for clinical efficacy were met and the subject was not classified by any of the following:

a. Infection not bacteriologically proven.
b. 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 microbiologic culture/evaluation was not on Days 1-10 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 unavailable. If a subject was discontinued due to a clinical failure and the posttherapy culture was not obtained, the subject was not considered unevaluable for this reason.

The hierarchy that guided the assignment of microbiologic unevaluability was:

a. Not evaluable for safety.
b. Infection not bacteriologically proven.
c. Clinical diagnosis unconfirmed.
d. Insufficient course of therapy.
e. Effective concomitant therapy.
f. Inappropriate bacteriologic culture.
g. Lost to follow-up but provided safety information.
h. Other protocol violation

For subjects who were determined by culture or nonculture methods to have infection due to *M. pneumonia*, *L. pneumophila*, or *C. pneumoniae*, the hierarchy was:

a. Not evaluable for safety
b. Insufficient course of therapy
c. Effective concomitant therapy
d. Lost to follow-up but provided safety information
e. Other protocol violation

If a subject fit into more than one of these categories, the highest reason was to be reported as the primary reason. Final classification regarding evaluability rested with the RWJPRI medical monitor.

9.1.2. As per NDA Study Summary:
Subject evaluability was categorized according to a specified hierarchy. The first category of the hierarchy into which a subject was classified was designated as the primary reason for nonevaluability.

9.1.2.1. Clinical Efficacy Criteria:

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

- not evaluable for safety (no postadmission data available or did not take at least one dose of study drug)
- unconfirmed clinical diagnosis on the basis of signs and symptoms and radiographic findings
- insufficient course of therapy (minimum of five days of levofloxacin therapy). The total planned duration of levofloxacin therapy was to be seven to 14 days, but therapy could be extended at the discretion of the investigator if indicated. A minimum of five days of levofloxacin therapy was required for analyses of clinical and microbiologic response; subjects who had failed clinically (in the judgment of the investigator) and had taken more than 48 hours of study drug were not classified as unevaluable due to insufficient course of therapy.
- effective concomitant antimicrobial therapy
- posttherapy culture/evaluation not done during Posttherapy Day 1-10 interval (window)
- lost to follow-up but provided safety information
- other protocol violation (e.g., subject reentered study or did not take at least 70% of assigned study medication corresponding to reported number of days on therapy).

9.1.2.2. Microbiologic Efficacy Criteria:

To be evaluable for microbiologic efficacy, subjects with any admission pathogen except *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* were not to have been classified in any of the following categories (in decreasing hierarchical order):

- not evaluable for clinical efficacy
- absence of bacteriologically proven infection
- inappropriate bacteriologic culture.

To be evaluable for microbiologic efficacy, subjects determined by culture or nonculture methods to have infections due to *M. pneumoniae*, *L. pneumophila*, or *C. pneumoniae* were not to have been classified in any of the following categories (in hierarchical order):

- not evaluable for safety
- insufficient course of therapy
- effective concomitant antimicrobial therapy
- lost to follow-up but provided safety information
- other significant protocol violation.

9.2. Evaluability criteria as per Medical Officer:

9.2.1. Clinical Evaluability Criteria as per Medical Officer:

1. The subject met the inclusion criteria
2. The subject did **NOT** meet any of the exclusion criteria at the time of enrollment
3. A **posttherapy/end-of therapy/EOT** clinical evaluation and an **poststudy/end-of study/EOS** clinical evaluation were performed. The exceptions were for patients who were:
   (1) declared clinical failures on-therapy, at the posttherapy visit, or in the interval between the posttherapy and poststudy visits, but did not have a poststudy follow-up, here the failure declared at the earlier time point was carried forward
   (2) declared clinical cures at the posttherapy evaluation (i.e., were completely asymptomatic, and had a normal chest X-ray at EOT visit), here the clinical cure was carried forward. This was specified by the sponsor in the original study protocol, and, therefore, could not be modified after the fact.
4. A symptomatic response could be evaluated at the **posttherapy** and (where applicable) the **poststudy** time point.
5. With regard to establishing time point for follow-up after treatment of community-acquired pneumonia, both (1) the **natural history of the disease** and (2) the **half-life of the antimicrobial agent** under investigation need to be taken into account. The windows for follow-up after an episode of community-acquired pneumonia be the same for patients treated with any **antimicrobial agent with a relatively short half-life**. It is only in the case of a prolonged half-life that the window for follow-up needs to be extended because blood levels and tissue levels persist far beyond the last dose of the antimicrobial drug. For levofloxacin, whose serum half-life is 6.34-6.39 hours in the clinical tablet, the window of follow-up can be the same as for other antibiotics with relatively short half-lives.

   5.1. The **IDSA Guidelines** recommend standard follow-up after an episode of community-acquired pneumonia as follows:

   > Hospitalized patients should be assessed every day during the course of therapy and within 5-7 days after the completion of treatment[1]

   5.2. Recent **regulatory precedent** for the appropriate time point for test of cure has been established in other reviews of antimicrobial agents with short half-lives for the indication of community-acquired pneumonia, and these confirm the need for late post-therapy follow-up to determine a stable point-estimate for clinical cure at the test-of-cure evaluation[2].

The original protocol 90-070 specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but with an End-of-Study evaluation at 3-6 weeks post-therapy to provide a late follow-up assessment and stable estimate for the test-of-cure. Protocol Amendment #T also specified that the clinical evaluation at the **posttherapy/EOT** (5-7 days posttherapy) visit was to be the primary clinical endpoint, but the late

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[1] Beam TR, Gilbert, DN, Kunin CM. Guidelines for the Evaluation of Anti-infective Drug Products. Clin Infect Dis 15(Suppl 1):S85, 1992

[2] Merepenam NDA Review. NDA 50706.

follow-up at 3-6 weeks was deleted from the protocol under this. **Therefore, acknowledging that the 5-7 day posttherapy visit is suboptimal for establishing a stable point estimate of the test-of-cure, the medical officer had no choice but to use the only existing endpoint for the follow-up clinical evaluation as the time point for the primary clinical endpoint for the purposes of this evaluation.**

6. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

(i) A patient was **fully clinically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

- Within 48 hours prior to enrollment in the protocol
- During the treatment period
- From the end of the treatment period to the poststudy evaluation
- At the evaluation for clinical relapse

(ii) if the patient received an antimicrobial agent prior to enrollment in the study, but there was **a pathogenic organism isolated on admission culture**, the patient was considered **clinically evaluable**

(iii) if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **clinically unevaluable.**

(iv) if the patient received an alternative antibiotic **AND** there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **clinically evaluable (only) as a treatment failure.**

7. Subjects must have completed an **adequate course of therapy** of study drug, with "adequate course" defined as follows:

(I) for patients who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the amended protocol

(ii) for patients designated a clinical failure, a minimum of 72 hours of study drug was to have been taken

(iii) no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 7-14 doses of therapy, as specified by the amended protocol.

8. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

9. The patient had no known history of AIDS and was not HIV seropositive.

9.2.2. Microbiologic evaluability criteria as per Medical Officer:

1. A subject met criteria for clinical evaluability at all time points during the study
2. Pretherapy (admission) sputum culture was positive for a microorganism known to be pathogenic in lower respiratory tract infections or there was evidence of infection by an atypical pathogen (see criteria for the diagnosis of atypical pathogens, below)
3. Any residual secretions present at the EOT visit were sent for culture. The medical officer would not accept the category of "presumed eradication" in cases in which there were persistent secretions that were not cultured. The medical officer felt that it was incumbent upon the sponsor and investigators to document eradication when and where possible.

   (i) Only in cases where there were no residual secretions would the designation "clinical cure/presumed eradication" be accepted.
   (ii) If there residual **purulent** secretions that were not cultured, the medical officer defaulted to "presumed persistence".
   (iii) If there were residual **nonpurulent** secretions that were not cultured, the medical officer defaulted to "microbiologically unevaluable".
   (iv) In cases of clinical failure, a microbiologic assessment of "presumed persistence" was universally applied.

4. In regards to the use of **concomitant antibiotic therapy from the time of enrollment through the end-of study visit**, the following criteria were applied:

   (i) A patient was **fully microbiologically evaluable** only if the patient did **NOT** receive concomitant antibiotic therapy:

   - For the 48 hour period prior to enrollment (see exception under item (ii) below)
   - During the treatment period
   - From the end of the treatment period to the poststudy evaluation
   - At the evaluation for clinical relapse

   (ii) if the patient received **pretherapy** antimicrobial treatment with another antibiotic, the patient was microbiologically evaluable if there was a pathogen isolated on admission culture. If **no** pathogen was isolated on admission culture, the patient was both clinically and microbiologically unevaluable.
   (iii) if the patient received an alternative antibiotic **AND** there was **clear documentation of an alternative diagnosis** for which the other antibiotic was prescribed, the patient was categorized as **microbiologically unevaluable**.
   (iv) if the patient received an alternative antibiotic **AND**

there was **no documentation of an alternative diagnosis** for which the alternative antibiotic may have been prescribed, the patient was deemed **microbiologically evaluable (only) as a persistent pathogen.**

5. Subjects must have completed an **adequate course of therapy** of either study drug, with "adequate course" defined as follows:

(I) for patients who were designated as a clinical cure at EOT, a minimum of 6 days or 80% of the minimum dose specified by the amended protocol
(ii) for patients designated a clinical failure, a minimum of 72 hours of study drug was to have been taken
(iii) no more than 1 missed dose within the dosing interval requiring extension of the dosing interval to complete the full 7-14 doses of therapy, as specified by the amended protocol.

6. Symptomatic response "unable to evaluate" at either the EOT or the EOS evaluation remained disqualified from the efficacy analysis. The exception to this was a patient who was declared a clinical failure during therapy or at the EOT visit: this failure was carried forward as "evaluable" regardless of the EOS evaluation.

7. Diagnostic criteria for an atypical pathogens, defined as follows:
7.1. LEGIONELLA CASE DEFINITION
Clinical and radiologic evidence of pneumonia in association with one or more of the following[3]:

A. A single IGM ELISA > 1:256 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up
B. A single IGG ELISA > 1:256 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up
C. A positive DFA (direct fluorescence antibody test) on sputum, bronchial lavage or tracheal aspirate)
D. A positive culture at admission for *Legionella pneumophila* from sputum or other respiratory fluid or material
E. Posftive urine antigen

7.2. CHLAMYDIA PNEUMONIAE CASE DEFINITION
Respiratory signs and symptoms compatible with *Chlamydia pneumoniae*, in association with one or more of the following[4]:

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[3] Ostergard L, Anderson PL. Etiology of Community-acquired Pneumonia: Evaluation by Transtracheal Aspiration, Blood Culture, or Serology. Chest 104:1400-07, 1993; Ruf B, Schurmann D, Horbach I. Prevalence and diagnosis of Legionella Pneumonia: A 3-year Prosective Study with Emphasis on Application of Urinary Antigen Detection. J Infect Dis 1990:1341-48, 1990; Myburgh J, Nagel GJ, Petschel E. Efficacy and tolerance of a three day course of azithromycin in the treatment of community-acquired pneumonia. J Antimicrob Chemother 31 Suppl E: 163-9, 1993; Ruf B, Schurmann D. Prevalence and diagnosis of Legionella pneumonia: a 3-year proseptive study with emphasis on applicaiton of urinary antigen detection. J Infect Dis 162(6):1341-8,-1990.

[4] Grayston JT, Campbell LA, Kuo CC, et.el. A New Respiratory Tract Pathogen: *Chlamydia pneumoniae* Strain TWAR. J Infect Dis 161:618-25, 1990; New and Emerging Etiologies for Community-acquired Pneumonia with Implications for Therapy: A Prospective Multicenter Study of 359 cases. Medicine 69(5):307-316, 1990; Ekman MR, Leinonen M. Evaluation of Serological Methods

A. A single microimmunofluorescence IGM titer ≥ 1:16 or a fourfold increase or decrease in the IGM titer at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

or

B. A single microimmunofluorescence IGG titer ≥ 1:512 or a fourfold increase or decrease in the IGG titer at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

or

C. A positive admission sputum or nasopharyngeal culture for *Chlamydia pneumoniae*

or

D. A positive culture from pleural fluid or other pertinent respiratory tissue or fluid

7.3. MYCOPLASMA CASE DEFINITION

Clinical and radiologic evidence of pneumonia in association with one or more of the following[5]:

A. A single IGM ELISA > 1:16 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

B. A single IGG ELISA > 1:28 or a fourfold increase or decrease at 3-4 weeks post therapy (5-6 weeks post study admission) follow-up

C. A positive culture at admission for *Mycoplasma pneumoniae* from sputum or other respiratory fluid or material

10. Study Population:

Approximately 245 subjects, men and women who were 18 years of age or older and who had community-acquired pneumonia, were to have been enrolled in this study to ensure microbiologically evaluable data from 80 subjects.

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in the Diagnosis of *Chlamydia pneumoniae* Pneumonia during and Epidemic in Finland. Eur J Clin Microbiol Infect Dis. 12(10): 756-60, 1993; Grayston JT, Aldous MB. Evidence that *Chlamydia pneumoniae* causes Pneumonia and Bronchitis. J Infect Dis 168:1231-5, 1993; Grayston JT, Kou CC, Et.al. A new *Chlamydia psittaci* strain, TWAR, isolated in acute respriatory tract infections. NEJM 315(3):161-68, 1986.

[5] Fang GD, Fine M, et.al., New and Emerging Etiologies for Community-acquired Pneumonia with Implications for Therapy: A Prospective Multicenter Study of 359 Cases. Medicine 69(5):307-16, 1990; Uldum SA, Jensen JS, et.al., Enzyme Immunoassay for Detection of Immunoglobulin M (IgM) and IgG Antibodies to *Mycoplasma pneumoniae*. J Clin Microbiol 30(5):1198-1204, 1992; Jacobs E, Bennewitz A, et.al., Reaction pattern of human anti-Mycoplasma pneumoniae antibodies in enzyme-linked immunosorbent assays and immunoblotting. J Clin Microbiol 23:517-522, 1986; Jacobs E, Fuchte K, et.al., A 168-kilodalton protein of *Mycoplasma pneumoniae* antibodies in enzyme-linked immunoabsorbant assay. Eur J Clin Microbiol Infect Dis 5:435-40, 1986; van Griethuysen AJA, de Graf R, et.al., Evaluation of a commercial enzyme immunoassay for detection of *Mycoplasma pneumoniae* specific immunoglobulin G antibodies. Eur J Clin Microbiol Infect Dis 9:221-223, 1990.

11. Investigators and study sites:

Protocol M92-075 was conducted by 27 investigators at a total of 33 separate sites, as delineated below.

Lawrence K. Alwine, D.O.	- Downington Family Medicine, Downington, PA; USA
H. Stephen Bjornson, M.D., Ph.D.a	- University of Cincinnati College of Medicine, Cincinnati, OH; USA
Jacques R. Caldwell, M.D.a	- Gainesville, FL; USA
	- Ocala, FL; USA
	- New Smyrna Beach, FL; USA
	- Halifax Clinical Research Center, Daytona Beach, FL; USA
John Carroll, M.D.	- Maricopa Medical Center, Phoenix, AZ; USA
Martin S. Chattman, M.D.	- Desert Foothills Medical Center, Scottsdale, AZ; USA
Richard D. Clover, M.D.a	- The University of Texas Medical Branch, Galveston, TX; USA
Lawrence A. Cone, M.D.a	- Eisenhower Medical Center, Rancho Mirage, CA; USA
Lawrence J. Epstein, M.D.	- Wilford Hall USAF Medical Center, Lackland AFB, TX; USA
Henry M. Faris, Jr., M.D.	- St. Francis Hospital and Woodward Medical Center, Greenville, SC; USA
Charles M. Fogarty, M.D.	- Spartanburg Regional Medical Center and Mary Black Memorial Hospital, Spartanburg, SC; USA
Walter N. Gaman, M.D.	- Irving, TX; USA
Cyril M. Grum, M.D.	- University of Michigan Medical Center, Ann Arbor, MI; USA
Douglas Kernodle, M.D.	- Nashville VA Medical Center, Nashville, TN; USA
Myron Liebhaber, M.D.	- Santa Barbara Medical Foundation Clinic, Santa Barbara, CA; USA
J. Tyler Martin, M.D.b	- Norfolk, NE; USA
Susan Mehnert-Kay, M.D.a	- IMTCI-O, Tulsa, OK; USA
Dennis J. Mikolich, M.D.c	- VA Medical Center, Providence, RI; USA
	- Independent Research Nurses, Cranston, RI; USA
Miguel Mogyoros, M.D.	- Kaiser Special Care, Saint Joseph Hospital, Saint Joseph Research Department, and Kaiser Permanente, Denver, CO; USA
Avi Nahum, M.D.	- St. Paul-Ramsey Medical Center, St. Paul, MN; USA
Michael E. Nelson, M.D.	- VA Medical Center, Kansas City, MO; USA
David Rodman, M.D.	- University Hospital, Denver, CO; USA
Robert D. Rosen, M.D.	- Salem Research Group, Inc., Winston-Salem, NC; USA
Jerome J. Schnapp, M.D.a	- Cushner, Schnapp, and Barth, MD, Silver Spring, MD; USA
William B. Smith, M.D.a	- Louisiana Cardiovascular Research Center and Mercy Hospital of New Orleans, New Orleans, LA; USA
	- Elmwood Medical Center, Jefferson, LA; USA
James G. Sullivan, M.D.	- Birmingham, AL; USA
Terry L. Swezey, M.D.	- Vero Beach; FL; USA;
	- Indian River Memorial Hospital and CPR, Inc., Vero Beach, FL; USA
John J. Upchurch, M.D.	- St. Vincent's Family Medical Center, Birmingham, AL; USA

a Did not enroll any subjects in this study. b Did not receive drug. c The study was prematurely terminated at this site for administrative reasons and data obtained at this site were not to have been used to support efficacy and were not to have been presented in the summary displays of safety or efficacy included in this report. This investigator was not terminated due to either lack of efficacy or serious adverse events.

12. Efficacy as per sponsor:

12.1 Overview of Analysis Groups:

12.1.1. Demographics of Intent-to Treat Population:

Two hundred sixty-four subjects were enrolled in this study at 18 of the 27 centers. Eight investigators did not enroll any subjects. The intent-to-treat group included all 264 subjects enrolled at the 18 centers. Data for the five additional subjects enrolled by the other investigator [D. Mikolich] are not included in data summaries presented in this report because the study was prematurely terminated at this site for administrative reasons. None of these five subjects reported serious adverse events and none were withdrawn from the study because of adverse events. This investigator was not terminated due to either lack of efficacy or serious adverse events. The intent-to-treat group included 146 (55.3%) men and 118 (44.7%) women, and had a mean age of 51.9 ± 17.8 years (range, 18-93 years) and a mean weight of 172.3 ± 44.4 pounds (range 82-370 pounds). The majority of the subjects were Caucasian (83.0%), with Black (15.2%), Hispanic (1.5%), and other racial groups (0.4%) accounting for smaller proportions of the study population. One hundred fifty-six (59.1%) subjects were enrolled as outpatients, and 108 (40.9%) as inpatients. The majority of the subjects (82.6%) had infections that were categorized as mild/moderate, with the remaining subjects (17.4%) having severe infections. 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 subject number assigned if the subject was enrolled. The most common reason for not entering a potential subject was prior or concurrent antimicrobial therapy that was not permitted by the protocol. Other reasons included concurrent illnesses or conditions specifically prohibited by the protocol, residence in a supervised care facility (e.g., nursing home), absence of required signs or symptoms of pneumonia or inability to produce sputum, and patient refusal.

Table 12.1.1.
Demographic and Baseline Characteristics:
Modified Intent-to-treat Cohort (Study M92-075)

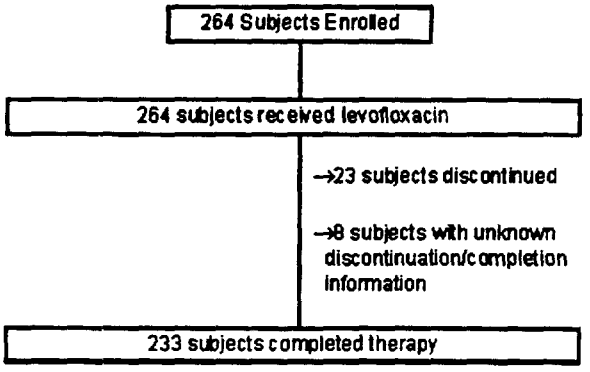
	Levofloxacin (N=264)	
	No.	%
Sex		
Men	146	(55.3)
Women	118	(44.7)
Race		
Caucasian	219	(83.0)
Black	40	(15.2)
Hispanic	4	(1.5)
Other	1	(0.4)
Age (yrs)		
≤45	108	(40.9)
46-64	77	(29.2)
≥65	79	(29.9)
N	264	
Mean±SD	51.9±17.8	
Range	[redacted]	
Weight (lbs)		
N	253	
Mean±SD	172.3±44.4	
Range	[redacted]	
Missing	11	
Severity		
Severe	46	(17.4)
Mild/Moderate	218	(82.6)
Status		
Inpatient	108	(40.9)
Outpatient	156	(59.1)

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.1.2. Discontinuation/Completion information:

All 264 subjects enrolled in the study received levofloxacin treatment, and, of the 256 subjects with known discontinuation/completion information, 23 (9.0%) subjects discontinued therapy prematurely and 233 (91.0%) subjects completed therapy according to the regimen prescribed by the investigator. Discontinuation/completion information is ho- did not return for the final visit.

Figure 12.1.2.A
Discontinuation/Completion Information:
Modified Intent-to-treat Subjects (Study M92-075)



The most common reasons for discontinuation of treatment were an adverse event or clinical failure.

Table 12.1.2.B
Reasons for Premature Discontinuation:
Modified Intent-to-Treat Subjects (Study M92-075)

	Levofloxacin (N=264)	
Reason	No.	(%)*
Adverse Event	9	(3.5)
Clinical Failure	8	(3.1)
Resistant Pathogen	1	(0.4)
Personal Reason	1	(0.4)
Other[b]	4	(1.6)
Total Discontinued	23	(9.0)
Total with Discontinuation/Completion Information	256	(100.0)
Total with Unknown Discontinuation/Completion Information	8	

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

[b] Subjects [redacted] required treatment with additional antibiotics and were withdrawn from the study after receiving levofloxacin treatment for three and 10 days, respectively. Subject [redacted] was dropped from the study after receiving levofloxacin therapy for one day because the investigator did not consider the infection to be severe enough to warrant participation in the study. Subject [redacted] was withdrawn after seven days of levofloxacin treatment because of persistent pre-existing diarrhea.

2.1.3. Demographic and Baseline Characteristics of Clinically and Microbiologically Evaluable Patients:

Two hundred thirty-four (88.6%) of 264 subjects were clinically evaluable, and 163 (61.7%) subjects were microbiologically evaluable. The main reasons that subjects were not clinically evaluable (were inappropriate clinical evaluation, insufficient course of therapy, and no posttherapy evaluation, whereas the major reason that subjects were not microbiologically evaluable was absence of bacteriologically proven infection.

Table 12.1.3.A
Number of Subjects by Analysis Group and Study Center (Study M92-075)

	Levofloxacin				
Investigator*	Intent-to-Treat	Clinically Evaluable		Microbiologically Evaluable	
Alwine	5	4	(80.0)	4	(80.0)
Carroll	13	9	(69.2)	7	(53.8)
Chattman	24	24	(100.0)	7	(29.2)
Epstein	11	10	(90.9)	7	(63.6)
Faris	9	9	(100.0)	7	(77.8)
Fogarty	68	60	(88.2)	50	(73.5)
Gaman	10	10	(100.0)	2	(20.0)
Grum	14	9	(64.3)	6	(42.9)
Kernodle	4	4	(100.0)	3	(75.0)
Liebhaber	6	6	(100.0)	3	(50.0)
Mogyoros	4	4	(100.0)	4	(100.0)
Nahum	6	4	(66.7)	4	(66.7)
Nelson	7	4	(57.1)	3	(42.9)
Rodman	20	17	(85.0)	10	(50.0)
Rosen	5	5	(100.0)	5	(100.0)
Sullivan	49	47	(95.9)	38	(77.6)
Swezey	4	4	(100.0)	2	(50.0)
Upchurch	5	4	(80.0)	1	(20.0)
Total	**264**	**234**	**(88.6)**	**163**	**(61.7)**

Numbers shown in parentheses are percentages for that category

*Eight investigators (Bjornson, Caldwell, Clover, Cone, Martin, Mehnert-Kay, Schnapp, Smith) did not enroll any subjects. The study was prematurely terminated at one site (Mikolich) for adminstrative reasons and the data from this site are not included

Table 12.1.3.B
Primary Reasons for Clinical or Microbiologic Nonevaluability: Sponsor's Modified Intent-to-Treat Cohort (Study M92-075

Reasons	Levofloxacin (N=264)	
Clinical Efficacy		
Inappropriate Clinical Evaluation	12	
Insufficient Course of Therapy	9	
No Posttherapy Evaluation	7	
Clinical Diagnosis Unconfirmed	1	
Unevaluable for Safety	1	
Total Unevaluable For Clinical Efficacy	30	(11.4%)
Microbiologic Efficacy		
Infection Not Bacteriologically Proven	79	
Inappropriate Clinical Evaluation	11	
Insufficient Course of Therapy	6	
No Posttherapy Evaluation	4	
Unevaluable for Safety	1	
Total Unevaluable For Microbiologic Efficacy	101	(38.3%)

*Subjects only counted once.

The demographic and baseline characteristics of the subjects included in the clinically and microbiologically evaluable groups were comparable to the previously described intent-to-treat group with respect to age, sex, racial composition, and weight. The groups differed slightly in the percentage of inpatient subjects, which was highest in the microbiologically evaluable group (44.2%), followed by the intent-to-treat group (40.9%) and the clinically evaluable group (37.6%). The microbiologically evaluable group also included a slightly higher proportion of subjects with severe infections (22.1%) than the intent-to-treat group (17.4%) and the clinically evaluable group (17.1%).

Table 12.1.3.C
Demographic and Baseline Characteristics:
Sponsor's Clinically and Microbiologically Evaluable Subjects
(Study M92-075)

	Levofloxacin	
	Clinically Evaluable (N=234)	Microbiologically Evaluable (N=163)
Sex		
Men	132	92
Women	102	71
Race		
Caucasian	195	130
Black	34	28
Hispanic	4	4
Other	1	1
Age (Years)		
≤45	97	61
46-64	64	49
≥65	73	53
N	234	163
Mean±SD	52.2±17.8	53.0±18.1
Range	[redacted]	[redacted]
Weight		
N	226	158
Mean±SD	173.5±43.8	168.1±40.8
Range	[redacted]	[redacted]
Missing	8	5
Severity		
Severe	40	36
Mild/Moderate	194	127
Status		
Inpatient	88	72
Outpatient	146	91

NOTE: Values represent numbers of subjects except as otherwise indicated.

12.1.4. Dosage/Extent of Exposure

The mean numbers of days of i.v. and oral levofloxacin therapy were 3.8 and 11.8, respectively, and the mean number of days of total therapy was 12.7. The median numbers of days of i.v., oral, and total therapy were 3, 14, and 14, respectively. Fourteen subjects received levofloxacin therapy for more than 14 days. Eighty-two subjects received both i.v. and oral therapy, nine subjects received only i.v., and 173 subjects received only oral therapy. The mean duration of therapy was 12.7 days for subjects who

received both i.v. and oral therapy, 2.1 days for subjects who received only i.v. therapy, and 13.2 days for subjects who received only oral therapy. Of the 264 subjects, 248 (93.9%) were administered their entire course of levofloxacin therapy at q24h or q48h intervals, and 16 (6.1%) subjects received one or more days of twice-daily dosing. Nineteen subjects had their levofloxacin dosage adjusted at some point during the study. Levofloxacin dosage was increased for 12 subjects and decreased for five subjects; two additional subjects had both increases and decreases in their levofloxacin dosage. Dosage reductions were made because of renal insufficiency (one subject), tolerance problems (one subject), and other reasons (three subjects).

Table 12.1.4
Extent of Exposure to Therapy:
Sponsor's Intent-to-treat Subjects (Study M92-075)

	Route of Therapy[a]		
Extent of Therapy	I.V. (N=91)	Oral (N=255)	Either I.V. or Oral Therapy (N=264)
Days On Therapy[b]			
Unknown	0	6	6
1	5	3	3
2	5	0	3
2.5	2	0	0
3	37	2	4
4	18	6	3
4.5	2	1	0
5	8	1	1
5.5	2	1	0
6	8	3	1
6.5	0	1	0
7	1	9	7
7.5	0	2	0
8	1	12	4
8.5	1	0	0
9	0	10	4
9.5	0	1	0
10	0	29	21
11	1	21	6
11.5	0	1	0
12	0	5	6
13	0	5	13
14	0	126	168
15	0	6	9
17	0	2	2
18	0	1	1
20	0	0	1
28	0	1	1
Mean±SD	3.8±1.64	11.8±3.35	12.7±3.24
Median	3	14	14
Number of Doses[c]			
Total With Dosing Information	91	250	259
Total With Unknown Dosing Information[c]	0	5	5
Mean±SD	4.1±2.4	11.9±3.75	12.9±3.99
Median	3	14	14
Range	[redacted]	[redacted]	[redacted]

[a] Subjects who received both i.v. and oral therapy are included in both categories.
[b] Days on therapy was defined as (last day - first day +1).
[c] One subject had missing data for days on therapy but had data for number of doses.

12.1.5. Concomitant Therapies:

Concomitant therapies administered during the study that were considered to possibly have a clinically relevant interaction with quinolones are summarized in Table 12.1.5, below, along with the total number of subjects who took any concomitant therapy. Two hundred fifty-five (96.6%) subjects took concomitant therapies during the study. Of the concomitant therapies of interest, the most frequently administered agents were central nervous system-acting medications, which were taken by 201 (76.1%) subjects.

Table 12.1.5
Summary of Concomitant Therapies:
Modified Intent-to-Treat Subjects (Study M92-075)

	Levofloxacin (N=264)	
Therapy Classification	No.	%
Total Who Took Any Concomitant Therapy	255	(96.6)
Central Nervous System*	201	(76.1)
Antimicrobials	73	(27.7)
Antacids	43	(16.3)
NSAIDs	40	(15.2)
Bronchodilators	32	(12.1)
Vitamins & Nutritional Supplements	28	(10.6)
Anticoagulants	16	(6.1)
Antidiabetic Therapy	15	(5.7)

* Besides the traditional central nervous system-acting drugs (antipsychotics, antidepressants, antiepileptics, hypnotics, sedatives, antiparkinson agents, opioid analgesics, and anesthetics), other drugs with secondary central nervous system effects were included. See Appendix 10 for complete drug list.

12.2. Clinical Results

This section of the report focuses on results of the secondary efficacy analyses of clinical response, based primarily on the groups of subjects evaluable for clinical and microbiologic efficacy. The results from the other analysis groups were generally consistent with those from the clinically and microbiologically evaluable groups and are provided as attachments in the

12.2.1.. Overall Clinical Response

12.2.1.1 Clinical Response Posttherapy (5 to 7 Days After Completion of Therapy):

The clinical response at the posttherapy visit for subjects who were clinically evaluable is summarized by study center in Table 12.2.1.1.A, on the following page. Among 234 clinically evaluable subjects, 182 (77.8%) were cured and 40 (17.1%) were improved. Twelve (5.1%) subjects failed treatment. Of the 234 clinically evaluable subjects, 220 (94.0%) received levofloxacin treatment at q24h or q48h intervals; clinical response rates for these subjects were cured for 172 (78.2%) subjects, improved for 38 (17.3%) subjects, and failed for 10 (4.5%) subjects. In the microbiologically evaluable group, levofloxacin treatment resulted in 78.5% cure, 17.2% improvement, and 4.3% failure. For the intent-to-treat group, 72.3% were cured, 20.1% were improved, 6.8% failed treatment, and 0.8% of subjects could not be evaluated.

Table 12.2.1.1.A
Clinical Response Rate 5 to 7 Days Posttherapy for Each Study Center: Sponsor's Clinically Evaluable Subjects (Study M92-075)

	Levofloxacin					
Investigator	N	Cured		Improved		Failed	
Alwine	4	4	(100.0)	0	(0.0)	0	(0.0)
Carroll	9	7	(77.8)	2	(22.2)	0	(0.0)
Chattman	24	16	(66.7)	5	(20.8)	3	(12.5)
Epstein	10	2	(20.0)	6	(60.0)	2	(20.0)
Faris	9	6	(66.7)	1	(11.1)	2	(22.2)
Fogarty	60	57	(95.0)	3	(5.0)	0	(0.0)
Gaman	10	9	(90.0)	1	(10.0)	0	(0.0)
Grum	9	7	(77.8)	1	(11.1)	1	(11.1)
Kernodle	4	1	(25.0)	3	(75.0)	0	(0.0)
Liebhaber	6	4	(66.7)	1	(16.7)	1	(16.7)
Mogyoros	4	0	(0.0)	3	(75.0)	1	(25.0)
Nahum	4	3	(75.0)	1	(25.0)	0	(0.0)
Nelson	4	3	(75.0)	0	(0.0)	1	(25.0)
Rodman	17	16	(94.1)	1	(5.9)	0	(0.0)
Rosen	5	2	(40.0)	3	(60.0)	0	(0.0)
Sullivan	47	40	(85.1)	6	(12.8)	1	(2.1)
Swezey	4	2	(50.0)	2	(50.0)	0	(0.0)
Upchurch	4	3	(75.0)	1	(25.0)	0	(0.0)
Total	**234**	**182**	**(77.8)**	**40**	**(17.1)**	**12**	**(5.1)**

Numbers shown in parentheses are percentages for that category.
*A window of 1-10 days posttherapy was used for determination of evaluability.

Furthermore, to provide a dichotomous assessment of clinical response for clinically evaluable subjects, the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success," and the clinical response category "failed" was designated as the category of "Clinical Failure." Among clinically evaluable subjects, levofloxacin treatment resulted in 94.9% clinical success at the posttherapy evaluation. The clinical success rates at the posttherapy visit for subjects who were clinically evaluable is summarized by study center in Table 12.2.1.1.B, on the following page.

Table 12.2.1.1.B
Clinical Success/Failure Rates 5 to 7 Days Posttherapy by Study Center: Sponsor's Clinically Evaluable Subjects (Study M92-075)

	Levofloxacin				
Investigator	N	Success		Failure	
Alwine	4	4	(100.0)	0	(0.0)
Carroll	9	9	(100.0)	0	(0.0)
Chattman	24	21	(87.5)	3	(12.5)
Epstein	10	8	(80.0)	2	(20.0)
Faris	9	7	(77.8)	2	(22.2)
Fogarty	60	60	(100.0)	0	(0.0)
Gaman	10	10	(100.0)	0	(0.0)
Grum	9	8	(88.9)	1	(11.1)
Kemodle	4	4	(100.0)	0	(0.0)
Liebhaber	6	5	(83.3)	1	(16.7)
Mogyoros	4	3	(75.0)	1	(25.0)
Nahum	4	4	(100.0)	0	(0.0)
Nelson	4	3	(75.0)	1	(25.0)
Rodman	17	17	(100.0)	0	(0.0)
Rosen	5	5	(100.0)	0	(0.0)
Sullivan	47	46	(97.9)	1	(2.1)
Swezey	4	4	(100.0)	0	(0.0)
Upchurch	4	4	(100.0)	0	(0.0)
Total	234	222	(94.9)	12	(5.1)

Numbers shown in parentheses are percentages for that category.
*A window of 1-10 days posttherapy was used for determination of evaluability.

12.2.1.2. Clinical Response Poststudy (21 to 28 Days After Completion of Therapy):

The poststudy clinical response for subjects who were clinically and microbiologically evaluable, who had a posttherapy clinical response of cured or improved, and who completed the poststudy evaluation is summarized for each study center in Table 12.2.1.2, on the following page. Of the 152 clinically evaluable subjects who completed the poststudy evaluation and who had a posttherapy clinical response of cured or improved, poststudy clinical responses were cure for 141 (92.8%) subjects, improved for seven(4.6%) subjects, and relapse for four (2.6%) subjects. Improvements in clinical responses from the posttherapy to the poststudy evaluations were noted for the 26 clinically evaluable subjects whose ratings changed from improved to cure. Among the 96 microbiologically evaluable subjects who completed the poststudy evaluation and who had a posttherapy response of cured or improved, poststudy clinical responses were cure for 90 (93.8%) subjects, improved for four (4.2%) subjects, and relapse for two (2.1%) subjects Improvements in clinical responses from the posttherapy to the poststudy evaluations were noted for 19 microbiologically evaluable subjects, whose ratings changed from improved to cure. Poststudy clinical response ratings for intent-to-treat subjects and modified intent-to-treat subjects with an admission pathogen were consistent with results for the clinically and microbiologically evaluable groups.

Table 12.2.1.2
Clinical Response Rate Poststudy (21 to 28 Days Posttherapy)
for Each Study Center:
Clinically and Microbiologically Evaluable Subjects (Study M92-075)

		Clinically Evaluable: Poststudy Response				Microbiological Evaluable: Poststudy Response			
Investigator	Posttherapy Response	N	Cured	Improved	Relapse	N	Cured	Improved	Relapse
Alwine	Cured	2	2	0	0	2	2	0	0
Carroll	Cured	5	5	0	0	3	3	0	0
	Improved	2	2	0	0	2	2	0	0
Chettman	Cured	16	16	0	0	4	4	0	0
	Improved	4	3	0	1	2	1	0	1
Epstein	Cured	1	1	0	0	1	1	0	0
	Improved	6	5	1	0	5	4	1	0
Faris	Cured	6	6	0	0	5	5	0	0
Fogarty	Cured	52	52	0	0	43	43	0	0
	Improved	3	2	1	0	2	2	0	0
Gaman	Cured	9	9	0	0	1	1	0	0
	Improved	1	1	0	0	1	1	0	0
Grum	Cured	1	1	0	0	0	0	0	0
Kernodle	Cured	1	1	0	0	1	1	0	0
	Improved	3	3	0	0	2	2	0	0
Liebhaber	Cured	4	4	0	0	1	1	0	0
	Improved	1	0	1	0	1	0	1	0
Mogyoros	Improved	3	1	2	0	3	1	2	0
Nahum	Cured	1	1	0	0	1	1	0	0
Nelson	Cured	1	1	0	0	1	1	0	0
Rodman	Cured	1	0	0	1	0	0	0	0
	Improved	1	0	1	0	0	0	0	0
Rosen	Cured	1	1	0	0	1	1	0	0
	Improved	3	3	0	0	3	3	0	0
Sullivan	Cured	14	12	0	2	8	7	0	1
	Improved	5	5	0	0	3	3	0	0
Swezey	Improved	2	1	1	0	0	0	0	0
Upchurch	Cured	3	3	0	0	0	0	0	0
Total	**Cured**	**118**	**115**	**0**	**3**	**72**	**71**	**0**	**1**
	Improved	**34**	**26**	**7**	**1**	**24**	**18**	**4**	**1**

NOTES: Data are presented for subjects who were evaluable for efficacy, had a posttherapy clinical response of cured or improved, and had their clinical response evaluated at the poststudy visit. One exception is Subject [redacted] (Investigator Sullivan), who had posttherapy and poststudy clinical responses of cured and reinfection, respectively; this subject not included in the summary. Of the 221 clinically evaluable subjects (excluding Subject [redacted]) who had posttherapy clinical responses of cured or improved, 69 subjects did not have a poststudy visit; this included 59 subjects who had a poststudy telephone contact that did not indicate relapse, and 10 subjects who were lost to follow-up. Of the 155 microbiologically evaluable subjects (excluding Subject [redacted]) who had posttherapy clinical responses of cured or improved, 59 subjects did not have a poststudy visit; this included 52 subjects who had a posttherapy telephone contact that did not indicate relapse, and seven subjects who were lost to follow-up.

12.2.2. Clinical Relapse Poststudy (21 to 28 Days After Completion of Therapy):

Four clinically evaluable subjects had a relapse poststudy. Three of these subjects had a posttherapy response of cured, and one had a posttherapy response of improved. Two of these subjects had a posttherapy microbiologic response of eradicated, and two were microbiologically unevaluable at posttherapy. Both of the subjects who were microbiologically evaluable at posttherapy evaluation had poststudy microbiologic responses of persistence. In the microbiologically evaluable subjects, the admission pathogens were *Escherichia coli* and *C. pneumoniae* (Subject [redacted] and *Moraxella (Branhamella) catarrhalis* (Subject [redacted].

Table 12.2.2
Subjects With a Poststudy (21 to 28 Days Posttherapy)
Clinical Response of Relapse:
Sponsor's Clinically Evaluable Cohort (Study M92-075)

Subject	Investigator	Admission Pathogen	Clinical Response at Posttherapy	Microbiologic Response at Posttherapy
	Chattman	*Escherichia coli*	Improved	Eradicated
		Chlamydia pneumoniae	Improved	Eradicated
	Rodman	None	Cure	Unevaluable
	Sullivan	*Moraxella (Branhamella) catarrhalis*	Cure	Eradicated
	Sullivan	None	Cure	Unevaluable

Subject [redacted] (Investigator Sullivan) had a poststudy response that was categorized as "reinfection." This subject had pneumonia caused by *M. (Branhamella) catarrhalis*, which was diagnosed from a culture of respiratory secretions taken at admission and was susceptible to levofloxacin. At the posttherapy evaluation, no specimen was available for culture, and the subject was assigned a clinical response of cure and a microbiologic response of eradicated. At the poststudy evaluation, the subject was noted to have chills, chest pain, dyspnea, and cough, all of which were absent at the posttherapy evaluation. A culture of respiratory secretions revealed *H. parainfluenzae*. Based on these findings, the subject was assigned a poststudy clinical response of reinfection.

12.2.3. Clinical Response by Pathogen

C. pneumoniae, *H. influenzae*, and *S. pneumoniae* were the most prevalent pathogens. Clinical success rates, i.e., percentages with clinical responses of cured or improved, ranged from 83.3% (*S. aureus*) to 100.0% (*S. pneumoniae*, *M. catarrhalis*, *K. pneumoniae*, and *E. coli*) for all prevalent pathogens isolated from respiratory or blood cultures. Clinical success rates for atypical pathogens ranged from 80.0%(*L. pneumophila*) to 100.0% (*M. pneumoniae*). The posttherapy clinical response rates by pathogen for the clinically evaluable and intent-to-treat groups, as well

as for modified intent-to-treat subjects with an admission pathogen, were consistent with the results for the microbiologically evaluable group. In general, for each analysis group, poststudy clinical response—rates of cure or improved by pathogen were similar to or higher than the respective posttherapy response rates.

Table 12.2.3
Clinical Response Rates 5 to 7 Days Posttherapy
Summarized by Method of Evaluation and Prevalent Pathogens:
Sponsor's Clinically Evaluable Subjects (Study M92-075)

Method of Evaluation/Pathogen[b]	Levofloxacin			
	N[c]	Cured	Improved	Failed
Respiratory Cultures				
Haemophilus influenzae	39	29 (74.4)	9 (23.1)	1 (2.6)
Streptococcus pneumoniae	34	28 (82.3)	6 (17.6)	0 (0.0)
Staphylococcus aureus	12	10 (83.3)	0 (0.0)	2 (16.7)
Moraxella (Branhamella) catarrhalis	11	10 (90.9)	1 (9.0)	0 (0.0)
Haemophilus parainfluenzae	9	6 (66.7)	2 (22.2)	1 (11.1)
Klebsiella pneumoniae	7	7 (100.0)	0 (0.0)	0 (0.0)
Escherichia coli	5	4 (80.0)	1 (20.0)	0 (0.0)
Blood Cultures				
Streptococcus pneumoniae	10	8 (80.0)	2 (20.0)	0 (0.0)
Serology/Other Diagnostic Procedures				
Chlamydia pneumoniae	75	60 (80.0)	11 (14.7)	4 (5.3)
Mycoplasma pneumoniae	10	7 (70.0)	3 (30.0)	0 (0.0)
Legionella pneumophila	5	3 (60.0)	1 (20.0)	1 (20.0)
Total Evaluable for Microbiologic Efficacy	163	128 (78.5)	28 (17.2)	7 (4.3)

Numbers shown in parentheses are percentages for that category.

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] The most prevalent pathogens (N≥5) are presented in this summary for each method of evaluation.
[c] N=number of subjects who had that pathogen, alone or in combination with other pathogens.

12.2.4. Clinical Response by Severity of Infection

One hundred twenty-seven (77.9%) of the 163 microbiologically evaluable subjects had mild/moderate infections and 36 (22.1%) had severe infections. Similar proportions of subjects with mild/moderate and severe infections had posttherapy clinical response ratings of cure (78.0% and 80.6%, respectively), improved (17.3% and 16.7%, respectively), and failed (4.7% and 2.8%, respectively). Clinical response by severity of infection is summarized for the sponsor's clinically evaluable subjects in Table 12.2.4, on the following page.

Table 12.2.4
Clinical Response 5 to 7 Days Posttherapy
Summarized by Severity of Infection:
Sponsor's Clinically Evaluable Subjects (Study M92-075)

	Levofloxacin					
	N	Cured		Improved		Failed	
Severe	36	29	(80.6)	6	(16.7)	1	(2.8)
Mild/Moderate	127	99	(78.0)	22	(17.3)	6	(4.7)
Total	163	128	(78.5)	28	(17.2)	7	(4.3)

Numbers shown in parentheses are percentages for that category.

* A window of 1-10 days posttherapy was used for determination of evaluability.

12.2.5. Clinical Signs and Symptoms

The proportions of clinically and microbiologically evaluable subjects with resolution of clinical symptoms of pneumonia were based on the posttherapy assessment of the subjects 5 to 7 days after completion of therapy. Levofloxacin treatment resulted in a clearing of chills, pleuritic chest pain, and purulent sputum in at least 87.6% of the clinically and microbiologically evaluable subjects, whereas shortness of breath and cough resolved in at least 73.2% and 50.6%, respectively, of subjects.

Table 12.2.5.A
Subjects with Resolution of Clinically Symptoms of Pneumonia
at Posttherapy Evaluation: Sponsor's Clinically
and Microbiologically Evaluable Subjects (Study M92-075)

	Clinically Evaluable		Microbiologically Evaluable	
Symptom	Resolved*		Resolved*	
Chills	162/165	(98.2)	113/114	(99.1)
Pleuritic Chest Pain	109/122	(89.3)	78/89	(87.6)
Shortness of Breath	136/178	(76.4)	93/127	(73.2)
Cough	118/233	(50.6)	86/162	(53.1)
Purulent Sputum	176/199	(88.4)	127/142	(89.4)

Numbers shown in parentheses are percentages for that category.

* Symptom present at admission and absent at posttherapy assessment.
† Denominator represents the number of subjects with that symptom at admission.

A trend toward improvement was evident for all positive admission chest examination findings, with at least 88.0% of subjects showing resolution or improvement in clinical signs of pneumonia at the posttherapy chest examination 5 to 7 days after completion of therapy.

Table 12.2.5.B
Proportion of Subjects with Resolution or Improvement of Pneumonia Based on the Posttherapy Chest Examination: Sponsor's Clinically and Microbiologically Evaluable Subjects (Study M92-075)

	Clinically Evaluable				Microbiologically Evaluable			
Sign	Resolved[a]		Improved[a]		Resolved[a]		Improved[a]	
Diminished Breath Sounds	58/74	(78.4)	10/74	(13.5)	35/50	(70.0)	9/50	(18.0)
Rales	170/187	(90.9)	11/187	(5.9)	122/134	(91.0)	9/134	(6.7)
Egophony	28/30	(93.3)	1/30	(3.3)	20/21	(95.2)	1/21	(4.8)
Rhonchi	102/112	(91.1)	5/112	(4.5)	72/78	(92.3)	5/78	(6.4)
Wheezes	69/75	(92.0)	3/75	(4.0)	46/51	(90.2)	2/51	(3.9)

Numbers shown in parentheses are percentages for that category.
[a] Sign present at admission (mild, moderate, or severe) and absent (none) at posttherapy evaluation.
[b] Signs were graded 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 at admission.

Table 12.2.5.C
Subjects with Resolution or Improvement in Abnormal Admission Chest X-Ray Findings: Sponsor's Clinically and Microbiologically Evaluable Subjects (Study M92-075)

	Clinically Evaluable		Microbiologically Evaluable	
Posttherapy Radiographic Findings	Resolved (%)	Improved (%)	Resolved (%)	Improved (%)
All Subjects:				
Infiltrate Present at Admission	159/231 (68.8)	61/231 (26.4)	109/161 (67.1)	45/161 (28.0)
Subjects with C. Pneumoniae:				
Infiltrate Present at Admission	52/74 (70.3)	18/74 (24.3)	52/74 (70.3)	18/74 (24.3)

Numbers shown in parentheses are percentages for that category.
[a] Abnormal findings were graded as resolved, improved, no change, or worsened at the posttherapy evaluation. Data are presented for clinically or microbiologically evaluable subjects who had infiltrates at admission and who had radiographic findings reported posttherapy. Data for three of 234 clinically evaluable subjects have been excluded: Subject [redacted] did not have an infiltrate at admission, and Subjects [redacted] and [redacted] did not have radiographic findings reported at posttherapy. Two of these subjects [redacted] and [redacted] were microbiologically evaluable; therefore, data are presented for 161 of 163 microbiologically evaluable subjects. One of these subjects [redacted] was infected with *C. pneumoniae*; therefore, data are presented for 74 of 75 clinically and microbiologically evaluable subjects who were infected with *C. pneumoniae*.

12.3. Microbiologic Results

Microbiologic response was the primary efficacy variable in this study. The analyses of microbiologic response, based primarily on the group of subjects evaluable for microbiologic efficacy, are presented in detail in this section, with results of other analysis groups provided in the Supporting Data section at the end of the text and briefly described here. The results from the other analysis groups were generally consistent with those from the microbiologically evaluable group.

12.3.1. *In Vitro* Susceptibility:

Susceptibility to levofloxacin was determined for all aerobic pathogens, except *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*. One hundred eighty-four subjects had pathogens isolated in respiratory or blood cultures at admission. The 184 subjects had 176 pathogens with known

Table 12.3.2.1
Microbiologic Eradication Rates (5 to 7 Days Posttherapy):[a] Sponsor's Microbiologically Evaluable Patients (Study M92-075)

	Levofloxacin						
Investigator	N	Eradicated[c]		Persisted[c]		Unknown[c]	
Alwine	4	4	(100.0)	0	(0.0)	0	(0.0)
Carroll	7	7	(100.0)	0	(0.0)	0	(0.0)
Chattman	7	6	(85.7)	1	(14.3)	0	(0.0)
Epstein	7	6	(85.7)	1	(14.3)	0	(0.0)
Faris	7	6	(85.7)	1	(14.3)	0	(0.0)
Fogarty	50	50	(100.0)	0	(0.0)	0	(0.0)
Gaman	2	2	(100.0)	0	(0.0)	0	(0.0)
Grum	6	5	(83.3)	1	(16.7)	0	(0.0)
Kernodle	3	3	(100.0)	0	(0.0)	0	(0.0)
Liebhaber	3	2	(66.7)	1	(33.3)	0	(0.0)
Mogyoros	4	2	(50.0)	2	(50.0)	0	(0.0)
Nahum	4	4	(100.0)	0	(0.0)	0	(0.0)
Nelson	3	2	(66.7)	1	(33.3)	0	(0.0)
Rodman	10	10	(100.0)	0	(0.0)	0	(0.0)
Rosen	5	5	(100.0)	0	(0.0)	0	(0.0)
Sullivan	38	38	(100.0)	0	(0.0)	0	(0.0)
Swezey	2	2	(100.0)	0	(0.0)	0	(0.0)
Upchurch	1	1	(100.0)	0	(0.0)	0	(0.0)
Total	**163**	**155**	**(95.1)**	**8**	**(4.9)**	**0**	**(0.0)**

[a] Eradication of all pathogens isolated for a subject at admission.
[b] A window of 1-10 days posttherapy was used for determination of evaluability.
[c] Numbers shown in parentheses are percentages for that category.

12.3.2.2. Microbiologic Eradication Rates by Pathogen

For all microbiologically evaluable subjects, the microbiologic eradication rates ranged from 83.3% to 100.0% for prevalent pathogens detected in respiratory cultures. Levofloxacin treatment eradicated 100.0% of *S. pneumoniae* detected in blood cultures, and from 80.0% to 100.0% of atypical pathogens diagnosed by serology or other diagnostic procedures. The microbiologic eradication rates for *C. pneumoniae*, *H. influenzae*, *S. pneumoniae* (detected in respiratory secretions), *S. aureus*, and *B. catarrhalis*, the most prevalent pathogens, were 94.7%, 97.4%, 97.1%, 83.3%, and 100.0%, respectively. Microbiologic eradication rates posttherapy for the clinically evaluable subjects were similar to those for the microbiologically evaluable subjects. For all efficacy analysis groups, microbiologic eradication rates poststudy were similar to or higher than the corresponding rates posttherapy. The posttherapy responses were comparable across the various sex, age, and race subgroups. These results are summarized in Table 12.3.2.2, on the following page.

Table 12.3.2.2.
Clinical Response 5 to 7 Days Posttherapy
Summarized by Method of Evaluation and Prevalent Pathogens:
Microbiologically Evaluable Subjects (Study M92-075)

Method of Evaluation/Pathogen[b]	Levofloxacin			
	N[c]	Cured	Improved	Failed
Respiratory Cultures				
Haemophilus influenzae	39	29 (74.4)	9 (23.1)	1 (2.6)
Streptococcus pneumoniae	34	28 (82.3)	6 (17.6)	0 (0.0)
Staphylococcus aureus	12	10 (83.3)	0 (0.0)	2 (16.7)
Moraxella (Branhamella) catarrhalis	11	10 (90.9)	1 (9.0)	0 (0.0)
Haemophilus parainfluenzae	9	6 (66.7)	2 (22.2)	1 (11.1)
Klebsiella pneumoniae	7	7 (100.0)	0 (0.0)	0 (0.0)
Escherichia coli	5	4 (80.0)	1 (20.0)	0 (0.0)
Blood Cultures				
Streptococcus pneumoniae	10	8 (80.0)	2 (20.0)	0 (0.0)
Serology/Other Diagnostic Procedures				
Chlamydia pneumoniae	75	60 (80.0)	11 (14.7)	4 (5.3)
Mycoplasma pneumoniae	10	7 (70.0)	3 (30.0)	0 (0.0)
Legionella pneumophila	5	3 (60.0)	1 (20.0)	1 (20.0)
Total Evaluable for Microbiologic Efficacy	163	128 (78.5)	28 (17.2)	7 (4.3)

Numbers shown in parentheses are percentages for that category.

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] The most prevalent pathogens (N≥5) are presented in this summary for each method of evaluation.
[c] N=number of subjects who had that pathogen, alone or in combination with other pathogens.

12.3.2.3. Clinical Response by Severity of Infection

One hundred twenty-seven (77.9%) of the 163 microbiologically evaluable subjects had mild/moderate infections and 36 (22.1%) had severe infections.

Table 12.3.2.3.
Microbiologic Eradication Rates 5 to 7 Days Posttherapy
Summarized by Severity of Infection:
Sponsor's Microbiologically Evaluable Subjects (Study M92-075)

	Levofloxacin					
	N	Eradicated[b]		Persisted[b]		Unknown[b]	
Severe							
Total Severe by Pathogen	69	68	(98.6)	1	(1.4)	0	(0.0)
Total Severe by Subject	36	35	(97.2)	1	(2.8)	0	(0.0)
Mild/Moderate							
Total Mild/Moderate by Pathogen	182	172	(94.5)	9	(4.9)	1	(0.5)
Total Mild/Moderate by Subject	127	120	(94.5)	7	(5.5)	0	(0.0)
Overall Total							
Total by Pathogen	251	240	(95.6)	10	(4.0)	1	(0.4)
Total by Subject	163	155	(95.1)	8	(4.9)	0	(0.0)

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Numbers shown in parentheses are percentages for that category.

12.3.3. Superinfection:

Three subjects treated with levofloxacin developed superinfections. Table 12.3.3 lists key information, including pathogen and susceptibility results, for the three subjects. The organism causing the superinfection of one of these subjects was resistant to levofloxacin. For Subject [redacted] bilateral sinusitis was confirmed by sinus X-ray, and the organism causing the superinfection was not isolated.

Table 12.3.3
List of Subjects with Superinfections:
Sponsor's Modified Intent-to-Treat Cohort (Study M92-075)

Subject Number	Period	Pathogen	Source	Susceptibility Levofloxacin
Levofloxacin				
	Posttherapy	Herpes Simplex Type 2	Skin & Skin Tissue/Exudate Culture	Not Done
	Posttherapy	*Staphylococcus aureus*	Skin & Skin Tissue/Exudate Culture	Resistant
	Unknown	Unknown	—	Not Done

[a] Bilateral sinusitis confirmed by sinus X-rays; culture and susceptibility testing not done.

12.4. Sponsor's Summary of Key Efficacy Results

The posttherapy clinical responses to levofloxacin treatment were evaluated for the modified intent-to-treat subjects with an admission pathogen, clinically evaluable group, and microbiologically evaluable group, and the posttherapy microbiologic responses for modified intent-to-treat subjects with an admission pathogen and microbiologically evaluable subjects and are summarized in the table below. Within response category (clinical or microbiologic), the results are comparable between the analysis groups. Moreover, there is concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response for microbiologically evaluable subjects, further confirming the consistency and reliability of the clinical and microbiologic responses. The clinical and microbiologic results demonstrate that levofloxacin is effective in the treatment of community-acquired pneumonia. The major clinical and microbiological efficacy results are summarized in Table 12.4, below.

Table 12.4
Summary of Key Efficacy Results:
Sponsor's Clinically and Microbiologically Evaluable Subjects
(Study M92-075)

Clinical and Microbiologic Response 5 to 7 Days Posttherapy [a]

Response/Group	Levofloxacin Clinical Success or Microbiologic Eradication Rate (Posttherapy)[b]
Clinical Response	
Clinically Evaluable	222/234 (94.9)
Microbiologically Evaluable	156/163 (95.7)
Modified Intent-to-Treat Subjects with an Admission Pathogen	173/184 (94.0)
Microbiologic Response	
Microbiologically Evaluable	155/163 (95.1)
Modified Intent-to-Treat Subjects With an Admission Pathogen	165/184 (89.7)

Microbiologic Response Versus Clinical Response 5 to 7 Days Posttherapy [a,c]

Microbiologic Response	N	Clinical Response Cured[d]	Improved[d]	Failed[d]
Eradicated	155	128 (82.6)	27 (17.4)	0 (0.0)
Persisted	8	0 (0.0)	1 (12.5)	7 (87.5)
Total Evaluable	163	128 (78.5)	28 (17.2)	7 (4.3)

NOTES: Numbers shown in parentheses are percentages for that category.

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

[a] A window of 1-10 days posttherapy was used for determination of evaluability.
[b] Denominator for clinical success rate = cured + improved + failed + unable to evaluate. Denominator for microbiologic eradication rate = eradication + persistence + unknown.
[c] Based on microbiologically evaluable subgroup.
[d] Cured, improved, or failed are clinical response outcomes.

13. Efficacy as per Medical Officer:

13.1.1. Patient Population:

Of the sponsor's intent-to-treat cohort, the medical officer considered 82% (217/264) clinically evaluable. Of these 217 clinically evaluable patients, the medical officer determined that 78% (170/217) of these were microbiologically evaluable and 22% (47/217) were microbiologically unevaluable. The reasons for both clinical and microbiologic nonevaluability are summarized in a series of tables under section 13.1.2. The breakdown of the intent-to-treat cohort into evaluable subgroups is summarized in Table 13.1.1.A and 13.1.1.B, below.

Table 13.1.1
FDA Clinically and Microbiologically Evaluable Patients:
Subgroups of Sponsor's Intent-to-treat Cohort (Study M92-075)

FDA Clinically Evaluable		FDA Clinically Nonevaluable	
FDA Microbiologically Evaluable N (%)	FDA Microbiologically Nonevaluable N(%)	FDA Microbiologically Evaluable N(%)	FDA Microbiologically Nonevaluable N(%)
170/217 (78%)	47/217 (22%)	0/264 (0%)	47/264 (18%)
FDA Clinically Evaluable 217/264 (82%)		FDA Clinically Nonevaluable 47/264 (18%)	
Intent-to-treat Cohort 264			

Table 13.1.1.B
FDA Clinically and Microbiologically Evaluable Patients: Subgroups of Sponsor's Intent-to-treat Cohort (Protocol M92-075)

Intent-to-treat Cohort
264 (100%)

Levofloxacin ALL DOSES 264/264 (100%)
Levofloxacin QD 248/264 (94%)
Levofloxacin BID 16/264 (6%)

FDA Clinically Evaluable 217/264 (82%)		FDA Clinically Nonevaluable 47/264 (18%)	
Levofloxacin ALL DOSES 217/264 (82%) Levofloxacin QD 203/264 (77%) 203/217 (94%) Levofloxacin BID 14/264 (5%) 14/217 (6%)		Levofloxacin ALL DOSES 47/264 (18%) Levofloxacin QD 45/264 (17%) 45/47 (96%) Levofloxacin BID 2/264 (<1%) 2/47 (4%)	
FDA Microbiologically Evaluable 170/264 (64%)	**FDA Microbiologically Nonevaluable 47/264 (18%)**	**FDA Microbiologically Evaluable**	**FDA Microbiologically Nonevaluable 47/264 (18%)**
Levofloxacin ALL DOSES 170/264 (64%) 170/217 (78%) Levofloxacin QD 161/217 (74%) 161/170 (95%) Levofloxacin BID 9/217 (4%) 9/170 (5%)	Levofloxacin ALL DOSES 47/264 (18%) 47/217 (22%) Levofloxacin QD 42/217 (19%) 42/47 (89%) Levofloxacin BID 5/217 (2%) 5/47 (11%)	0/264 (0%)	Levofloxacin ALL DOSES 47/264 (18%) Levofloxacin QD 45/264 (17%) 45/47 (96%) Levofloxacin BID 2/264 (<1%) 2/47 (4%)

13.1.2. Demographics of FDA Clinically and Microbiologically Evaluable Cohorts

Of the 217 patients in the FDA clinically evaluable patient cohort, 126 (58%) were male and 91 (32%) were female. In the cohort of 170 patients who were both clinically and microbiologically evaluable, there were 96 (56%) males and 74 (44%) females. These are similar to the gender distribution found in the intent-to-treat cohort, as summarized in Table 12.1.2. The distribution among racial groups and age ranges was similar for both the clinically and clinically/microbiologically evaluable cohorts, and these were similar to the demographics of the intent- to-treat cohort. The demographics of the clinically and clinically/microbiologically evaluable cohorts are summarized in Table 13.1.2.A, below.

Table 13.1.2.A
Demographic and Baseline Characteristics:
FDA Clinically And Microbiologically Evaluable Cohorts (Study M92-075)

		FDA Clinically Evaluable Patients N (%)	FDA Clinically and Microbiologically Evaluable Patients N (%)
TOTAL		217	170/217 (78%)
Sex	M	126/217 (58%)	96/170 (56%)
	F	91/217 (32%)	74/170 (44%)
Race	Caucasian	182/217 (84%)	137/170 (80%)
	Black	30/217 (14%)	38/170 (22%)
	Hispanic	4/217 (2%)	4/170 (2%)
	Asian	1/217 (<1%)	1/170 (<1%)
Age (yrs)	≤45	92/217 (42%)	68/170 (40%)
	46-64	61/217 (28%)	51/170 (30%)
	≥65	64/217 (30%)	51/170 (30%)

13.1.3. Reasons for Nonevaluability

13.1.3.1. Reasons for Clinical Nonevaluability

Of the sponsor's intent-to-treat cohort, the medical officer considered 18% (47/264) clinically unevaluable. The reasons for nonevaluability are summarized in the Table 13.1.3.1.A, on the following page. The main reasons for clinical nonevaluablility were (1) inappropriate clinical evaluation date, (2) lost to follow-up, and (3) insufficient course of therapy.

Table 13.1.3.1.A
Reasons for Clinical Nonevaluability:
ALL FDA Nonevaluable Patients (Protocol M92-075)

Reason for Nonevaluability	Total N	
Inappropriate clinical evaluation date	12	Includes those with early EOT visit and no EOS visit
AIDS or HIV Seropositivity	4	
Drug therapy Insufficient Course of therapy Concomitant Antibiotic Therapy Multiple Missed Doses	 8 6 3	 Missed more than two doses of study drug
Clinical Diagnosis Unconfirmed	1	
Lost to Follow-up	8	
Protocol violation Creatinine Clearance	 5	 1. Protocol-specified dosage adjustment for CrCl ≤50 mL/min was not implemented. 2. Baseline CrCl ≤20mL/min
TOTAL Reasons **TOTAL Patients**	**47** **47**	

Of the 47 patients considered clinically nonevaluable by the medical officer, the medical officer differed with the sponsor's assessment in 40% (19/47) of the cases (i.e., the patient was considered clinically evaluable by the sponsor, but not by the medical officer). The reasons for clinical nonevaluability in this subgroup of patients are summarized in Table 13.1.3.1.B, below.

Table 13.1.3.1.B.
Reasons for Clinical Nonevaluability:
Patients Evaluable by Sponsor but Nonevaluable by FDA (Protocol M92-075)

Reason for Nonevaluability	Total N	Subgroups of Reasons for Nonevaluability
AIDS or HIV Seropsitivity	4	
Protocol violation Creatinine Clearance	 5	 1. Protocol-specified dosage adjustment for CrCl ≤50 mL/min was not implemented. 2. Baseline CrCl ≤20mL/min
Drug therapy Concomitant Antibiotic Therapy Multiple Missed Doses	 6 3	
Inappropriate clinical evaluation date	1	Early EOT visit with no EOS visit
TOTAL Reasons **TOTAL Patients**	**19** **19**	

13.1.3.2. Reasons for Microbiologic Nonevaluability

Of the 264 patients in the intent-to-treat cohort, the medical officer determined that 18% (47/264) of these were clinically, but not microbiologically, evaluable, and 18% (47/264) were neither clinically nor microbiologically evaluable. Thus, a total of 36% (94/264) were microbiologically unevaluable. The main reasons for microbiologic nonevaluablility were (1) no pathogen isolated on admission culture, (2) inappropriate bacteriologic culture, and (3) insufficient course of therapy. The reasons for microbiologic nonevaluability for each of these subgroups are as summarized in the Table 13.1.3.2.A, below.

Table 13.1.3.2.A
Reasons for FDA Microbiologic Nonevaluability:
All Admission Pathogens (Protocol M92-075)

	FDA Clinically Evaluable/ Microbiologically Unevaluable	FDA Clinically and Microbiologically Unevaluable
No Admission Pathogen	45	15
Drug Therapy		
Insufficient duration of therapy	--	5
Concomitant antibiotic therapy	--	4
Inappropriate Clinical Evaluation Date		
Early EOT visit with no EOS visit	--	1
Lost to Follow-up	--	4
Protocol Violation		
Inappropriate bacteriologic culture	--	10
Missed more than 2 doses	--	2
Creatinine clearance**	--	3
AIDS or HIV seropositivity	--	3
Residual sputum at posttherapy visit not cultured	2	--
Total Microbiologically Nonevaluable Patients	47	47
	94	

** Protocol violation of either (1) Protocol-specified dosage adjustment for CrCl ≤50 mL/min was not implemented, OR (2) baseline CrCl ≤20mL/min

Of the 94 patients considered microbiologically nonevaluable by the medical officer, the medical officer differed with the sponsor's assessment in 16% (15/94) of the cases (i.e., the patient was considered microbiologically evaluable by the sponsor, but not by the medical officer). The reasons for microbiologic nonevaluability in this subgroup of patients are summarized in Table 13.1.3.2.B, on the following page.

Table 13.1.3.2.B.
Reasons for Clinical Nonevaluability:
Patients Evaluable by Sponsor but Nonevaluable by FDA (Protocol M92-075)

Reason for Nonevaluability	Total N	Subgroups of Reasons for Nonevaluability
Residual Sputum at EOT never cultured	4	
AIDS or HIV Seropsitivity	3	
Protocol violation Creatinine Clearance**	3	
Drug therapy Concomitant Antibiotic Therapy Multiple Missed Doses	4 2	
Inappropriate clinical evaluation date	1	Early EOT visit with no EOS visit
TOTAL Reasons TOTAL Patients	17 15	

** Protocol violation of either (1) Protocol-specified dosage adjustment for CrCl ≤50 mL/min was not implemented, OR (2) baseline CrCl ≤20mL/min

13.2. Clinical Efficacy as per Medical Officer:

Using the medical officer's clinical evaluability criteria delineated in Section 10.2.1 of this review, a total of 217 clinically evaluable patients were selected from the intent-to-treat cohort. As discussed earlier in this review, the investigators were given the option of increasing the dosage of levofloxacin to 500 mg BID for cases of severe community-acquired pneumonia. Of the 217 clinically evaluable patients, 203 received levofloxacin 500 mg QD and 14 received levofloxacin 500 mg BID. The analysis of efficacy was conducted on the subgroup of patients who received levofloxacin 500 mg QD, as this was the dose and duration requested by the sponsor in the proposed labeling. Those patients who were treated with levofloxacin 500 mg BID are included in the tables for the purpose of completeness, but the total number of patients was too small to allow for any definitive conclusions to be drawn from this dosing group.

13.2.1. Clinical Cure Rates as per Medical Officer:

The overall cure rate at the posttherapy evaluation was 52% (105/203) for those patients treated with levofloxacin 500 mg QD. Cure rates by investigator are summarized in Table 13.2.1.A, on the following page. Note the variability in cure rates across study centers.

Table 13.2.1.A
Posttherapy Clinical Cure Rates By Investigator:
Levofloxacin 500 mg QD and Levofloxacin 500 mg QD BID
FDA Clinically Evaluable Subjects with (Study M92-075)

	Levofloxacin 500 mg QD				Levofloxacin 500 mg BID			
Investigator	N	Cure	Improve	Fail	N	Cure	Improve	Fail
Carroll	4	2 (50)	2 (50)	0 (0)	4	2 (50)	2 (50)	0 (0)
Chattman	18	11 (61)	6 (33)	1 (6)	6	3 (50)	1 (17)	2 (33)
Fogarty	50	19 (38)	31 (62)	0 (0)	---	---	---	---
Gaman	10	5 (50)	5 (50)	0 (0)	4	1 (25)	3 (75)	0 (0)
Grum	11	7 (64)	2 (18)	2 (18)	---	---	---	---
Rodman	14	6 (43)	8 (57)	0 (0)	---	---	---	---
Sullivan	41	31 (76)	9 (22)	1 (2)	---	---	---	---
Other	55	24 (44)	20 (37)	11 (19)	---	---	---	---
Total	203	105 (52)	83 (41)	15 (7)	14**	6 (43)	6 (43)	2 (14)

Results are presented for investigators with 10 or more evaluable patients in each treatment group, with the exception of Dr. Carroll, who is presented because of his large contribution of patients to the BID dosing cohort. All other investigators are combined under "other".
*N=Number of patients in that category. Numbers shown in parentheses are percentages for that category.
**14/225 (6%) of levofloxacin-treated patients were treated with levofloxacin 500 mg BID

13.2.2. Clinical Success Rates as per Medical Officer:

The clinical success rate is defined as the combined rate of patients clinically "cured" or "improved" at the follow-up evaluation. Using this definition, the overall clinical success rate was 93% (188/203) for the levofloxacin-QD-treated cohort, and 86% (12/14) for the levofloxacin-BID-treated cohort. Clinical success rates by investigator for levofloxacin-treated patients are summarized in Table 13.2.2.A, below.

Table 13.2.2.A
Posttherapy Clinical Success Rates By Investigator:
Levofloxacin 500 mg QD and Levofloxacin 500 mg QD BID
FDA Clinically Evaluable Subjects (Study M92-075)

	Levofloxacin 500 mg QD		Levofloxacin 500 mg BID	
Investigator	N	Success*	N	Success*
Chattman	18	17 (94)		
Fogarty	50	50 (100)		
Gaman	10	10 (100)		
Grum	11	9 (82)		
Rodman	14	14 (100)		
Sullivan	41	40 (98)		
Other	59	48 (81)		
Total	203	188 (93)	14	12 (86)

Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other".
*Clinical success is defined as either clinical cure or clinical improvement.
Numbers shown in parentheses are percentages for that category.

13.2.3. Clinical Cure Rates by Pathogen:

Using the medical officer's clinical and microbiologic evaluability criteria delineated in Sections 10.2.1 and 10.2.2 of this review, a total of 133 patients were both clinically and microbiologically evaluable. It is this subgroup on which the following analysis is based.

The clinical cure rates by pathogen for levofloxacin-QD-treated patients are summarized in comparison to ceftriaxone/cefuroxime-treated patients in Table 13.2.3.A, below.

Table 13.2.3.A
Poststudy Clinical Cure Rates for Subjects with Pathogens of Primary Interest:
Levofloxacin 500 mg QD
FDA Clinically Evaluable Subjects (Study M92-075)

Pathogen	Levofloxacin 500 mg QD							
	N[a]	Cure		Improve		Fail	
Routine Bacterial Pathogens							
Haemophilus influenzae	29	17	(59)	9	(31)	3	(10)
Haemophilus parainfluenzae	11	5	(45)	5	(45)	1	(9)
Klebsiella pneumoniae	5	4	(80)	1	(20)	0	(0)
Moraxella (Branhamella) catarrhalis	11	9	(82)	1	(9)	1	(9)
Staphylococcus aureus	11	7	(64)	1	(9)	3	(27)
Streptococcus pneumoniae	34	12	(35)	30	(88)	4	(12)
Other Pathogens							
Chlamydia pneumoniae	103	53	(51)	45	(44)	5	(5)
Legionella pneumophila	4	1	(25)	1	(25)	2	(50)
Mycoplasma pneumoniae	6	3	(50)	3	(50)	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.

13.2.4. Clinical Success Rates by Pathogen:

The clinical success rates by pathogen for levofloxacin-QD-treated patients are summarized in Table 13.2.4.A, on the following page.

Table 13.2.4.A
Poststudy Clinical Success Rates by Pathogen
Levofloxacin 500 mg QD
All FDA Clinically Evaluable Subjects (Protocol K90-071)

Pathogen	Levofloxacin 500 mg QD	
	N*	Clinical Success
Routine Bacterial Pathogens		
Haemophilus influenzae	29	26 (90)
Haemophilus parainfluenzae	11	10 (91)
Klebsiella pneumoniae	5	5 (100)
Moraxella catarrhalis	11	10 (91)
Staphylococcus aureus	11	8 (73)
Streptococcus pneumoniae	34	30 (88)
Other Pathogens	103	98 (95)
Chlamydia pneumoniae	4	2 (50)
Legionella pneumophila	6	6 (100)
Mycoplasma pneumoniae		

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

13.2.5. Clinical Response by Severity of Infection: FDA Clinically Evaluable Subjects

The clinical response rate was analyzed by severity of infection for the dichotomous grouping of mild-to-moderate infections and severe infections. While there was a large difference in the clinical cure rates by severity of infection (56% cured in mild-moderate group vs. 31% cured in the severe group), this discrepancy disappeared when the clinical success rate (clinically cured + improved) was calculated by severity of infection (93% clinical success in mild-moderate group vs. 92% clinical success in the severe group). These results are summarized in Table 13.2.5, below.

Table 13.2.5
Clinical Response by Severity of Infection:
FDA Clinically Evaluable Subjects (Study M92-075)

Severity	Levofloxacin 500 mg QD			
	N	Cure	Improve	Fail
Mild/Moderate	167	94 (56)	61 (37)	12 (7)
Severe	36	11 (31)	22 (61)	3 (8)
Severity	**N**	**Clinical Success**		**Fail**
Mild/Moderate	167	155 (93)		12 (7)
Severe	36	33 (92)		3 (8)

Numbers shown in parentheses are percentages for that category

13.3 Microbiologic Response as per Medical Officer

13.3.1 Microbiologic Response by Study Center

The overall eradication rate in the levofloxacin-QD-treated patients was 94% (151/161), and this ranged from 84-100% across the major study centers of the trial. The overall eradication rate in the levofloxacin-BID-treated patients was 89% (8/9). These results are summarized in Table 13.3.1, below.

Table 13.3.1
Microbiologic Eradication Rates by Investigator:
Levofloxacin 500 mg QD and Levofloxacin 500 mg BID
FDA Microbiologically Evaluable Subjects (Study M92-075)

	Levofloxacin 500 mg QD		Levofloxacin 500 mg BID	
Investigator	N	Eradicated*	N	Eradicated*
Chattman	13	12 (92)	-	-
Fogarty	47	47 (100)	-	-
Rodman	10	10 (100)	-	-
Sullivan	35	35 (100)	-	-
Other	56	47 (84)	-	-
Total	161	151 (94)	9	8 (89)

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

13.3.2. Microbiologic Response by Pathogen

The overall eradication rates in the levofloxacin-QD-treated patients are summarized by pathogen in Table 13.3.2, on the following page. The overall eradication rates are all in the range of 90-100%, with two exceptions: *S. aureus* and *Legionella pneumophilia*. *S. aureus* had an eradication rate of 80% (8/10), and *Legionella pneumophilia* had an eradication rate of 75% (3/4). Of note, these estimates are limited by the small number of isolates for each organism.

Table 13.3.2
Overall Microbiologic Eradication Rates by Pathogen Category and Pathogen:
Levofloxacin 500 mg QD vs. Levofloxacin 500 mg BID
FDA Microbiologically Evaluable Subjects[a] (Study M92-075)

Pathogen Category/Pathogen	Levofloxacin 500 mg QD		Levofloxacin 500 mg BID	
	N	Eradicated[a]	N	Eradicated[a]
Pathogen Category				
Gram-positive aerobic pathogens	75	70 (93)	4	4 (100)
Gram-negative aerobic pathogens	84	79 (94)	4	3 (75)
Other	95	91 (96)	N/A	N/A
Total by pathogen	254	240 (94)	16	15 (94)
Total by subject	161	151 (94)	9	8 (91)
Routine Bacterial Pathogen				
Haemophilus influenzae	28	27 (96)	3	3 (100)
Haemophilus parainfluenzae	10	9 (90)	-	-
Klebsiella pneumoniae	5	5 (100)	-	-
Moraxella catarrhalis	11	11 (100)	-	-
Staphylococcus aureus	10	8 (80)	-	-
Streptococcus pneumoniae	34	32 (94)	2	2 (100)
Chlamydia pneumoniae *IgG≥1:512 and/or IgM≥1:16*	103	98 (95)	5	4 (80)
Legionella pneumophila	4	3 (75)	1	1 (100)
Mycoplasma pneumoniae	6	6 (100)	1	1 (100)

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

13.4. Overall Success Rates:

The overall success rates for the two dosing subgroups of clinically and microbiologically evaluable patients are summarized by study center in Table 13.4.A, on the following page. The overall success rate for patients treated with levofloxacin 500 mg QD was 94% (151/161), with a range of 84-100% across study centers. The overall success rate for patients treated with levofloxacin 500 mg BID was 91% (8/9).

Table 13.4.A
Overall Success Rates[a] By Study Center:
Levofloxacin 500 mg QD and Levofloxacin 500 mg BID
FDA Microbiologically AND Clinically Evaluable Subjects (Study M92-075)

Investigator	Levofloxacin 500 mg QD		Levofloxacin 500 mg BID	
	N	Overall Success	N	Overall Success
Chattman	13	12 (92)	--	--
Fogarty	47	47 (100)	--	--
Rodman	10	10 (100)	--	--
Sullivan	35	35 (100)	--	--
Other	56	47 (84)	--	--
Total	161	151 (94)	9/175 (5)	8 (91)

Results are presented for investigators with 10 or more evaluable patients in each treatment group. All other investigators are combined under "other". [a]Overall success is defined as either clinical cure or improvement with microbiologic eradication.
[b]Numbers shown in parentheses are percentages for that category.

The overall success rates for FDA microbiologically evaluable patients are summarized by pathogen in Table 13.4.B, below. The the estimates for the overall success rate are limited by the number of casess for several organisms (*Klebsiella pneumoniae, Legionella pneumophilia, and Mycoplasma pneumoniae*). The overall success rate for patients with Streptococcus pneumoniae is 69%, which is below the more favor Overall success rates seen with other pathogens.

Table 13.4.B
Overall Success Rates[a] by Pathogen: Levofloxacin 500 mg QD
FDA Microbiologically Evaluable Subjects (Protocol K90-071)

Investigator	Levofloxacin 500 mg QD		
	N	Overall Success	
Routine Bacterial Pathogens			
Haemophilus influenzae	28	28	(100)
Haemophilus parainfluenzae	10	8	(80)
Klebsiella pneumoniae	5	5	(100)
Moraxella catarrhalis	11	10	(91)
Staphylococcus aureus	10	8	(80)
Streptococcus pneumoniae	34	32	(94)
Other Pathogens			
Chlamydia pneumoniae *IgG≥1:512 and/or IgM≥1:16*	103	98	(95)
Legionella pneumophila	4	2	(50)
Mycoplasma pneumoniae	6	6	(100)

[a]Overall success is defined as either clinical cure or improvement with microbiologic eradication.
Numbers shown in parentheses are percentages for that category.

14. Safety Results as per Sponsor:

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any postadmission data were available. Two hundred sixty-three (99.6%) of 264 subjects enrolled were evaluated for safety. Subject [redacted] was lost to follow-up with no safety information and, therefore, was excluded from the safety analysis. Therapy discontinuation/completion information for this subject was unknown.

14.2. Overview of Safety Data

The most frequently reported adverse events occurred in the gastrointestinal system (22.1% incidence), followed by the nervous, respiratory, and body as a whole systems, each with an incidence of approximately 8%. The most common adverse events were nausea, diarrhea, headache, insomnia, and dizziness. Twenty-six subjects reported adverse events that were considered marked in severity, including marked dyspnea in three subjects, and marked nausea, headache, supraventricular tachycardia, cardiac arrest, and myocardial infarction in two subjects each. Fourteen (5.3%) subjects had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to the study drug. Only one subject had a marked, drug-related adverse event (nausea). Drug-related adverse events reported by ≥1.0% of subjects were diarrhea (1.5%) and nausea (1.1%). Nine subjects discontinued levofloxacin therapy due to adverse events, including three subjects with rash, two with respiratory depression/ insufficiency, and one each with hepatic function abnormalities, nausea, cardiac arrest, and tinnitus. Twenty-two subjects reported serious or potentially serious adverse events, mostly respiratory or cardiovascular events, and seven of these subjects died during or shortly after the study. All seven subjects who died had conditions or illnesses that have been associated with increased mortality from pneumonia. All of the serious or potentially serious adverse events were considered unrelated, remotely related, or possibly related to levofloxacin treatment except for one event for which the relationship to study drug was unknown; these events were most likely related to the subject's underlying condition. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs occurred infrequently.

14.3. Treatment-Emergent Adverse Events

14.3.1.. Summary of All Adverse Events

One hundred twenty-five (47.5%) of 263 safety-evaluable subjects reported at least one treatment-emergent adverse event, including events considered by the investigator as related or unrelated to study drug. Body systems with the highest reported frequency of adverse events were the gastrointestinal system (22.1% incidence), followed by the central and peripheral nervous system, the respiratory system, and the body as a whole, each with an incidence of approximately 8%. These results are summarized in Table 14.3.1.A, on the following page.

Table 14.3.1.A
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol M92-075)

Body System	Levofloxacin (N=263)	
	N	%
Gastrointestinal System Disorders	58	(22.1)
Central & Peripheral Nervous System Disorders	22	(8.4)
Respiratory System Disorders	21	(8.0)
Body as a Whole--General Disorders	21	(8.0)
Psychiatric Disorders	18	(6.8)
Skin and Appendages Disorders	16	(6.1)
Heart Rate and Rhythm Disorders	11	(4.2)
Resistance Mechanism Disorders	8	(3.0)
Musculo-Skeletal System Disorders	6	(2.3)
Metabolic and Nutritional Disorders	5	(1.9)
Application Site Disorders	5	(1.9)
White Cell and RES Disorders	4	(1.5)
Hearing and Vestibular Disorders	3	(1.1)
Liver and Biliary System Disorders	3	(1.1)
Vascular (Extracardiac) Disorders	3	(1.1)
Urinary System Disorders	3	(1.1)
Cardiovascular Disorders, General	2	(0.8)
Myo-, Endo-, Pericardial & Valve Disorders	2	(0.8)
Neoplasms	2	(0.8)
Autonomic Nervous System Disorders	1	(0.4)
Vision Disorders	1	(0.4)
Special Senses (Other) Disorders	1	(0.4)
Red Blood Cell Disorders	1	(0.4)
Platelet, Bleeding & Clotting Disorders	1	(0.4)
Reproductive Disorders, Female*	1	(0.8)
Total With Adverse Events (%)	125	(47.5)

RES = Reticuloendothelial System.
*Percentage for this body system is based on the total number of women evaluable for safety (N=118).

The most frequently reported adverse events were nausea (10.3%), diarrhea (6.5%), headache (4.2%), insomnia (3.4%), and dizziness (3.0%). In general, the overall incidence of adverse events among subjects who took concomitant anticoagulant, antidiabetic, bronchodilator, or central nervous system-acting therapies as well as for subjects who took NSAIDs or vitamins or other nutritional supplements was comparable to that for all subjects evaluable for safety. A higher incidence of all gastrointestinal adverse events (46.5%), including nausea (23.3%), with a corresponding increase in the overall frequency of adverse events, was noted for subjects who received concomitant antacid therapy. These subjects also had a higher incidence of psychiatric disorders (14.0%), including insomnia (7.0%), and body as a whole adverse events (18.6%), including back pain (4.7%). Other body systems and primary terms with higher incidences of adverse events reported by subjects taking various classes of concomitant medications include: psychiatric disorders (18.8%), including insomnia (18.8%), gastrointestinal system disorders (31.3%), including dyspepsia (12.5%) and nausea (12.5%), in subjects who took anticoagulants; gastrointestinal system disorders (33.3%), including diarrhea (20.0%), in subjects who took antidiabetic medications; and headache (15.0%) in subjects who took NSAIDs. These results are summarized in Table 14.3.1.B, below.

Table 14.3.1.B
Incidence of Frequently Reported Adverse Events (≥2%)
Summarized by Primary Term:
Subjects Evaluable for Safety (Study M92-075)

	Levofloxacin (N=263)	
Body System/Primary Term	No.	(%)
All Body Systems	125	47.5
Gastrointestinal System Disorders		
Nausea	27	10.3
Diarrhea	17	6.5
Constipation	7	2.7
Abdominal Pain	6	2.3
Vomiting	6	2.3
Central & Peripheral Nervous System Disorders		
Headache	11	4.2
Dizziness	8	3.0
Psychiatric Disorders		
Insomnia	9	3.4

*Primary term reported by ≥2.0% of subjects.

The majority of adverse events were assessed as mild or moderate in severity. Twenty-six subjects reported one or more adverse events of marked severity, including marked dyspnea in three subjects, and marked nausea, headache, supraventricular tachycardia, cardiac arrest, and myocardial infarction in two subjects each. No other events of marked severity occurred in more than one subject, and only one (nausea, Subject 1018) was considered by the investigator as having a probable relationship to the study drug. Sixteen subjects, including three who discontinued levofloxacin therapy because of adverse events, had marked adverse events that were considered serious potentially serious. Fourteen (5.3%) subjects had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to the study drug. Drug-related adverse events reported by ≥1.0% of subjects were diarrhea (1.5%) and nausea (1.1%). In general, the nature and frequency of adverse events was comparable between men and women. However, the overall incidence of adverse events was greater among men (52.4%) than among women (41.5%) due primarily to a greater incidence of psychiatric, respiratory, and body as a whole adverse events among men (10.3%, 11.0%, and 11.0%, respectively) than among women (2.5%, 4.2%, and 4.2%). In contrast, adverse events in the central and peripheral nervous system (particularly dizziness and headache) were more commonly reported by women (11.0%) than by men (6.2%). The significance of these findings as it relates to levofloxacin treatment is unclear, however, since adverse events in these three body systems generally were not considered by the investigators to be drug-related. Adverse events in the gastrointestinal body system were similar between men and women. The incidence of adverse events was relatively low in the other body systems. There was no consistent pattern of age-related differences in the adverse event profile with levofloxacin treatment. Adverse events were more commonly reported among the 218 Caucasians (50.9% overall incidence) than among the 40 Blacks (30.0%), but the significance of this finding is unclear given the relatively small number of Blacks in this study population; the difference between Caucasians and Blacks was most evident for gastrointestinal system adverse events (incidence of 24.8% and 7.5%, respectively).

14. Safety Results as per Sponsor:

14.1. Data Set Analyzed

A subject was included in the safety summaries if he/she received study drug and any postadmission data were available. Two hundred sixty-three (99.6%) of 264 subjects enrolled were evaluated for safety. Subject [redacted] was lost to follow-up with no safety information and, therefore, was excluded from the safety analysis. Therapy discontinuation/completion information for this subject was unknown.

14.2. Overview of Safety Data

The most frequently reported adverse events occurred in the gastrointestinal system (22.1% incidence), followed by the nervous, respiratory, and body as a whole systems, each with an incidence of approximately 8%. The most common adverse events were nausea, diarrhea, headache, insomnia, and dizziness. Twenty-six subjects reported adverse events that were considered marked in severity, including marked dyspnea in three subjects, and marked nausea, headache, supraventricular tachycardia, cardiac arrest, and myocardial infarction in two subjects each. Fourteen (5.3%) subjects had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to the study drug. Only one subject had a marked, drug-related adverse event (nausea). Drug-related adverse events reported by ≥1.0% of subjects were diarrhea (1.5%) and nausea (1.1%). Nine subjects discontinued levofloxacin therapy due to adverse events, including three subjects with rash, two with respiratory depression/ insufficiency, and one each with hepatic function abnormalities, nausea, cardiac arrest, and tinnitus. Twenty-two subjects reported serious or potentially serious adverse events, mostly respiratory or cardiovascular events, and seven of these subjects died during or shortly after the study. All seven subjects who died had conditions or illnesses that have been associated with increased mortality from pneumonia. All of the serious or potentially serious adverse events were considered unrelated, remotely related, or possibly related to levofloxacin treatment except for one event for which the relationship to study drug was unknown; these events were most likely related to the subject's underlying condition. Clinically significant treatment-emergent changes in clinical laboratory tests, physical examinations, and vital signs occurred infrequently.

14.3. Treatment-Emergent Adverse Events

14.3.1.. Summary of All Adverse Events

One hundred twenty-five (47.5%) of 263 safety-evaluable subjects reported at least one treatment-emergent adverse event, including events considered by the investigator as related or unrelated to study drug. Body systems with the highest reported frequency of adverse events were the gastrointestinal system (22.1% incidence), followed by the central and peripheral nervous system, the respiratory system, and the body as a whole, each with an incidence of approximately 8%. These results are summarized in Table 14.3.1.A, on the following page.

Table 14.3.1.A
Incidence of Adverse Events Summarized by Body System: Subjects Evaluable for Safety (Protocol M92-075)

Body System	Levofloxacin (N=263)	
	N	%
Gastrointestinal System Disorders	58	(22.1)
Central & Peripheral Nervous System Disorders	22	(8.4)
Respiratory System Disorders	21	(8.0)
Body as a Whole--General Disorders	21	(8.0)
Psychiatric Disorders	18	(6.8)
Skin and Appendages Disorders	16	(6.1)
Heart Rate and Rhythm Disorders	11	(4.2)
Resistance Mechanism Disorders	8	(3.0)
Musculo-Skeletal System Disorders	6	(2.3)
Metabolic and Nutritional Disorders	5	(1.9)
Application Site Disorders	5	(1.9)
White Cell and RES Disorders	4	(1.5)
Hearing and Vestibular Disorders	3	(1.1)
Liver and Biliary System Disorders	3	(1.1)
Vascular (Extracardiac) Disorders	3	(1.1)
Urinary System Disorders	3	(1.1)
Cardiovascular Disorders, General	2	(0.8)
Myo-, Endo-, Pericardial & Valve Disorders	2	(0.8)
Neoplasms	2	(0.8)
Autonomic Nervous System Disorders	1	(0.4)
Vision Disorders	1	(0.4)
Special Senses (Other) Disorders	1	(0.4)
Red Blood Cell Disorders	1	(0.4)
Platelet, Bleeding & Clotting Disorders	1	(0.4)
Reproductive Disorders, Female*	1	(0.8)
Total With Adverse Events (%)	125	(47.5)

RES = Reticuloendothelial System.
*Percentage for this body system is based on the total number of women evaluable for safety (N=118).

The most frequently reported adverse events were nausea (10.3%), diarrhea (6.5%), headache (4.2%), insomnia (3.4%), and dizziness (3.0%). In general, the overall incidence of adverse events among subjects who took concomitant anticoagulant, antidiabetic, bronchodilator, or central nervous system-acting therapies as well as for subjects who took NSAIDs or vitamins or other nutritional supplements was comparable to that for all subjects evaluable for safety. A higher incidence of all gastrointestinal adverse events (46.5%), including nausea (23.3%), with a corresponding increase in the overall frequency of adverse events, was noted for subjects who received concomitant antacid therapy. These subjects also had a higher incidence of psychiatric disorders (14.0%), including insomnia (7.0%), and body as a whole adverse events (18.6%), including back pain (4.7%). Other body systems and primary terms with higher incidences of adverse events reported by subjects taking various classes of concomitant medications include: psychiatric disorders (18.8%), including insomnia (18.8%), gastrointestinal system disorders (31.3%), including dyspepsia (12.5%) and nausea (12.5%), in subjects who took anticoagulants; gastrointestinal system disorders (33.3%), including diarrhea (20.0%), in

subjects who took antidiabetic medications; and headache (15.0%) in subjects who took NSAIDs. These results are summarized in Table 14.3.1.B, below.

Table 14.3.1.B
Incidence of Frequently Reported Adverse Events (≥2%) Summarized by Primary Term: Subjects Evaluable for Safety (Study M92-075)

	Levofloxacin (N=263)	
Body System/Primary Term	No.	(%)
All Body Systems	125	47.5
Gastrointestinal System Disorders		
Nausea	27	10.3
Diarrhea	17	6.5
Constipation	7	2.7
Abdominal Pain	6	2.3
Vomiting	6	2.3
Central & Peripheral Nervous System Disorders		
Headache	11	4.2
Dizziness	8	3.0
Psychiatric Disorders		
Insomnia	9	3.4

* Primary term reported by ≥2.0% of subjects.

The majority of adverse events were assessed as mild or moderate in severity. Twenty-six subjects reported one or more adverse events of marked severity, including marked dyspnea in three subjects, and marked nausea, headache, supraventricular tachycardia, cardiac arrest, and myocardial infarction in two subjects each. No other events of marked severity occurred in more than one subject, and only one (nausea, Subject 1018) was considered by the investigator as having a probable relationship to the study drug. Sixteen subjects, including three who discontinued levofloxacin therapy because of adverse events, had marked adverse events that were considered serious potentially serious. Fourteen (5.3%) subjects had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to the study drug. Drug-related adverse events reported by ≥1.0% of subjects were diarrhea (1.5%) and nausea (1.1%). In general, the nature and frequency of adverse events was comparable between men and women. However, the overall incidence of adverse events was greater among men (52.4%) than among women (41.5%) due primarily to a greater incidence of psychiatric, respiratory, and body as a whole adverse events among men (10.3%, 11.0%, and 11.0%, respectively) than among women (2.5%, 4.2%, and 4.2%). In contrast, adverse events in the central and peripheral nervous system (particularly dizziness and headache) were more commonly reported by women (11.0%) than by men (6.2%). The significance of these findings as it relates to levofloxacin treatment is unclear, however, since adverse events in these three body systems generally were not considered by the investigators to be drug-related. Adverse events in the gastrointestinal body system were similar between men and women. The incidence of adverse events was relatively low in the

other body systems. There was no consistent pattern of age-related differences in the adverse event profile with levofloxacin treatment. Adverse events were more commonly reported among the 218 Caucasians (50.9% overall incidence) than among the 40 Blacks (30.0%), but the significance of this finding is unclear given the relatively small number of Blacks in this study population; the difference between Caucasians and Blacks was most evident for gastrointestinal system adverse events (incidence of 24.8% and 7.5%, respectively).

Table 14.3.1.C
Subjects with Adverse Events of Marked Severity:
Subjects Evaluable for Safety (Study M92-075)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Relationship To Study Drug*
Levofloxacin				
	49	M	Nausea	Possible
			Vomiting	Possible
	42	M	Hepatic Function Abnormal^	Possible
	30	F	Asthma†	Remote
	50	M	Respiratory Depression†	None
	20	F	Headache	Possible
	29	M	Chest Pain	None
	32	M	Anxiety	Possible
	68	M	Chest Pain Substernal†	None
			Dyspnea†	None
	74	M	Dyspnea†	None
	52	F	Nausea	Probable
	62	M	Hepatic Neoplasm†	None
	49	M	Tachycardia Supraventricular	Remote
	80	M	Edema Peripheral	Remote
	45	M	Sepsis†	Possible
			Myocardial Infarction†	None
	70	M	Hypotension Postural	None
			Pulmonary Carcinoma†	None
	56	M	Respiratory Insufficiency†	Possible
	61	F	Gastrointestinal Hemorrhage†	None
	79	M	Face Edema	None
			Headache	None
	60	M	Cardiac Arrest†	None
	68	F	Tachycardia Supraventricular†	None
			Thrombosis Arterial Leg†	None
	75	M	Depression	None
			Drug Level Increased	Possible
			Dyspnea†	Remote
	72	M	Fibrillation Atrial†	Possible
			Cardiac Arrest†	Possible
	72	F	Esophagitis	None
	49	M	Myocardial Infarction†	None
	67	M	Cholecystitis	None
			Cholelithiasis	None
			Fibrillation Ventricular†	None
	73	M	Hypoxia†	None
			Pleural Effusion†	None
			Renal Function Abnormal†	None

* Based on investigator's assessment.
^ Elevated liver enzymes (alkaline phosphatase, SGOT, SGPT, and LDH).
^ Subject discontinued therapy due to this adverse event(s) (see Table 27).
^^ Subject also had markedly abnormal laboratory value(s) (See Table 32).
† Serious or potentially serious adverse event (see Table 28).

14.4. Discontinuations Due to Adverse Events

Nine subjects discontinued levofloxacin therapy due to adverse events, including three subjects with rash, two with respiratory depression/insufficiency, and one each with hepatic function abnormalities, nausea, cardiac arrest, and tinnitus. The treatment-limiting adverse events were considered serious or potentially serious in three subjects (subject [redacted] respiratory depression, subject 1607-respiratory insufficiency, subject 2415-cardiac arrest), who died as a result of these adverse events after study therapy was discontinued. Four other subjects died during the study.

Table 14.4
Subjects who Discontinued due to Adverse Events:
Subjects Evaluable for Safety (Study M92-075)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day Of Onset*	Severity	Relationship To Study Drug‡	Duration Of Therapy (Days)
Levofloxacin							
	42	M	Hepatic Function Abnormal	3	Marked	Possible	4
	50	M	Respiratory Depression†	2	Marked	None	2[a]
	61	F	Rash	8	Moderate	Possible	8
	50	F	Rash Erythematous	4	Mild	Possible	4
	52	F	Nausea	7	Marked	Probable	8
	56	M	Respiratory Insufficiency†	1	Marked	Possible	1
	60	M	Cardiac Arrest†	8	Marked	None	6
	70	F	Tinnitus	4	Mild	Possible	3
	82	F	Rash	3	Moderate	Probable	2

* Relative to start of therapy (Day 1).
‡ Based on investigator's assessment.
[a] Only one 500-mg dose administered during this period.
[b] Subject also had markedly abnormal laboratory values (see Table 32).
[c] Subject died as a result of the adverse event.
† Serious or potentially serious adverse event (see Table 28).

14.5. Serious or Potentially Serious Adverse Events, Including Death

Twenty-two subjects reported a serious or potentially serious adverse event, including seven subjects who died during or up to approximately one month after completing levofloxacin therapy. These results are summarized in Table 14.5, on the following page. The serious or potentially serious adverse events for three of these subjects and some of the serious adverse events for six subjects were not included as serious adverse events in the individual study report database but do appear on the RWJPRI serious adverse event reporting database; two of these subjects reported the adverse event after the poststudy contact or visit. Most of the serious or potentially serious adverse events were respiratory or cardiovascular events. Three of the 22 subjects with serious or potentially serious adverse events withdrew from the study because of these adverse events. All serious or potentially serious adverse events were considered by the investigator to be unrelated, remotely related, or possibly related to the study drug (one event was of unknown relationship to study drug), and, in most cases, the adverse events appeared to be related to the subject's underlying condition. All seven subjects who died had conditions or illnesses that have been associated

with increased mortality from pneumonia: One subject had severe pneumonia, the other six subjects had various comorbid conditions (e.g., chronic obstructive pulmonary disease, cardiovascular disease, renal failure, diabetes mellitus, age greater than 60 years), and six of these seven subjects required hospitalization for treatment of pneumonia.

Table 14.5
Subjects with Serious Adverse Events:
Subjects Evaluable for Safety (Study M92-075)

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset[a]		Severity	Relationship To Study Drug[b]	Duration Of Therapy (Days)
	30	F	Asthma	4		Marked	Remote	14
	50	M	Delirium[c]	1		Mild	None	2
			Respiratory Depression	2		Marked	None	
	M	38	Rhabdomyolysis[d]	4		Mild	None	13
	68	M	Chest Pain, Substernal	1		Marked	None	14
			Dyspnea	1		Marked	None	
	75	F	Pulmonary Embolism[e]	34	(20PT)	—	Remote	14
	74	M	Dyspnea	8		Marked	None	14
	62	M	Hepatic Neoplasm	25	(8PT)	Marked	None	17
	29	F	Fibrosis Mediastinal/ Malignant Neoplasm	1		Mild	None	12
	35	M	Gastrointestinal Hemorrhage	22	(8PT)	Moderate	Remote	14
	45	M	Sepsis	2		Marked	Possible	2
			ARDS[f]	3		—	Remote	
			Abscess[g]	4		—	Remote	
			Myocardial Infarction	5		Marked	None	
	70	M	Pulmonary Carcinoma	4		Marked	None	3
	56	M	Respiratory Insufficiency	1		Marked	Possible	1
			Cardiac Arrest[f]	2		—	—	
	81	F	Gastrointestinal Hemorrhage	21	(7PT)	Marked	None	14
	60	M	Cardiac Arrest	8	(2PT)	Marked	None	6
	68	F	Tachycardia, Supraventricular	5		Marked	None	14
			Thrombosis Arterial, Leg	5		Marked	None	
	75	M	Drug Level Increased	20	(5PT)	—	Remote	15
			Dyspnea	21	(6PT)	Marked	Remote	
	72	M	Fibrillation Atrial	9		Marked	Possible	9
			Hypoxia[f]	10	(1PT)	—	Possible	
			Myocardial Infarction[f]	11	(2PT)	—	Possible	
			Cardiac Arrest	11	(2PT)	Marked	Possible	
	49	M	Myocardial Infarction	8	(5PT)	Marked	None	3
	67	M	Cardiac Failure	18	(4PT)	Moderate	None	14
			Fibrillation, Ventricular	30	(16PT)	Marked	None	
	48	F	Depression[f]	39	(25PT)	—	Remote	14
	79	F	Fracture, Pathological	25	(11PT)	Moderate	None	14
	73	M	Hypoxia	26	(12PT)	Marked	None	14
			Pleural Effusion	26	(12PT)	Marked	None	
			Renal Function Abnormal	26	(12PT)	Marked	None	
			Sepsis[g]	26	(12PT)	—	Remote	
			Cardiac Failure[f]	26	(12PT)	—	Remote	
			Acidosis[g]	26	(12PT)	—	Remote	
			Circulatory Failure[f]	26	(12PT)	—	Remote	
			Pulmonary Collapse[f]	26	(12PT)	—	Remote	

[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 database but was captured as serious in the RWJPRI serious adverse event reporting database; it is therefore reflected as serious in the pooled safety database for the NDA Integrated Safety Summary.
[d] This serious adverse event, which appears as non-serious in the individual study report database, was captured as serious in the RWJPRI serious adverse event reporting database; it is therefore reflected as serious in the pooled safety database for the NDA Integrated Safety Summary.
[e] This poststudy serious adverse event occurred after the poststudy contact or visit and therefore does not appear on the case report form or in the database for this individual study report. However, this event was collected as part of th RWJPRI serious adverse event reporting database and therefore is reflected in the pooled safety database for the NDA Integrated Safety Summary.
[f] An arteriogram for peripheral vascular disease (coded as peripheral ischemia) for which the subject was hospitalized, also appears in the database for the NDA Integrated Safety Summary.
†Subject died as a result of the serious adverse event(s). IND safety reports of these cases were submitted to FDA.
* Subject discontinued therapy due to adverse events (see Table 27).
**Subject also had treatment-emergent, markedly abnormal laboratory value(s) (see Table 32).

Cross-reference: Attachments 19 and 23

14.6. Dosage Reductions and Concomitant Therapies

Nine subjects had levofloxacin therapy stopped due to adverse events, three of which were considered serious. An additional 19 subjects reported serious or potentially serious adverse events. Several of the treatment-limiting or serious or potentially serious adverse events required treatment with concomitant therapies, as described in the individual narrative descriptions. None of the subjects required a dosage reduction.

Table 14.6
Subjects who Required Concomitant Therapy for Adverse Events: Subjects Evaluable for Safety (Study M92-075)

Subject Number	Age	Sex	Adverse Event	Day of Onset[b]	Severity	Concomitant Therapy
	29	F	Moniliasis Genital	12	Moderate	Clotrimazole
	68	F	Nausea	13	Mild	Metoclopramide
	55	F	Stomatitis	2	Mild	Nystatin

[a] Includes events considered by the investigator to be probably or definitely related to study drug, except for those resulting in study drug discontinuation or considered serious or potentially serious as discussed in Sections IV.I.3.b. and IV.I.3.c.
[b] Relative to start of therapy (Day 1).

14.7. Clinical Laboratory Tests

14.7.1. Overall Changes

There were no clinically significant mean changes from admission for any laboratory analyte. No summaries were provided for basophils, monocytes, bicarbonate, or urinalysis parameters. The means and mean changes from admission baseline to posttherapy for chemistry and hematology laboratory analytes are summarized in Table 14.7.1, on the following page.

Table 14.7.1

Means and Mean Changes From Admission to Posttherapy for Laboratory Analytes: All Subjects Evaluable for Safety with Data Available at Admission and Posttherapy (Protocol M92-075)

		Levofloxacin					
		Admission		Posttherapy		Change	
Laboratory Test	N	Mean	(SD)	Mean	(SD)	Mean	(SD)
Blood Chemistry							
Glucose (mg/dL)	231	115.2	(54.19)	107.1	(55.52)	-8.0	(50.58)
Calcium (mg/dL)	242	8.7	(0.62)	8.9	(0.47)	0.2	(0.66)
Sodium (mEq/L)	241	136.9	(3.53)	138.7	(2.77)	1.8	(3.96)
Potassium (mEq/L)	236	4.1	(0.60)	4.3	(0.43)	0.2	(0.64)
Chloride (mEq/L)	241	100.7	(4.91)	103.1	(3.67)	2.4	(4.78)
Phosphorus, Inorg. (mg/dL)	229	3.2	(0.75)	3.6	(0.62)	0.5	(0.89)
Blood Urea Nitrogen (mg/dL)	242	14.2	(7.68)	13.4	(5.45)	-0.8	(6.45)
Lactic Dehydrogenase (IU/L)	238	155.8	(67.63)	163.8	(57.64)	-31.9	(65.57)
Total Protein (g/dL)	242	6.9	(0.78)	7.0	(0.61)	0.1	(0.75)
Albumin (g/dL)	233	3.5	(0.60)	3.7	(0.49)	0.2	(0.50)
Uric Acid (mg/dL)	241	5.2	(1.79)	5.5	(1.53)	0.3	(1.36)
Creatinine (mg/dL)	242	1.2	(0.36)	1.1	(0.24)	-0.1	(0.30)
Alkaline Phosphatase (IU/L)	240	84.2	(45.55)	81.3	(41.72)	-2.9	(23.72)
SGOT (IU/L)	242	29.2	(28.63)	26.1	(34.05)	-3.1	(31.66)
SGPT (IU/L)	242	27.3	(33.13)	23.0	(22.95)	-4.4	(34.04)
Total Bilirubin (mg/dL)	231	0.6	(0.39)	0.5	(0.26)	-0.1	(0.33)
Hematology							
Hemoglobin (g/dL)	224	13.7	(1.93)	13.7	(1.56)	0.1	(1.34)
Hematocrit (%)	219	40.6	(5.40)	40.9	(4.24)	0.3	(4.35)
WBC (x10³/µL)	224	11.0	(5.46)	7.5	(2.49)	-3.5	(5.37)
RBC (x10⁶/µL)	224	4.5	(0.62)	4.6	(0.52)	0.0	(0.45)
Neutrophils (x10³/µL)	224	8.6	(5.18)	4.8	(2.23)	-3.9	(5.13)
Lymphocytes (x10³/µL)	224	1.5	(0.77)	2.0	(0.75)	0.5	(0.79)
Eosinophils (x10³/µL)	224	0.1	(0.11)	0.2	(0.15)	0.1	(0.14)
Platelet Count (x10³/µL)	216	273.2	(95.38)	321.5	(109.17)	48.3	(110.44)

N = Number of subjects with admission and posttherapy results.

14.7.2. Marked Abnormalities in Laboratory Values

The laboratory values were classified as markedly abnormal according to standard criteria developed by RWJPRI, which take into account absolute values as well as percentage or absolute value changes from admission. The incidence of markedly abnormal test results for individual analytes was low (≤5.3%). Abnormalities in SGPT, SGOT, glucose (both increases and decreases), and lymphocyte count were the most common markedly abnormal laboratory test results. Fifteen subjects had markedly abnormal liver function tests (elevations in SGOT, SGPT, alkaline phosphatase, or LDH). Although 13 subjects had hypoglycemia, 10 subjects had hypoglycemia that was classified as mild (serum glucose values of 60 mg/dL or higher). Eight subjects had hyperglycemia, which was mild (serum glucose levels less than 220 mg/dL) for three of these subjects. A total of seven subjects had lymphopenia, which was the only markedly abnormal laboratory finding and was classified as mild (lymphocyte counts > 0.45 x $10^3/\mu L$) for four of these subjects. As further described below, some abnormalities were related to the underlying disease state of the subject or to concomitant therapy.

Table 14.7.2.A
Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Levofloxacin-treated Subjects Evaluable for Safety (Study M92-075)

	Levofloxacin	
Laboratory Test	Proportion*	%
Blood Chemistry		
Decreased Glucose	13/243	5.3
Elevated SGPT	12/253	4.7
Elevated SGOT	10/253	4.0
Elevated Glucose	8/243	3.3
Decreased Phosphorus	3/241	1.2
Elevated LDH	3/249	1.2
Decreased Albumin	1/245	0.4
Elevated Alkaline Phosphatase	1/251	0.4
Elevated Phosphorus	1/241	0.4
Decreased Potassium	1/247	0.4
Decreased Calcium	1/253	0.4
Elevated BUN	1/253	0.4
Hematology		
Decreased Lymphocytes	7/237	3.0
Decreased Hemoglobin	2/237	0.8
Decreased Neutrophils	1/237	0.4

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

Table 14.7.3.B
Subjects with Treatment-Emergent Markedly Abnormal Laboratory Values: Levofloxacin-treated Subjects Evaluable for Safety (Study M92-075)

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								
	50	M	Lactic Dehydrogenase (>600 IU/L)	392.00	631.00	16(2PT)	–	14
			Glucose (<70 or >200 mg/dL)	145.00	276.00	3	–	14
			Lymphocytes (<1.0 x 10⁹/μL)	7.42	0.13	3	–	14
	56	F	Glucose (<70 or >200 mg/dL)	116.00	69.00	20(6PT)	–	14
	42	M	SGOT (>75 IU/L)	73.00	474.00	3	–	4
					418.00	5(1PT)	34.00 (5PT)	4
			Lactic Dehydrogenase (>600 IU/L)	253.00	609.00	3	149.00 (16PT)	4
			SGPT (>75 IU/L)	35.00	126.00	3	–	4
					274.00	5(1PT)	–	4
					76.00	13(5PT)	30.00 (16PT)	4
	63	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.10	1.40	4	3.60 (5PT)	20
	45	F	Glucose (<70 or >200 mg/dL)	134.00	748.00	3	–	14
					442.00	20(6PT)	–	14
	71	M	Hemoglobin (<12.0 g/dL)	13.40	10.00	20(6PT)	–	14
	73	M	Glucose (<70 or >200 mg/dL)	84.00	56.00	21(7PT)	–	14
	69	F	Glucose (<70 or >200 mg/dL)	105.00	66.00	21(7PT)	–	14
	42	F	Neutrophils (<1.0 x 10⁹/μL)	9.63	0.59	19(5PT)	–	14
	33	M	Potassium (<3.0 or > 6.0 mEq/L)	3.50	2.20	3	–	UNK[c]
			Calcium (<7.5 or >11.5 mg/dL)	9.70	5.20	3	–	UNK[c]
			Albumin (<2.0 g/dL)	3.30	1.60	3	–	UNK[c]
			Hemoglobin (<12.0 g/dL)	14.10	8.30	3	–	UNK[c]
	27	F	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	2.50	1.40	2	–	2
	69	F	Glucose (<70 or >200 mg/dL)	487.00	47.00	21(7PT)	–	14

[a] Only range given in table. For complete criteria, see Attachment 29a.
[b] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days post therapy, relative to the last day of study drug administration.
[c] Duration of therapy unknown; subject lost to follow-up.
[d] Subject discontinued therapy due to adverse events (see Table 27).

(Continued)

Table 14.7.3.B.(cont.)
Subjects with Treatment-Emergent Markedly Abnormal Laboratory Values: Levofloxacin-treated Subjects Evaluable for Safety (Study M92-075)

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								
	38	M	SGOT (>75 IU/L)	52.00	852.00	4	–	13
					286.00	7	43.00 (7PT)	13
			Lactic Dehydrogenase (>600 IU/L)	228.00	1516.00	4	286.00 (7PT)	13
			SGPT (>75 IU/L)	42.00	126.00	4	–	13
					124.00	7	22.00 (7PT)	13
	50	M	SGOT (>75 IU/L)	15.00	78.00	5	–	UNK[c]
			SGPT (>75 IU/L)	9.00	79.00	5	–	UNK[c]
	31	F	SGOT (>75 IU/L)	58.00	116.00	3	27.00 (5PT)	15
	29	M	SGOT (>75 IU/L)	35.00	192.00	5	34.00 (3PT)	13
			SGPT (>75 IU/L)	19.00	207.00	5	48.00 (3PT)	13
	32	M	SGOT (>75 IU/L)	36.00	104.00	4	33.00 (4PT)	14
			SGPT (>75 IU/L)	31.00	164.00	4	–	14
					77.00	18(4PT)	–	14
	69	M	Glucose (<70 or >200 mg/dL)	103.00	205.00	24(10PT)	–	14
	56	M	Glucose (<70 or >200 mg/dL)	110.00	203.00	19(5PT)	–	14
	58	F	Glucose (<70 or >200 mg/dL)	116.00	63.00	21(7PT)	–	14
	69	F	Glucose (<70 or >200 mg/dL)	108.00	213.00	19(5PT)	–	14
	69	M	SGPT (>75 IU/L)	28.00	100.00	3	32.00 (7PT)	15

[a] Only range given in table. For complete criteria, see Attachment 29a.
[b] Relative to start of therapy (Day 1). NOTE: PT refers to the number of days post therapy, relative to the last day of study drug administration.
[c] Duration of therapy unknown; subject lost to follow-up.
† Subject also had a serious or potentially serious adverse event (see Table 28).

(Continued)

Table 14.7.3.B.(cont.)
Subjects with Treatment-Emergent Markedly Abnormal Laboratory Values: Levofloxacin-treated Subjects Evaluable for Safety (Study M92-075)

Subject Number	Age	Sex	Laboratory Test (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day*	Follow-up Value (Therapy Day)	Duration of Therapy (Days)
Levofloxacin								
	49	M	Glucose (<70 or >200 mg/dL)	224.00	41.00	4	250.00 (5PT)	13
	79	M	Lymphocytes	1.51	0.47	4	–	12
					0.79	21 (5PT)	–	12
	38	F	SGOT (>75 IU/L)	37.00	100.00	19 (5PT)	–	14
			SGPT (>75 IU/L)	40.00	84.00	19 (5PT)	–	14
	42	M	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	1.60	6.20	3	3.90 (5PT)	10
			SGPT (>75 IU/L)	32.00	85.00	3	29.00 (5PT)	10
	27	M	SGPT (>75 IU/L)	56.00	132.00	4	48.00 (7PT)	28
	25	M	Glucose (<70 or >200 mg/dL)	122.00	67.00	2	72.00 (5PT)	10
	63	F	Phosphorus, Inorg. (<2.0 or >6.0 mg/dL)	3.20	1.40	3	3.20 (6PT)	14
			Glucose (<70 or >200 mg/dL)	62.00	264.00	3	93.00 (6PT)	14
	51	M	Lymphocytes (<1.0 x 10^9/µL)	2.04	0.56	4	1.41 (7PT)	14
	66	F	Lymphocytes (<1.0 x 10^9/µL)	1.23	0.77	4	1.17 (5PT)	14
	37	M	Glucose (<70 or >200 mg/dL)	91.00	60.00	3	73.00 (7PT)	14
	33	M	Glucose (<70 or >200 mg/dL)	107.00	225.00	3	–	14
					285.00	7	95.00 (8PT)	14
	69	M	Glucose (<70 or >200 mg/dL)	117.00	67.00	2	115.00 (7PT)	14
	21	M	Glucose (<70 or >200 mg/dL)	108.00	63.00	30 (16PT)	73.00 (28PT)	14

*Only range given in table. For complete criteria, see Attachment 29a.
(Continued)
†Relative to start of therapy (Day 1). NOTE: PT refers to the number of days post therapy, relative to the last day of study drug administration.
‡Duration of therapy unknown; subject lost to follow-up.
§Subject also had a serious or potentially serious adverse event (see Table 28).

Table 14.7.3.B.(cont.)
Subjects with Treatment-Emergent Markedly Abnormal Laboratory Values: Levofloxacin-treated Subjects Evaluable for Safety (Study M92-075)

Subject Number	Age	Sex	Laboratory Test (Markedly Abnormal Range)	Admission Value	Abnormal Value	Study Day*	Follow-up Value (Therapy Day)	Duration of Therapy (Days)
Levofloxacin								
	75	M	Alkaline Phosphatase (>250 IU/L)	133.00	466.00	14	–	15
			SGOT (>75 IU/L)	48.00	105.00	14	–	15
			SGPT (>75 IU/L)	38.00	168.00	14	–	15
			Glucose (<70 or >200 mg/dL)	110.00	301.00	8	–	15
					372.00	14	–	15
			Lymphocytes (<1.0 x 10^9/µL)	0.88	0.29	8	0.65 (14PT)	15
	79	M	Glucose (<70 or >200 mg/dL)	102.00	62.00	4	92.00 (4PT)	12
	72	F	Glucose (<70 or >200 mg/dL)	135.00	65.00	4	130.00 (8PT)	14
	22	M	Lymphocytes (<1.0 x 10^9/µL)	1.58	0.71	4	1.34 (3PT)	12
	49	M	SGOT (>75 IU/L)	30.00	82.00	3	–	3
	67	M	Glucose (<70 or >200 mg/dL)	96.00	61.00	4	87.00 (4PT)	14
	49	M	SGPT (>75 IU/L)	16.00	94.00	4	27.00 (5PT)	14
	72	F	Blood Urea Nitrogen (>40 mg/dL)	23.00	42.00	3	11.00 (8PT)	14
			SGOT (>75 IU/L)	22.00	259.00	3	18.00 (8PT)	14
			SGPT (>75 IU/L)	17.00	153.00	3	25.00 (8PT)	14
			Lymphocytes (<1.0 x 10^9/µL)	1.00	0.58	16 (2PT)	1.57 (8PT)	14

*Only range given in table. For complete criteria, see Attachment 29a.
†Relative to start of therapy (Day 1). NOTE: PT refers to the number of days post therapy, relative to the last day of study drug administration.
‡Duration of therapy unknown; subject lost to follow-up.

14.7.4. Physical Examinations and Vital Signs

There were no clinically significant changes from admission to posttherapy. In general, the observed mean changes in vital signs were consistent with the resolution or improvement in the signs and symptoms of pneumonia. Clinically significant treatment-emergent hypotension was observed in one subject [redacted], who discontinued from the study because of marked respiratory depression and subsequently died. No other subjects had clinically significant treatment-emergent vital signs changes, and there were no clinically significant treatment-emergent physical examination abnormalities.

Table 14.7.4.
Summary of Changes in Vital Signs From Admission to Posttherapy: Subjects Evaluable for Safety (Study M92-075)

		Levofloxacin					
		Admission		Posttherapy		Change	
Vital Sign	N*	Mean	(SD)	Mean	(SD)	Mean	(SD)
Oral Temperature (°F)	245	99.7	(1.81)	98.1	(1.06)	-1.6	(2.01)
Respiratory Rate (breaths/min)	244	22.4	(5.34)	19	(3.27)	-3.3	(6.05)
Pulse Rate (beats/min)	253	95.8	(19.30)	83.1	(14.15)	-12.7	(18.62)
Systolic Blood Pressure (mm Hg)	255	130.5	(23.19)	123.4	(18.89)	-7.2	(21.85)
Diastolic Blood Pressure (mm Hg)	255	75.3	(13.21)	73.1	(10.92)	-2.2	(12.56)

*N = Number of subjects with admission and posttherapy vital signs data.

15. Medical Officer's Conclusions from Study M92-075:

15.1. Clinical and Microbiologic Efficacy

15.1.1. Protocol M92-075 was an uncontrolled study evaluating the clinical and microbiologic efficacy of levofloxacin in the treatment of community-acquired pneumonia due to typical and atypical pathogens.

15.1.2. Protocol M92-075 has significant flaws in the protocol design including:

15.1.2.1. The window for clinical evaluation at the End-of-therapy was inappropriate. In this protocol, the window for EOT evaluation was changed to span from post-therapy day 1-10. This is not in keeping with either (1) the IDSA guidelines, which recommend follow-up on posttherapy day 5-7 or (2) DAIDP consultants, which recommend that follow-up evaluations for this indication be conducted no earlier than day 7 posttherapy.

15.1.2.2. Post-study clinical evaluation, was conducted at 21-28 days post-therapy and was within an appropriate time frame for late follow-up, but was not conducted on all patients. Patients without clinical symptoms at the posttherapy evaluation and without X-ray evidence of pneumonia at the posttherapy evaluation were not brought back for late follow-up. This results in the introduction of bias into the cohort evaluated at the late follow-up.

15.1.3. Protocol M92-075 has significant flaws in the protocol implementation including:

15.1.3.1. Omission of culture of persistent pulmonary secretions at the follow-up visits (both EOT and EOS), with overuse of the designation of "presumed eradication" in cases where documentation of microbiologic outcome was possible.

15.1.3.2. Changes in drug dosage and duration were made during the course of the study

15.1.3.3. Provisions for addition of doxycycline antimicrobial coverage for atypical pneumonia, as an alternative to erythromycin, was added to the cephalosporin-treatment arm during the course of the study.

15.1.3.4. Changes in the days of the post-therapy follow-up evaluation were made during the course of the study

15.1.4. Clinical Outcome

In protocol M92-075, the **clinical cure rate** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 52% (105/203). The **clinical success rate** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 93% (188/203). In protocol M92-075, the **overall success rate (clinically cured or improved plus microbiologically eradicated)** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 94% (151/161).

For comparison, in protocol K90-071, the **clinical cure rate** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 62% (129/207) for levofloxacin-treated patients, and the **clinical success (cured or improved) rate** was 95% (197/207) for levofloxacin-treated patients. The **overall success rate (clinically cured or improved plus microbiologically eradicated)** in FDA evaluable patients with a diagnosis of community-acquired pneumonia was 96% (113/118) for levofloxacin-treated patients.

Thus, although the clinical cure rate for levofloxacin-treated patients was higher in Protocol M90-071, the clinical success rates and overall success rates of M92-075 were comparable to K90-071 and support the efficacy of levofloxacin in the treatment of community acquired pneumonia.

15.1.5. Microbiologic Outcome and Clinical Outcome by Pathogen

15.1.5.1. Bacterial Pathogens

15.1.5.1.1. *Haemophilus influenzae*

The total number of isolates[2] of *Haemophilus influenzae* was 29, of which 28 were microbiologically evaluable. The clinical cure rate for patients with *Haemophilus influenzae* in levofloxacin-treated patients was 59% (17/29), and the clinical success rate was 90% (26/29). The eradication rate of *Haemophilus influenzae* was 96% (27/28). ***The overall success rate for patients with Haemophilus influenzae in levofloxacin-treated patients was 96%.*** Thus, the total number of isolates is adequate, and the absolute eradication rate supports the inclusion of this organism in the labeling.

15.1.5.1.2. *Haemophilus parainfluenzae*

The total number of isolates of *Haemophilus parainfluenzae* was 11, of which 10 were microbiologically evaluable. The clinical cure rate for patients with *Haemophilus parainfluenzae* in levofloxacin-treated patients was 45% (5/11), and the clinical success rate was 91% (10/11). The eradication rate of *Haemophilus parainfluenzae* was 90% (9/10). Thus, the total number of isolates is adequate, and the absolute rate supports the inclusion of this organism in the labeling.

15.1.5.1.3. *Streptococcus pneumoniae*

The total number of isolates of *Streptococcus pneumoniae* patients was 49, of which 48 were microbiologically evaluable. The clinical cure rate for patients with *Streptococcus pneumoniae* was 31% (15/49), and the clinical success rate was 92% (45/49). The eradication rate of *Streptococcus pneumoniae* was 94% (45/48). Thus, the total number of isolates is adequate, and the absolute and relative eradication rates all support the inclusion of this organism in the labeling.

15.1.5.1.4. *Klebsiella pneumoniae*

The total number of isolates of *Klebsiella pneumoniae* was 5, all of which were microbiologically evaluable. The clinical cure rate for patients with *Klebsiella pneumoniae* was 80% (4/5), and the clinical success rate was 100% (5/5). The eradication rate of *Klebsiella pneumoniae* was 100% (5/5). Thus, the total number of isolates is inadequate, although the absolute eradication rate would support the inclusion of this organism in the labeling.

15.1.5.1.5. *Moraxella catarrhalis*

The total number of isolates of *Moraxella catarrhalis* was 11, all of which were microbiologically evaluable. The clinical cure rate for patients with *Moraxella catarrhalis* was 82% (9/11). The clinical success rate for patients with *Moraxella catarrhalis* was 91% (10/11). The eradication rate of *Moraxella catarrhalis* was 100% (11/11). Thus, the total number of

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[2] All isolates are reported as (1) total number of isolates obtained on admission culture and (2) the number of these that were microbiologically evaluable. Clinical responses were calculated on the basis of total number of isolates on admission culture, and eradication rates were calculated on the number of microbiologically evaluable isolates.

isolates is adequate, and the absolute eradication rate would support the inclusion of this organism in the labeling.

15.1.5.1.6. ***Staphylococcus aureus***

The **total number of isolates** of *Staphylococcus aureus* was 11, of which 10 were microbiologically evaluable. The **clinical cure rate** for patients with *Staphylococcus aureus* was 64% (7/11). The **clinical success rate** for patients with *Staphylococcus aureus* was 73% (8/11). The **eradication rate** of *Staphylococcus aureus* was 82%. Thus, the total number of isolates is adequate, aand the absolute eradication rate would support the inclusion of this organism in the labeling.

15.1.5.2. **Atypical Pathogens**

15.1.5.2.1. ***Legionella pneumoniae***

The **total number of microbiologically evaluable patients** with *Legionella pneumoniae* as an admission pathogen was 4. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, 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. There were no cases defined by isolation of the organism from culture of respiratory secretions. The **clinical cure rate** for patients with *Legionella pneumoniae* was 25% (1/4). The **clinical success rate** for patients with *Legionella pneumoniae* was 50% (2/4). The **eradication rate** of *Legionella pneumoniae* was 75% (3/4). Thus, the total number of isolates is inadequate, although the absolute eradication rate in would support the inclusion of this organism in the labeling by a narrow margin.

15.1.5.2.2. ***Chlamydia pneumoniae***

The **total number of microbiologically evaluable patients** with *Chlamydia pneumoniae* as an admission pathogen was 103. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, allowed for both culture and serologic methods in the diagnosis of *Chlamydia pneumoniae* infection, the microbiologically evaluable patient cohort was composed entirely of cases diagnosed by serologic methods. There were no cases defined by isolation of the organism from culture of respiratory secretions. The **clinical cure rate** for patients with *Chlamydia pneumoniae* was 51% (53/103). The **clinical success rate** for patients was 95% (98/103). The **eradication rate** of *Chlamydia pneumoniae* was 95% (98/103). Thus, the total number of isolates is adequate, and the absolute eradication rate would support the inclusion of this organism in the labeling.

15.1.5.2.3. ***Mycoplasma pneumoniae***

The **total number of microbiologically evaluable patients** with *Mycoplasma pneumoniae* as an admission pathogen was 6. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, allowed for both culture and serologic methods in the diagnosis of *Mycoplasma pneumoniae* infection, the microbiologically evaluable patient cohort was composed entirely of cases diagnosed by serologic methods. There were no cases defined by isolation of the organism from culture of respiratory secretions. The **clinical cure rate** for patients with *Mycoplasma pneumoniae* was 50% (3/6). The **clinical**

Pathogen	Levofloxacin 500 mg QD			Ceftriaxone/ cefuroxime (K90-071)			95% Confidence Intervals
	N*	Cure		N*	Cure		
Routine pathogens							
Haemophilus influenzae	56	39	(64)	24	10	(42)	(-61, -19)
Haemophilus parainfluenzae	20	10	(50)	20	7	(35)	(-45, 15)
Klebsiella pneumoniae	6	5	(83)	7	2	(29)	-----
Moraxella catarrhalis	18	13	(72)	6	4	(67)	-----
Staphylococcus aureus	18	14	(78)	7	6	(86)	-----
Streptococcus pneumoniae	63	32	(51)	34	22	(65)	(-6, 34)
Other pathogens							
Chlamydia pneumoniae	162	89	(55)	91	44	(48)	(-20, 6)
Legionella pneumophilia	7	5	(57)	2	0	(0)	-----
Mycoplasma pneumoniae	27	15	(56)	20	12	(60)	(-24, 32)

*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 eradication rate for organisms with ≥10 isolates per treatment arm.

16.1.5. Clinical Success Rate by Pathogen

Table 16.1.5 summarizes the **clinical success rate (defined as the combined percentage of patients who were clinically cured or improved at the posttherapy clinical evaluation)** by pathogen for the pathogens requested by the sponsor in the proposed package insert. The absolute **clinical success rate** for levofloxacin ranges from %. The accuracy of the estimate for clinical success rate in the treatment of *Legionella pneumophilia* is limited the small number of isolates. The estimate of the clinical success rate for *Klebsiella pneumoniae* is also limited by the small number of isolates. Thus, when restricted to pathogens with ten or more cases per treatment arm, the **clinical success rate** for levofloxacin ranges from %. In addition, the 95% confidence intervals around the difference in clinical success rates (competitor minus levofloxacin) all overlap zero or lie within the negative range, indicating that levofloxacin is statistically equivalent to the comparative treatment regimen of ceftriaxone/cefuroxime in the treatment of the major pathogens of community-acquired pneumonia when assessed by post-therapy clinical success rate.

success rate for patients with *Mycoplasma pneumoniae* was 100% (6/6). The eradication rate of *Mycoplasma pneumoniae* was 100% (6/6). Thus, the total number of isolates is inadequate, although the absolute and relative eradication rates in would support the inclusion of this organism in the labeling.

16. Combined Analysis of Protocols 90-071 and 92-075:

A combined analysis was made of the two pivotal studies (Protocols K90-071 and M92-075) submitted to support the approval of levofloxacin for the treatment of community-acquired pneumonia. This section contains summary tables and concise discussion of this analysis. Section 16.1 discusses the analysis of clinical efficacy results for this indication. Section 16.2 discusses the microbiologic efficacy results for this indication, including a summary by individual pathogen for those microorganisms requested by the sponsor in the proposed product labeling.

16.1. Clinical Efficacy:

16.1.1 Clinical Cure Rate by Protocol

Protocol K90-071 demonstrated a **clinical cure rate** for levofloxacin of 62% (129/207) and for ceftriaxone/cefuroxime of 46% (105/226). The 95% confidence interval around the difference in cure rates in the two treatment arms of Protocol K90-071 was $_{226,207}$ (-25, -7) $_{48\%,62\%}$, indicating superiority of levofloxacin in the treatment of community-acquired pneumonia. Protocol M92-075 demonstrated a clinical cure rate of levofloxacin was 52% (105/203) in the treatment of community-acquired pneumonia, which was slightly lower than that in the levofloxacin arm of Protocol K90-071.

A combined analysis of the clinical response for protocols K90-017 and M92-075 is summarized in the Tables 16.1.A and 16.1.B, below. The overall clinical cure rate for levofloxacin-QD-treated patients was 57% (234/410) and that for the ceftriaxone/cefuroxime-treated patients was 46% (105/226). The 95% confidence interval around the difference in cure rates was $_{226,\ 410}$(-19, -3)$_{46\%,\ 57\%}$, indicating that levofloxacin was statistically superior to competitor in the treatment of community-acquired pneumonia.

Table 16.1.1.A
Community-acquired Pneumonia
Clinical Response Rate by Protocol:
FDA Clinically Evaluable Subjects (Protocols K90-071 and M92-075)

Protocol	Levofloxacin 500 mg QD						Ceftriaxone/ cefuroxime (K90-071)					
	N*	Cure		Improve		Fail	N	Cure		Improve		Fail
K90-071	207	129	(62)	68	(33)	10 (5)	226	105	(46)	82	(36)	39 (17)
M92-075	203	105	(52)	83	(41)	15 (7)	---	---	--	--	--	-- --
Total	410	234	(57)	151	(37)	25 (6)	226	105	(46)	82	(36)	39 (17)

*N=Number of patients for that category. Numbers shown in parentheses are percentages for that category.

Table 16.1.1.B
Community-acquired Pneumonia
Clinical Cure Rates and Confidence Intervals by Protocol:—
FDA Clinically Evaluable Subjects (Protocols K90-071 and M92-075)

Protocol	Levofloxacin 500 mg QD		Ceftriaxone/cefuroxime (K90-071)		95% Confidence Interval**
	N*	Cure	N	Cure	
K90-071	207	129 (62)	226	105 (46)	(-25, -7)
M92-075	203	105 (52)	---	--- ---	-----
Total	410	234 (57)	226	105 (46)	(-19, -3)

*N=Number of patients for that category. Numbers shown in parentheses are percentages for that category.

**Two-sided confidence interval for the difference (competitor minus levofloxacin) in clinical success rate.

16.1.2. Clinical Success Rate by Protocol

Protocol K90-071 demonstrated a **clinical success rate (defined as the combined percentage of patients who were clinically cured or improved at the posttherapy clinical evaluation)** for levofloxacin of 95% (197/207) and for ceftriaxone/cefuroxime of 83% (193/226). The 95% confidence interval around the difference in clinical success rates in the two treatment arms of Protocol K90-071 was $_{226,255}(-18.6, -6.2)_{95\%,83\%}$, indicating superiority of levofloxacin in the treatment of community-acquired pneumonia. Protocol M92-075 demonstrated a clinical success rate of levofloxacin was 93% (188/203) in the treatment of community-acquired pneumonia, which was comparable to that seen in the levofloxacin arm of Protocol K90-071.

A combined analysis of the clinical success rates for protocols K90-017 and M92-075 is summarized in the Table 16.1.C, on the following page. The overall clinical success rate for levofloxacin-QD-treated patients was 94% (385/410) and that for the ceftriaxone/cefuroxime-treated patients was 83% (187/226). The 95% confidence interval around the difference in cure rates was $_{226,410}(-16, -6)_{83\%,94\%}$, indicating that levofloxacin was statistically superior to competitor in the treatment of community-acquired pneumonia.

Table 16.1.2
Community-acquired Pneumonia
Clinical Success Rates and Confidence Intervals By Study Center:
FDA Clinically Evaluable Subjects (Protocols K90-071 and M92-075)

Protocol	Levofloxacin 500 mg QD			Ceftriaxone/cefuroxime (K90-071)			95% Confidence Interval***
	N*	Success**		N	Success		
K90-071	207	197	(95)	226	187	(83)	(-19, -6)
M92-075	203	188	(93)	---	---	--	-----
Total	410	385	(94)	226	187	(83)	(-16, -6)

*N=Number of patients for that category. Numbers in parentheses are percentages for that category.
**Clinical success is defined as either clinical cure or clinical improvement.
***Two-sided confidence interval for the difference (competitor minus levofloxacin) in clinical success rate.

16.1.3. Overall Success Rate by Protocol

Protocol K90-071 demonstrated an **overall success rate (defined as the combined percentage of patients who were clinically cured or improved at the posttherapy clinical evaluation PLUS had eradication of their admission pathogen)** for levofloxacin of 96% (113/118) and for ceftriaxone/cefuroxime of 80% (122/152). The 95% confidence interval around the difference in overall success rates in the two treatment arms of Protocol K90-071 was $_{152,118}(-23.5, -7.4)_{80\%,96\%}$, indicating superiority of levofloxacin in the treatment of community-acquired pneumonia. Protocol M92-075 demonstrated an overall success rate of levofloxacin was 94% (151/161) in the treatment of community-acquired pneumonia, which was comparable to that seen in the levofloxacin arm of Protocol K90-071.

A combined analysis of the overall success rates for protocols K90-017 and M92-075 is summarized in the Table 16.1.D, below. The overall clinical cure rate for levofloxacin-QD-treated patients was 95% (264/279) and that for the ceftriaxone/cefuroxime-treated patients was 80% (122/152). The 95% confidence interval around the difference in overall success rates was $_{226,410}(-22, -8)_{80\%,95\%}$ indicating that levofloxacin was statistically superior to competitor.

Table 16.1.D
Community-acquired Pneumonia
Overall Success Rates by Protocol:
FDA Clinically and Microbiologically Evaluable Subjects
(Protocols K90-071 and M92-075)

Protocol	Levofloxacin		Ceftriaxone/ cefuroxime (K90-071)		95% Confidence Interval***
	N*	Overall Success**	N	Overall Success	
K90-071	118	113 (96)	152	122 (80)	(-24, -7)
M92-075	161	151 (94)	---	--- ---	----
Total	279	264 (95)	152	122 (80)	(-22, -8)

*N=Number of patients for that category. Numbers in parentheses are percentages for that category.
**Overall success is defined as clinical cure or improvement with microbiologic eradication.
***Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in overall success rate.

16.1.4. Clinical Cure Rate by Pathogen

Tables 16.1.4.A and 16.1.4.B summarize the clinical response by pathogen for the pathogens requested by the sponsor in the proposed package insert. The absolute **clinical cure rate** for levofloxacin ranges from 50-83%, which would appear suboptimal to support the use of levofloxacin for the treatment of community-acquired pneumonia. However, the 95% confidence intervals around the difference in cure rates (competitor minus levofloxacin) all overlap zero or lie within the negative range, indicating that levofloxacin is at least statistically equivalent to the comparative treatment regimen of ceftriaxone/cefuroxime in the treatment of the major pathogens of community-acquired pneumonia when assessed by post-therapy clinical cure rate.

Table 16.1.4.A
Clinical Response by Pathogen:
FDA Clinically Evaluable Subjects (Protocols K90-071 and M92-075)

Pathogen	Levofloxacin 500 mg QD								Ceftriaxone/ cefuroxime (K90-071)							
	N*	Cure		Improve		Fail			N*	Cure		Improve		Fail		
Routine pathogens																
Haemophilus influenzae	56	39	(64)	14	(25)	3	(5)		24	10	(42)	5	(21)	9	(38)	
Haemophilus parainfluenzae	20	10	(50)	9	(45)	1	(5)		20	7	(35)	6	(30)	7	(35)	
Klebsiella pneumoniae	6	5	(83)	1	(17)	0	(0)		7	2	(29)	0	(0)	5	(71)	
Moraxella catarrhalis	18	13	(72)	3	17)	2	(11)		6	4	(67)	1	(17)	1	(17)	
Staphylococcus aureus	18	14	(78)	1	(6)	3	(17)		7	6	(86)	1	(14)	0	(0)	
Streptococcus pneumoniae	63	32	(51)	28	(44)	3	(5)		43	22	(65)	7	(21)	5	(15)	
Other pathogens																
Chlamydia pneumoniae	162	89	(55)	66	(41)	7	(4)		91	44	(48)	34	(37)	13	(14)	
Legionella pneumophilia	7	4	(57)	1	(14)	2	(29)		2	0	(0)	0	(0)	2	(100)	
Mycoplasma pneumoniae	27	15	(56)	11	(41)	1	(4)		20	12	(60)	7	(35)	1	(5)	

*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 16.1.4.B
Clinical Cure Rates and Confidence Intervals by Pathogen:
FDA Clinically Evaluable Subjects (Protocols K90-071 and M92-075)

Pathogen	Levofloxacin 500 mg QD			Ceftriaxone/ cefuroxime (K90-071)			95% Confidence Intervals - -
	N*	Cure		N*	Cure		
Routine pathogens							
Haemophilus influenzae	56	39	(64)	24	10	(42)	(-61, -19)
Haemophilus parainfluenzae	20	10	(50)	20	7	(35)	(-45, 15)
Klebsiella pneumoniae	6	5	(83)	7	2	(29)	-----
Moraxella catarrhalis	18	13	(72)	6	4	(67)	-----
Staphylococcus aureus	18	14	(78)	7	6	(86)	-----
Streptococcus pneumoniae	63	32	(51)	34	22	(65)	(-6, 34)
Other pathogens							
Chlamydia pneumoniae	162	89	(55)	91	44	(48)	(-20, 6)
Legionella pneumophilia	7	4	(57)	2	0	(0)	-----
Mycoplasma pneumoniae	27	15	(56)	20	12	(60)	(-24, 32)

*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 eradication rate for organisms with ≥10 isolates per treatment arm.

16.1.5. Clinical Success Rate by Pathogen

Table 16.1.5 summarizes the **clinical success rate (defined as the combined percentage of patients who were clinically cured or improved at the posttherapy clinical evaluation)** by pathogen for the pathogens requested by the sponsor in the proposed package insert. The absolute **clinical success rate** for levofloxacin ranges from 71-100%. The accuracy of the estimate for clinical success rate in the treatment of *Legionella pneumophilia* is limited the small number of isolates. The estimate of the clinical success rate for *Klebsiella pneumoniae* is also limited by the small number of isolates. Thus, when restricted to pathogens with ten or more cases per treatment arm, the **clinical success rate** for levofloxacin ranges from 83-96%. In addition, the 95% confidence intervals around the difference in clinical success rates (competitor minus levofloxacin) all overlap zero or lie within the negative range, indicating that levofloxacin is statistically equivalent to the comparative treatment regimen of ceftriaxone/cefuroxime in the treatment of the major pathogens of community-acquired pneumonia when assessed by post-therapy clinical success rate.

Table 16.1.5
Community-acquired Pneumonia
Clinical Success Rates by Pathogen:
FDA Clinically Evaluable Subjects (Protocols K90-071 and M92-075)

Pathogen	Levofloxacin 500 mg QD		Ceftriaxone/ cefuroxime (K90-071)		95% Confidence Interval***
	N*	Clinical Success**	N*	Clinical Success	
Routine pathogens					
Haemophilus influenzae	56	53 (95)	24	15 (62)	(-57, -19)
Haemophilus parainfluenzae	20	19 (95)	20	13 (65)	(-53, -7)
Klebsiella pneumoniae	6	6 (100)	7	2 (29)	- - -
Moraxella catarrhalis	18	16 (89)	6	5 (83)	- - -
Staphylococcus aureus	18	15 (83)	7	7 (100)	- - -
Streptococcus pneumoniae	63	60 (95)	34	29 (85)	(-23, 3)
Other pathogens					
Chlamydia pneumoniae	162	155 (96)	91	78 (86)	(-18, -2)
Legionella pneumophilia	7	5 (71)	2	0 (0)	- - -
Mycoplasma pneumoniae	27	26 (96)	20	19 (95)	(-13, 13)

*N=number of subjects who had that pathogen alone or in combination with other pathogens. Numbers shown in parentheses are percentages for that category.
**Clinical success is defined as clinical cure or improvement
***Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in clinical success rate.

16.2. Microbiologic outcome of FDA clinically and microbiologically evaluable patient cohort

A combined analysis of protocols K90-071 and M92-075 is summarized in the following sections. Sections 6.2.1 and 16.2.2 contain an overall analysis, and Sections 16.2.3 and 16.2.4 contain an analysis by individual pathogen for routine bacterial pathogens and atypical pathogens, respectively.

16.2.1. Microbiologic eradication rates by pathogen

Summary tables for the combined microbiologic efficacy results from Protocols K90-071 and M92-075 are provided. Table 16.2.1 summarizes the microbiologic eradication rates by pathogen and pathogen category for the pathogens requested by the sponsor in the proposed package insert. With the exceptions of *Legionella pneumophilia* and *Klebsiella pneumoniae*, each microorganism was isolates with a sufficient number of microbiologically evaluable cases to support the inclusion of that organism in the labeling.

Table 16.2.1.
Community-acquired Pneumonia
Eradication Rates by Pathogen Category and Pathogen:
FDA Clinically and Microbiologically Evaluable Subjects
(Protocols K90-071 and M92-075)

Pathogen Category/Pathogen	Levofloxacin 500 mg QD		Ceftriaxone/ cefuroxime (K90-071)		95% Confidence Interval**
	N*	Eradicated	N	Eradicated	
Pathogen Category					
Gram-positive aerobic pathogens	130	112 (86)	63	58 (92)	(-3, 15)
Gram-negative aerobic pathogens	138	132 (96)	79	53 (67)	(-40, -18)
Other	165	159 (96)	91	83 (91)	(-12, 2)
Total by pathogen	433	413 (95)	233	194 (83)	(-17, -7)
Total by subject	280	265 (95)	152	123 (81)	(-21, -7)
Routine Pathogens					
Haemophilus influenzae	55	54 (98)	20	14 (70)	(-48, -8)
Haemophilus parainfluenzae	19	18 (95)	19	12 (63)	(-56, -8)
Klebsiella pneumoniae	6	6 (100)	7	3 (43)	---
Moraxella catarrhalis	18	17 (94)	6	5 (83)	---
Staphylococcus aureus	17	15 (88)	7	7 (100)	---
Streptococcus pneumoniae	60	57 (95)	31	26 (84)	(-25, 3)
Other Pathogens					
Chlamydia pneumoniae	161	154 (96)	90	78 (87)	(-17, -1)
Legionella pneumoniae	7	6 (86)	2	0 (0)	---
Mycoplasma	27	26 (96)	20	19 (95)	(-13, 11)

*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 microbiologic eradication rate was calculated for pathogens with 10 or more microbiologically evaluable isolates in each treatment group.

The microbiologic eradication rates for levofloxacin are all ≥86%, indicating that the absolute eradication rates for levofloxacin would all support the use of levofloxacin for this indication and the inclusion of these organisms in the package insert. In addition, the 95% confidence intervals all overlap zero or lie within the negative range, indicating that levofloxacin is at least statistically equivalent to the comparative regimen of ceftriaxone/cefuroxime.

16.2.2. Overall success rates by pathogen

Table 16.2.2 summarizes the **overall success rates (defined as the combined percentage of patients who were clinically cured or improved at the posttherapy clinical evaluation PLUS had eradication of their admission pathogen)** by pathogen and pathogen category for the pathogens requested by the sponsor in the proposed package insert. The overall success rates for those organisms with ≥10 cases per treatment arm range from 75-98%. In addition, the 95% confidence interval around the difference in treatment arms (competitor minus levofloxacin) all overlap zero of lie within the negative range, indicating that levofloxacin is at least statistically equivalent to the comparative regiment of ceftriaxone/cefuroxime.

Table 16.2.2
Community-acquired Pneumonia
Overall Success Rates by Pathogen:
FDA Microbiologically Evaluable Subjects (Protocols K90-071 and M92-075)

Pathogen	Levofloxacin 500 mg QD		Ceftriaxone/ cefuroxime (K90-071)		95% Confidence Interval***
	N*	Overall Success**	N*	Overall Success	
Routine pathogens					
Haemophilus influenzae	55	54 (98)	20	14 (70)	(-48, -8)
Haemophilus parainfluenzae	19	15 (79)	19	12 (63)	(-44, 12)
Klebsiella pneumoniae	6	6 (100)	7	2 (29)	-----
Moraxella catarrhalis	18	16 (89)	6	6 (100)	-----
Staphylococcus aureus	17	15 (88)	7	7 (100)	-----
Streptococcus pneumoniae	60	57 (95)	31	26 (84)	(-25, 3)
Other pathogens					
Chlamydia pneumoniae	161	154 (96)	90	78 (87)	(-17, -1)
Legionella pneumophilia	7	5 (71)	2	0 (0)	-----
Mycoplasma pneumoniae	27	25 (93)	20	19 (95)	(-12, 16)

*N=number of subjects who had that pathogen alone or in combination with other pathogens. Numbers shown in parentheses are percentages for that category.
**Overall success is defined as clinical cure or improvement PLUS microbiologic eradication
***Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in clinical success rate.

16.2.3. Routine Bacterial Pathogens

16.2.3.1. *Haemophilus influenzae*

The total number of microbiologically evaluable isolates of *Haemophilus influenzae* from levofloxacin-QD-treated patients was 55: 27 in K90-071 and 28 in M92-075. The total number of isolates of *Haemophilus influenzae* was 20 in ceftriaxone/cefuroxime-treated patients in protocol K90-071.

Table 16.2.3.1
Overall analysis for *Haemophilus influenzae*
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 Overall	22/27 (81) 17/29 (59) 39/56 (64)	(-65, -13) --- (-47, 3)
	Ceftriaxone/cefuroxime	K90-071	10/24 (42)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	27/27 (100) 26/29 (90) 53/56 (95)	(-57, -19) --- (-53, -13)
	Ceftriaxone/cefuroxime	K90-071	15/24 (62)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	27/27 (100) 27/28 (96) 54/55 (98)	(-50, -10) --- (-48, -8)
	Ceftriaxone/cefuroxime	K90-071	14/20 (70)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	27/27 (100) 27/28 (96) 54/55 (98)	(-50, -10) --- (-48, -8)
	Ceftriaxone/cefuroxime	K90-071	14/20 (70)	---

*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 *Haemophilus influenzae* 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

With the exception of the combined analysis of clinical cure rate, the 95% confidence intervals for the difference (ceftriaxone/cefuroxime minus levofloxacin) in the parameters of efficacy (cure rate, clinical success rate, eradication rate, overall success rate) all lie within the negative range, indicating the superiority of levofloxacin over competitor in the treatment of community-acquired pneumonia due to *Haemophilus influenzae*. Thus, the total number of isolates is adequate, and the absolute and relative efficacy rates support the inclusion of *Haemophilus influenzae* in the labeling.

16.2.3.2. Haemophilus parainfluenzae

The total number of microbiologically evaluable isolates of Haemophilus parainfluenzae from levofloxacin-treated patients was 19: 9 in K90-071 and 10 in M92-075. The total number of isolates of *Haemophilus parainfluenzae* was 19 in ceftriaxone/cefuroxime-treated patients in protocol K90-071.

Table 16.2.3.2
Overall analysis for *Haemophilus parainfluenzae*
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 Overall	5/9 (56) 5/11 (45) 10/20 (50)	N/A --- (-45, 15)
	Ceftriaxone/cefuroxime	K90-071	7/20 (35)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	9/9 (100) 10/11 (91) 19/20 (95)	N/A --- (-83, -37)
	Ceftriaxone/cefuroxime	K90-071	13/20 (65)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	9/9 (100) 9/10 (90) 18/19 (95)	N/A --- (-56, -8)
	Ceftriaxone/cefuroxime	K90-071	12/19 (63)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	7/9 (78) 8/10 (80) 15/19 (79)	N/A --- (-44, 12)
	Ceftriaxone/cefuroxime	K90-071	12/19 (63)	---

*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 *Haemophilus parainfluenzae* 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 the 95% confidence intervals for the difference (ceftriaxone/cefuroxime minus levofloxacin) in the parameters of efficacy (cure rate, clinical success rate, eradication rate, overall success rate) all either (1) overlap zero, indicating statistical equivalence, or (2) lie within the negative range, indicating the superiority of levofloxacin over competitor in the treatment of community-acquired pneumonia due to *Haemophilus parainfluenzae*. Thus, the total number of isolates is adequate, and the absolute and relative efficacy rates support the inclusion of *Haemophilus parainfluenzae* in the labeling.

16.2.3.3. Klebsiella pneumoniae

The total number of microbiologically evaluable isolates of *Klebsiella pneumoniae* from levofloxacin-treated patients was 6: 1 in K90-071 and 5 in M92-075. The total number of isolates of *Klebsiella pneumoniae* was 7 in ceftriaxone/cefuroxime-treated patients in protocol K90-071.

Table 16.2.3.4
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 Overall	1/1 (100) 4/5 (80) 5/6 (83)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	2/7 (29)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	1/1 (100) 5/5 (100) 6/6 (100)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	2/7 (29)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	1/1 (100) 5/5 (100) 6/6 (100)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	3/7 (43)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	1/1 (100) 5/5 (100) 6/6 (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 inadequate to support the inclusion of *Klebsiella pneumoniae* in the labeling, even though the absolute eradication rates would support the use of levofloxacin for the treatment of community-acquired pneumoniae due to *Klebsiella pneumoniae*.

16.2.3.4. Moraxella catarrhalis

The total number of microbiologically evaluable isolates of *Moraxella catarrhalis* from levofloxacin-treated patients was 18: 7 in K90-071 and 11 in M92-075. The total number of isolates of *Moraxella catarrhalis* was 6 in ceftriaxone/cefuroxime-treated patients in protocol K90-071.

Table 16.2.3.5
Overall analysis for *Moraxella catarrhalis*
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 Overall	4/7 (57) 9/11 (82) 13/18 (72)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	4/6 (67)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	6/7 (86) 10/11 (91) 16/18 (89)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	5/6 (83)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	6/7 (86) 11/11 (100) 17/18 (94)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	5/6 (83)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	6/7 (86) 10/11 (91) 16/18 (89)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	5/6 (83)	---

*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 *Moraxella catarrhalis* 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 in the comparator arm to calculate 95% confidence intervals for any of the parameters of efficacy. However, the total number of isolates in the levofloxacin-treated arm is adequate to support the inclusion of *Moraxella catarrhalis* in the labeling. In addition, the absolute rates for all parameters of efficacy are adequate to support the use of levofloxacin for the treatment of community-acquired pneumoniae due to *Moraxella catarrhalis*.

16.2.3.5. Staphylococcus aureus

The total number of microbiologically evaluable isolates of *Staphylococcus aureus* from levofloxacin-treated patients was 17: 7 in K90-071 and 10 in M92-075. The total number of isolates of *Staphylococcus aureus* was 7 in ceftriaxone/cefuroxime-treated patients in protocol K90-071.

Table 16.2.3.6
Overall analysis for *Staphylococcus aureus*
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 Overall	7/7 (100) 7/11 (64) 14/18 (78)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	6/7 (86)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	7/7 (100) 8/11 (73) 15/18 (83)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	7/7 (100)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	7/7 (100) 8/10 (80) 15/17 (88)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	7/7 (100)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	7/7 (100) 8/10 (80) 15/17 (88)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	7/7 (100)	---

*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 *Staphylococcus aureus* 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 in the comparator arm to calculate 95% confidence intervals for any of the parameters of efficacy. However, the total number of isolates in the levofloxacin-treated arm is adequate to support the inclusion of *Staphylococcus aureus* in the labeling. In addition, the absolute rates for all parameters of efficacy are adequate to support the use of levofloxacin for the treatment of community-acquired pneumoniae due to *Staphylococcus aureus* .

16.2.3.3. Streptococcus pneumoniae

The total number of microbiologically evaluable isolates of *Streptococcus pneumoniae* from levofloxacin-treated patients was 60: 26 in K90-071 and 34 in M92-075. The total number of microbiologically evaluable patients with isolates of *Streptococcus pneumoniae* was 31 in the ceftriaxone/cefuroxime-treated arm of protocol K90-071.

Table 16.2.3.3
Overall analysis for *Streptococcus 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 Overall	20/29 (69) 12/34 (35) 32/63 (51)	(-27, 19) --- (-6, 34)
	Ceftriaxone/cefuroxime	K90-071	22/34 (65)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	28/29 (97) 30/34 (88) 60/63 (95)	(-26, 2) --- (-23, 3)
	Ceftriaxone/cefuroxime	K90-071	29/34 (85)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	25/26 (96) 32/34 (94) 57/60 (95)	(-27, 3) --- (-25, 3)
	Ceftriaxone/cefuroxime	K90-071	26/31 (84)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	25/26 (96) 32/34 (94) 57/60 (95)	(-27, 3) --- (-25, 3)
	Ceftriaxone/cefuroxime	K90-071	26/31 (84)	---

*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 *Streptococcus 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 the 95% confidence intervals for the difference (ceftriaxone/cefuroxime minus levofloxacin) in the parameters of efficacy (cure rate, clinical success rate, eradication rate, overall success rate) all overlap zero, indicating the statistical equivalence of levofloxacin to ceftriaxone/cefuroxime in the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae*. Thus, the total number of isolates is adequate, and the absolute and relative efficacy rates support the inclusion of *Streptococcus pneumoniae* in the labeling.

16.2.3.6. Streptococcus pneumoniae

The total number of microbiologically evaluable isolates of *Streptococcus pneumoniae* from levofloxacin-treated patients was 83: 35 in K90-071 and 48 in M92-075. The total number of isolates of *Streptococcus pneumoniae* was 42 in ceftriaxone/cefuroxime-treated patients in protocol K90-071.

Table 16.2.3.3
Overall analysis for *Streptococcus 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 Overall	30/38 (79) 15/49 (31) 45/87 (52)	(-33, 5) --- (-5, 31)
	Ceftriaxone/cefuroxime	K90-071	28/43 (65)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	37/38 (97) 45/49 (92) 82/87 (94)	(-20, 2) --- (-17, 5)
	Ceftriaxone/cefuroxime	K90-071	38/43 (88)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	34/35 (97) 45/48 (94) 79/83 (95)	(-20, 2) --- (-15, 5)
	Ceftriaxone/cefuroxime	K90-071	38/42 (90)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	28/35 (80) 33/48 (69) 61/83 (73)	(-36, 4) --- (-26, 8)
	Ceftriaxone/cefuroxime	K90-071	27/42 (64)	---

*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 *Streptococcus 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 the 95% confidence intervals for the difference (ceftriaxone/cefuroxime minus levofloxacin) in the parameters of efficacy (cure rate, clinical success rate, eradication rate, overall success rate) all overlap zero, indicating the statistical equivalence of levofloxacin to ceftriaxone/cefuroxime in the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae*. Thus, the total number of isolates is adequate, and the absolute and relative efficacy rates support the inclusion of *Streptococcus pneumoniae* in the labeling.

16.2.4. Atypical Pathogens

16.2.4.1. Chlamydia pneumoniae

The total number of microbiologically evaluable cases of *Chlamydia pneumoniae* from levofloxacin-treated patients was 161: 58 in K90-071 and 103 in M92-075. The total number of cases of *Chlamydia pneumoniae* was 90 in ceftriaxone/cefuroxime-treated patients in protocol K90-071. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, allowed for both culture and serologic methods in the diagnosis of *Chlamydia pneumoniae* infection, the microbiologically evaluable patient cohort was composed entirely of cases diagnosed by serologic methods. There were no cases defined by isolation of the organism from culture of respiratory secretions. The large number of cases this organism can be explained by the fact that Chlamydia pneumoniae is most frequently seen as part of a polymicrobial infection[1].

Table 16.2.4.1
Overall analysis for *Chlamydia 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 Overall	36/59 (61) 53/103 (51) 89/162 (55)	(-32, 6) --- (-24, 10)
	Ceftriaxone/cefuroxime	K90-071	44/91 (48)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	57/59 (97) 98/103 (95) 155/162 (96)	(-19, -3) --- (-18, -2)
	Ceftriaxone/cefuroxime	K90-071	78/91 (86)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	56/58 (96) 98/103 (95) 154/161 (96)	(-18, -2) --- (-17, -1)
	Ceftriaxone/cefuroxime	K90-071	78/90 (87)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	56/58 (96) 98/103 (95) 154/161 (96)	(-18, -2) --- (-17, -1)
	Ceftriaxone/cefuroxime	K90-071	78/90 (87)	---

*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 *Chlamydia 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 the 95% confidence intervals for the difference

[1]File TM, Plouffe JF. Community-acquired pneumonia requiring hospitalization (CAPRH) due to *Chlamydia pneumoniae* as the sole pathogen. Abstract 613, presented 34th IDSA Annual Meeting, New Orleans, LA September, 1996.

(ceftriaxone/cefuroxime minus levofloxacin) in the parameters of efficacy (cure rate, clinical success rate, eradication rate, overall success rate) all either (1) overlap zero, indicating statistical equivalence, or (2) lie within the negative range, indicating the superiority of levofloxacin over competitor in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae*. Thus, the total number of cases is adequate, and the absolute and relative efficacy rates support the inclusion of *Chlamydia pneumoniae* in the labeling.

16.2.4.2. Legionella pneumophilia

The total number of microbiologically evaluable cases of *Legionella pneumoniae* from levofloxacin-treated patients was 7: 3 in K90-071 and 4 in M92-075. 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, 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. There were no cases defined by isolation of the organism from culture of respiratory secretions.

Table 16.2.4.2
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 Overall	3/3 (100) 1/4 (25) 4/7 (57)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	0/2 (0)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	3/3 (100) 2/4 (50) 5/7 (71)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	0/2 (0)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	3/3 (100) 3/4 (75) 6/7 (86)	N/A --- N/A
	Ceftriaxone/cefuroxime	K90-071	1/1 (100)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	3/3 (100) 2/4 (50) 5/7 (71)	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 interval s for any of the parameters of efficacy. Thus, the total number of cases is inadequate to support the inclusion of ~~*Legionella*~~ *pneumophilia* in the labeling, even though the absolute eradication rates would support the use of levofloxacin for the treatment of community-acquired pneumoniae due to *Legionella pneumophilia*.

16.2.4.3. Mycoplasma pneumoniae

The total number of microbiologically evaluable cases of *Mycoplasma pneumoniae* from levofloxacin-QD-treated patients was 27: 21 in K90-071 and 6 in M92-075. The total number of cases of *Mycoplasma pneumoniae* was 20 in ceftriaxone/cefuroxime-treated patients in protocol K90-071. Although the Medical Officer's Evaluability Criteria, Section 11.2.2, allowed for both culture and serologic methods in the diagnosis of *Mycoplasma pneumoniae* infection, the microbiologically evaluable patient cohort was composed entirely of cases diagnosed by serologic methods. There were no cases defined by isolation of the organism from culture of respiratory secretions.

Table 16.2.4.3
Overall analysis for *Mycoplasma 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 Overall	12/21 (57) 3/6 (50) 15/27 (56)	(-27, 33) --- (-24, 32)
	Ceftriaxone/cefuroxime	K90-071	12/20 (60)	---
Clinical success rate**	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	20/21 (95) 6/6 (100) 25/27 (96)	(-13, 13) --- (-13, 11)
	Ceftriaxone/cefuroxime	K90-071	19/20 (95)	---
Eradication rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	20/21 (95) 6/6 (100) 25/27 (96)	(-13, 13) --- (-13, 11)
	Ceftriaxone/cefuroxime	K90-071	19/20 (95)	---
Overall success rate***	Levofloxacin 500 mg QD	K90-071 M92-075 Overall	20/21 (95) 6/6 (100) 25/27 (96)	(-13, 13) --- (-13, 11)
	Ceftriaxone/cefuroxime	K90-071	19/20 (95)	---

*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 *Mycoplasma 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 the 95% confidence intervals for the difference (ceftriaxone/cefuroxime minus levofloxacin) in the parameters of efficacy (cure rate, clinical success rate, eradication rate, overall success rate) all overlap zero, indicating the statistical equivalence of levofloxacin to ceftriaxone/cefuroxime in the treatment of community-acquired pneumonia due to *Mycoplasma pneumoniae*. Thus, the total number of cases is adequate, and the absolute and relative efficacy rates support the inclusion of *Mycoplasma pneumoniae* in the labeling.

In summary, based on the above data, the Division is justified in granting the Sponsor the claim of efficacy in the treatment of community-acquired pneumonia caused by *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pneumoniae, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*. The small number of isolates for *Klebsiella pneumoniae* and *Legionella pneumophilia* are insufficient to support inclusion of these organisms in the label.

16.3. Issues regarding Antibiotic Resistance:

The use of a quinolone antibiotics for infections involving *Streptococcus pneumoniae* and *Staphylococcus aureus* may be problematic, since resistance of these organisms to other quinolone antimicrobial agents has been shown to occur relatively rapidly. The use of levofloxacin for the treatment of community-acquired pneumonia in the community will, in general, be empiric, thus, its coverage for organisms in which there could be pre-existing or rapid development of resistance may be suboptimal and may not be known with great accuracy.

16.3.1. Quinolone-resistance in *Staphylococcus aureus*

Quinolone-resistance has been documented to occur rapidly in *Staphylococcus aureus*, with methicillin-resistant *S. aureus* (MRSA) developing resistance at a more rapid rate than methicillin-sensitive *S. aureus* (MSSA). Ciprofloxacin-resistance in *S. aureus* is well documented, with reports resistance developing during therapy with these agents[2]. One study

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[2] Daum TE, Schaberg DR. Increasing resistance of *S. aureus* to ciprofloxacin. Antimicrob Agents Chemother 34:1862-3, 1990; Blumberg HM, Rimland D, et.al. Rapid development of ciprofloxacin resistance in Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. J Infect Dis 163:1279-85, 1991; Mulligan ME, Ruane PJ, et.al. Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization. Am J Med 82 (Suppl.4A):215-9, 1987; Piercy EA, Barbaro D, et.al. Ciprofloxacin for methicillin-resistant *Staphylococcus aureus* infections. Antimicrob Agents Chemother 33:128-30, 1989; Scaefler S. Methicillin-resistant strains of *Staphylococcus aureus* resistant to the quinolones. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Widespread quinolone resistance among methicillin resistant S. aureus. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Ciprofloxacin resistance in epidemic methicillin-resistant *S. aureus*. Lancet 2:843, 1988.

resistant to ciprofloxacin two years after introduction of the drug[3]. Piercy et.al. reported development of resistance in 16% (6/37) of patients who were being treated with ciprofloxacin for MRSA colonization and Mulligan et.al. reported 32% (7/22) of treatment episodes were associated with the development of ciprofloxacin-resistant MRSA during the course of antibiotic therapy[4]. Resistance among methicillin-susceptible *S. aureus* (MSSA) has been less widespread than with MRSA, but has still been reported[5].

While the mechanism of resistance of *S. aureus* to quinolones is not completely understood, there are authors who suggest that the rapid emergence of ciprofloxacin resistance in *S. aureus* may be due to the fact that a single-step point mutation alone can lead to high-level resistance[6]. For *S. aureus*, the frequency of alterations in DNA gyrase caused by single-step mutations increases from 1 in 10^2 to 1 in 10^5 when bacteria are exposed to concentrations close to the minimal inhibitory concentration. The frequency of single-step mutation to fluoroquinolone resistance in *S. aureus* ranges from 1.5 x10-5 at twice the MIC to ≤3.6 x 10 -12 at eight times the MIC; and high level resistance occurs with serial exposure of bacteria to increasing concentrations of fluoroquinolones[7].

16.3.2. Quinolone-resistance in *Streptococcus pneumoniae*

The incidence and geographic dissemination of penicillin-resistant and multi-drug-resistant strains of *Streptococcus pneumoniae* has been increasing. The mechanism of penicillin resistance has been shown to result from altered penicillin-binding proteins with decreased binding affinity for the penicillins. There are reports of resistance arising from genetic transformation (i.e., the ability of *S. pneumoniae* to capture loose DNA molecules from the environment and incorporate these DNA fragments into the bacterial genome) leading to mosaic penicillin-binding proteins with decreased affinity to the penicillins. Thus, the need for alternative antibiotics for the treatment of pneumococcal pneumonia is of

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[3] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

[4] Piercy EA. Antimicrob Agents Chemother 33:128-30, 1989; Mulligan ME, Ruane PJ, et.al. Am J Med 82 (Suppl.4A):215-9, 1987.

[5] Scaefler S. J Clin Microbiol 27:335-6, 1989; Shalit I, Berger SA. Antimicrob Agents Chemother 33:593-4, 1989; Isaacs RD, Kunke PJ, et.al. Lancet 2:843, 1988; Daum TE, Schaberg DR. Antimicrob Agents Chemother 34:1862-3, 1990.

[6] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991; Oshita Y, Hiramatsu K. A point mutation in *norA* gene is responsible for quinolone resistance in *Staphylococcus aureus*. Biochem Biophys Res Commun 172:1028-34, 1990; Yoshida H, Bogaki M, et.al. Nucleotide sequence and characterization of the Staphylococcus *norA* gene, which confers resistance to the quinolones. J Bacteriol 172:6942-9, 1990; Neu HC. Bacterial resistance to the fluoroquinolones. Rev Infect Dis 10(suppl.1):57-63, 1988; Sreedharan S, Oram M. DNA gyrase *gyrA* mutations in ciprofloxacin-resistant strains of *S. aureus*: close similarity with quinolone resistant mutations in *E. coli*. J Bacteriol 172:7260-2, 1990.

[7] Blumberg HM, Rimland D. J Infect Dis 163:1279-85, 1991.

primary importance. However, quinolone-resistance has been documented to occur in *Streptococcus pneumoniae*.

The mechanism for pneumococcal resistance to the quinolones is a one-step point mutation in the bacterial genome leading to a single amino acid substitution at the quinolone- binding site of either the bacterial DNA gyrase[8] or Topoisomerase IV[9] leading to decreased high level quinolone resistance. Pneumococcal resistance to ciprofloxacin is more prevalent than resistance to ofloxacin, with one paper in 1992 reporting 95% of pneumococcal isolates susceptible to ofloxacin and only 68% of isolates susceptible to ciprofloxacin[10]. However, it should be noted that development of resistance to antimicrobial agents is a time-dependent phenomenon, and that ciprofloxacin has been in use longer than ofloxacin. Data presented by the Center for Disease Control[11] at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy showed that there could be significant development of resistance to ofloxacin in the period of one year, such that the point prevalence for pneumococcal intermediate resistance to ofloxacin was 1% in 1993 and 9.5% in 1994. However, it should be noted that there was no absolute resistance detected in this study.

Pharmacokinetic/pharmacodynamic data have been used to attempt to predict the clinical efficacy of antimicrobial agents against specific microorganisms. In the case of the quinolone antimicrobials, the inhibitory quotient, defined as the AUC/MIC ratio (the ratio of the Area Under the Concentration-time Curve (AUC) of the antibiotic to the minimum inhibitory concentration (MIC) of the *S. pneumoniae* isolate) has been shown to be predictive of clinical efficacy, with an AUC/MIC value of 40 being the breakpoint for *S. pneumonaie*[12]. Levofloxacin, being the active isomer of ofloxacin, achieves higher blood level of the active

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[8] Willmot CJR, Maxwell A. A Single Point Mutation in the DNA Gyrase A Protein Greatly Reduces Binding of Fluoroquinolones to the Gyrase-DNA Complex. Antimicrob Agents Chemo 37(1):126-27, 1993.

[9] Pan XS, Ambler J. Involvement of Topoisomerase IV and DNA gyrase as Ciprofloxacin Targets in *Streptococcus pneumoniae*. Antimicrob Agents Chemother 40(10):2321-2326, 1992; Munoz R, de la Campa AG. ParC Subunit of DNA Topoisomerase IV of *Streptococcus pneumoniae* is a Primary Target of Fluoroquinolones and Cooperates with DNA Gyrase A Subunit in Forming Resistance Phenotype. Antimicrobial Agents Chemother 40(10):2252-2257, 1992; Piddock LJV, Wise R. The selection and frequency of streptococci with decreased susceptibility to ofloxacin and the other quinolones. J Antimicrobial Chemo 22(suppl C):45-51, 1988.

[10] Jones RN, Reller LB, Rosati LA. Ofloxacin, a new Broad Spectrum Fluoroquinolone: Results from a Multicenter, National Comparative Activity Surveillance Study. Diag. Microbial Infect Dives 15:425-34, 1992.

[11] Butler JC, Hofman J, Elliot JA, et.al. Late breaking abstract. 35th ICAAC, San Francisco, CA, September 17-20, 1995.

[12] Dr. David C. Hooper . Presented at the 35th ICAAC, San Francisco, CA, September, 1995.

isomer, and thus has a better inhibitory quotient for *S. pneumonaie*, as described in the table below. However, it should be noted that the MIC90 of some strains of *S. pneumonaie* is now ≥4 mcg/mL for both ciprofloxacin and ofloxacin. At this higher MIC, the inhibitory quotient for levofloxacin falls below the breakpoint of 40. Thus, the margin for coverage of organisms with even a marginal drift in MIC afforded even by the higher blood levels of levofloxacin is borderline.

It should be noted that all these calculations are theoretical based on the pharmacokinetic/pharmacodynamic data of these compounds. For ofloxacin, there remains a discrepancy between the theoretically inadequate inhibitory quotient and the clinical efficacy, with the clinical efficacy being better than would be predicted by the marginal inhibitory quotient against *S. pneumonaie*.

Table 16.3.1
Inhibitory quotients against *Streptococcus pneumonaie* for several of the Fluoroquinolone Antibiotics: Calculated for MICs of 2 mcg/mL and 4 mcg/mL

Quinolone Antimicrobial	Inhibitory Quotient (AUC/MIC) for MIC 2 mcg/mL		Inhibitory Quotient (AUC/MIC) for MIC 4 mcg/mL	
	MIC	AUC/MIC	MIC	AUC/MIC
Ciprofloxacin	2 mcg/mL	11.6	4 mcg/mL	5.8
Ofloxacin	2 mcg/mL	43.5	4 mcg/mL	21.8
Levofloxacin	2 mcg/mL	60.7	4 mcg/mL	30.4

16.4. The CNS/meningeal penetration of levofloxacin has not been adequately investigated.

The intrathecal concentration of an antibiotic is particularly important in assessing the adequacy of this drug for coverage against the hematogenous spread of infection and development of meningitis in cases of bacteremic pneumococcal pneumonia. Review of the literature would suggest that (1) *S. pneumoniae* is the causative organism in 16-75% (average 25-30%) of cases community-acquired pneumonia and (2) the incidence of bacteremia in pneumococcal pneumonia is 16-30%[13]. According to the biopharmaceutics reviewer, the pharmacokinetics and distribution of levofloxacin are comparable to that of ofloxacin, such that extrapolation of the CSF penetration of ofloxacin to levofloxacin can be used to calculate the theoretical CSF penetration of levofloxacin. The CNS penetration ofloxacin is generally 40-50% of its blood level. Theoretically, if the CNS levels of levofloxacin were 50% of the blood levels of the drug, the inhibitory quotient (AUC/MIC) within the CNS for *S. pneumoniae* (at an MIC of 2 MIC/mL)

[13] Musher DM. Infections caused by *Streptococcus pneumoniae*: Clinical Spectrum, Pathogenesis, Immunity, and Treatment. Clin Infect Dis 14:801-9, 1992.

would be apporximately 30, which is below the breakpoint of 40 which correlates with cliniclaly efficacy for the quinolones. Thus, the coverage for *S. pneumoniae* within the CNS could, hypothetically, be marginal, particularly for pneumococcal bacteremia. Again, this is based on a theoretical calculation using a breakpoint calculated by Hooper for use win predicting the clinical efficacy of the fluoroquinones. The reader is referred to Section 16.2.2. for a discussion of the use of the inhibitory quotient in extrapolating pharmacokinetic/pharmacodynamic data to clinical efficacy.

16.5. Phase 4 agreement requiring surveillance for the development of resistance to levofloxacin:

The extensive discussion above regarding the resistance of both *S. aureus* and *S. pneumoniae* to these agents emphasizes the medical officer's concerns regarding the long term efficacy of levofloxacin for this indication. The Medical officer would recommend that a condition of the approval be a Phase 4 surveillance program to document the development of resistance to this antimicrobial so that product labelling can be updated accordingly.

16.5.1. *Streptococcus pneumoniae*:

According to an DAIDP advisory committee recommendation in October 1991, there exist significant concern about the resistance of *S. pneumonaie* to the quinolone antibiotics, such that there was a recommendation of a labeling change warning of the development of resistance in *S. pneumoniae* and recommending that the "quinolones not be used as first line agent for the treatment of infection due to presumed or confirmed [pneumonia] *S. pneumonaie*". As per the discussion of inhibitory quotients of several of the quinolone antibiotics for *S. pneumonaie*, there does not exist a large safety margin for levofloxacin in regards to the achievable blood levels (AUC) and the MIC of this organism. In addition, the eradication rate of *S. pneumoniae* in both Protocol K90-071 and Protocol M92-075 is below the historic susceptibility rate of 95% for ofloxacin against *S. pneumoniae*. Since granting *S. pneumoniae* as a pathogen requires that the Division overturn a recommendation of this advisory committee, the Medical Officer would thus recommend some type of post-marketing surveillance for the development of resistance in this organism.

16.5.2. *Staphylococcus aureus*:

Although the Medical Officer has recommended the approval of levofloxacin for the treatment of community-acquired pneumonia due to *S. aureus*, the use of this antibiotic for the treatment of this indication will generally be empiric, and, therefore, involve empiric coverage of this organism. Thus, the development of resistance in this organism is important to the labeling regardless of whether or not *S. aureus* is included in the labeling, as this drug will most frequently be used empirically in the treatment of community-acquired pneumonia.

17. Recommendations for the use of levofloxacin for the treatment of community-acquired pneumonia due to routine bacterial pathogens and atypical pathogens:

In summary, based on the above data, the Division is justified in granting the Sponsor the claim of efficacy in the treatment of community-acquired pneumonia caused by *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pneumoniae, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae.*

The small number of isolates for *Klebsiella pneumoniae* and *Legionella pneumophilia* are insufficient to support inclusion of these organisms in the label. However, the sponsor has requested reconsideration of the exclusion of these two organisms by the inclusion of cases from the supportive trials. This reanalysis is summarized in an addendum attached to this review.

The recommended dose of levofloxacin for the treatment of community-acquired pneumonia is 500 mg given either intravenously or orally every 24 hours for 7-14 days.

The Medical Officer recommends a Phase 4 agreement for surveillance for the development of resistance to levofloxacin in *Staphylococcus aureus* and *Streptococcus pneumoniae.*

18-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
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