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STATISTICAL REVIEW AND EVALUATION

NOV 2 1 1996

NDA#(s):	20-634 20-635
Name of Drug:	LEVAQUIN® (levofloxacin) tablets (NDA 20-634) LEVAQUIN® (levofloxacin injection) I.V. (NDA 20-635)
Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Indication(s):	(1) Acute bacterial sinusitis, (2) Acute bacterial exacerbation of chronic bronchitis, (3) Community-acquired bacterial pneumoniae, (4) Uncomplicated skin and skin structure infections, (5) Complicated skin and skin structure infections, (6) Complicated urinary tract infection, and (7) Acute pyelonephritis.
Documents Reviewed:	Volumes 1 and 304 - 432, stamp dated December 22, 1995, and an electronic CANDA submission.
Review Type:	Clinical.
Statistical Reviewer:	Nancy Paul Silliman, Ph.D., HFD-725
Medical Officers:	Karen Frank, M.D., HFD-520 and Bob Hopkins, M.D., HFD-520
Project Manager:	Frances LeSane, HFD-520

I. INTRODUCTION

The sponsor is requesting approval for the use of LEVAQUIN (levofloxacin) tablets for the above seven indications. Levofloxacin is the levorotatory isomer of the D,L-racemate of ofloxacin and a synthetic fluorinated carboxyquinolone.

There are two pivotal clinical trials supporting each of the above indications, with the exception that acute pyelonephritis was studied as a subset in the two complicated urinary tract infection studies. Thus, a total of 12 pivotal clinical trials were reviewed in support of this application. Acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired bacterial pneumoniae are reviewed in this document. For the statistical review (by this reviewer) of uncomplicated skin and skin structure infections, complicated skin and skin structure infections, complicated urinary tract infections, acute pyelonephritis, and the integrated summary of safety, please see the joint medical and statistical review by Drs. Hopkins and Silliman.

II. EVALUATION

The following protocols are reviewed in this document (reviews are attached):

Acute bacterial sinusitis
- M92-040 (pages 5-16)
- N93-006 (pages 17-28)

Acute bacterial exacerbation of chronic bronchitis
- K90-070 (pages 29-44)
- M92-024 (pages 45-59)

Community-acquired bacterial pneumoniae
- K90-071 (pages 60-76)
- M92-075 (pages 77-91)

In each case, the study supported the safety and efficacy of levofloxacin for use in the specified indication.

III. CONCLUSIONS (Which May be Conveyed to the Sponsor)

Levofloxacin was found to be safe and effective in the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired bacterial pneumoniae.

1. Protocols M92-040 and N93-006 support the safety and efficacy of the use of levofloxacin in treating acute bacterial sinusitis.

Results for Protocol M92-040:
For FDA clinically evaluable patients, clinical cure rates at poststudy were considered therapeutically equivalent for patients taking levofloxacin and amoxicillin/clavulanate (95% confidence interval for the difference in cure rate at poststudy, amoxicillin/clavulanate minus levofloxacin, of $_{266,263}(-13.0, 2.2)_{74\%,79\%}$ *).*

Results for Protocol N93-006:
Among patients considered clinically evaluable by FDA, 71% were cured at poststudy. Among patients considered microbiologically evaluable by FDA, overall microbiologic eradication (by subject) was 73%. (Note: This study was noncomparative.)

2. Protocols K90-070 and M92-024 support the safety and efficacy of the use of levofloxacin in treating acute bacterial exacerbation of chronic bronchitis.

Results for Protocol K90-070:
Among FDA clinically evaluable patients, clinical response rates were considered therapeutically equivalent for patients taking levofloxacin and cefaclor (95% confidence interval for the difference, cefaclor minus levofloxacin, of $_{127,95}(-6.2, 4.1)_{97\%,98\%}$ *).*
Among FDA microbiologically evaluable patients, overall subject microbiologic eradication

rates were considered therapeutically equivalent for patients taking levofloxacin and cefaclor (95% confidence interval for the difference, cefaclor minus levofloxacin, of $_{65,61}(-15.6, 7.1)_{89\%,93\%}$).

Results for Protocol M92-024:
Among FDA clinically evaluable patients, clinical response rates were considered therapeutically equivalent for patients taking levofloxacin and cefuroxime axetil (95% confidence interval for the difference, cefuroxime axetil minus levofloxacin, of $_{203,196}(-7.9, 2.3)_{93\%,95\%}$).
Among FDA microbiologically evaluable patients, overall subject microbiologic eradication rates were considered therapeutically equivalent for patients taking levofloxacin and cefuroxime axetil (95% confidence interval for the difference,cefuroxime axetil minus levofloxacin, of $_{129,116}(-13.8, 3.0)_{87\%,93\%}$).

3. Protocols K90-071 and M92-075 support the safety and efficacy of the use of levofloxacin in treating community-acquired bacterial pneumoniae.

Results for Protocol K90-071:
Among FDA clinically evaluable patients, clinical response rates were statistically significantly different for patients taking levofloxacin and ceftriaxone/cefuroxime, with levofloxacin patients performing better (95% confidence interval for the difference, ceftriaxone/cefuroxime minus levofloxacin, of $_{226,207}(-18.6, -6.2)_{83\%,95\%}$).
Among FDA microbiologically evaluable patients, overall subject microbiologic eradication rates were statistically significantly different for patients taking levofloxacin and ceftriaxone/cefuroxime, with levofloxacin patients performing better (95% confidence interval for the difference,ceftriaxone/cefuroxime minus levofloxacin, of $_{152,119}(-22.8, -6.9)_{81\%,96\%}$).

Results for Protocol M92-075:
Among patients considered clinically evaluable by FDA, 93% had a clinical response of either cure or improvement. Among patients considered microbiologically evaluable by FDA, overall microbiologic eradication (by subject) was 94%. (Note: This study was noncomparative.)

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the conclusion that levofloxacin is safe and effective in the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired bacterial pneumoniae. The statistical reviewer recommends that this application be approved for these indications.

Nancy Paul Silliman 11/19/96

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cc:
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Orig. NDA #20-635
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HFD-725/Dr. Harkins
HFD-725/Dr. Lin
HFD-725/Dr. Silliman
HFD-344/Dr. Thomas
Chron.
This review contains 91 pages.

Study M92-040

Title
A multicenter, randomized, open-label (i.e., unblinded) study to compare the safety and efficacy of oral levofloxacin with amoxicillin/clavulanate potassium in the treatment of acute sinusitis in adults.

Objectives
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.

Study Design
This was a randomized, open-label (i.e., unblinded), active-control multicenter study. Subjects who met the entry criteria were assigned randomly to receive levofloxacin or amoxicillin/clavulanate for 10 to 14 days (randomization was performed in blocks of four and stratified by center). Assuming clinical success rates of 85% for amoxicillin/clavulanate and 81% for levofloxacin and a significance level of 2.5%, 183 subjects per treatment group were necessary to demonstrate, with 80% power, that the difference in clinical success rates was less than 15%. With an estimated clinical evaluability rate of 75%, approximately 490 total subjects were to be enrolled.

Efficacy evaluations were based on assessments of signs and symptoms of sinusitis and on stabilization or improvement in abnormal admission radiographic findings. The clinical signs and symptoms were assessed at admission (**baseline**; Study Day 1), **on-therapy** (Days 3 to 6), **posttherapy** (defined in the protocol as two to five days after completion of therapy, but later changed to 2-10 days after completion of therapy), and **poststudy** (28 to 32 days after the end of therapy). Clinical response at posttherapy (defined as either cured, improved, or failed) in the group of subjects evaluable for clinical efficacy represented the primary efficacy variable for this study. (Note: please see the medical officer's review for the definition of clinical evaluability, both for the sponsor and for FDA.)

Safety evaluations consisted of treatment-emergent adverse events reported during the study and of clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, and physical examinations performed at admission and posttherapy.

Reviewer's Note: The posttherapy visit was considered by the reviewing medical officer to be too early to assess clinical outcome. Thus, clinical outcome at poststudy will be the primary efficacy variable for FDA analyses. In addition, clinical outcome at poststudy will be defined as either cure or failure (note: failures at posttherapy will be carried forward to poststudy). Patients who are only improved at poststudy will be considered failures.

To compare treatment differences (e.g., in cure rates) the sponsor provides 95% confidence intervals for the difference "comparator drug minus new drug", or in this case "amoxicillin/clavulanate minus levofloxacin". FDA usually calculates these confidence intervals for the difference "new drug minus comparator drug", or in this case "levofloxacin minus amoxicillin/clavulanate". To be consistent, FDA confidence intervals are calculated

the same way as those provided by the sponsor. Thus, in this application we will be interested in the upper bound of the confidence interval instead of the lower bound. The same rules will apply (e.g., if the cure rates for levofloxacin and the comparator drug are both between 80% and 90%, to show equivalence of levofloxacin to the comparator drug, the confidence interval for the difference must include zero and the upper limit must be less than 15%). All confidence intervals, both those produced by the sponsor and those produced by the statistical reviewer, are based on the normal approximation to the binomial distribution incorporating the continuity correction.

Analysis Groups

Treatment comparisons are based on several analysis groups to assess relative efficacy and consistency across different, standard approaches. The discussion and displays presented here focus mainly on the efficacy analyses based on subjects classified by the sponsor and by FDA as clinically evaluable.

Supportive efficacy analyses are based on all subjects enrolled, i.e., randomized to a treatment group. These analyses are done in two ways. One approach — Intent-to-Treat — adheres strictly to randomization; thus subjects are counted in their assigned treatment group regardless of any dosing or dispensing errors. An alternative approach — Modified-Intent-to-Treat — takes into account the small number of drug dispensing errors that occurred by grouping subjects according to the drug actually received. These two approaches classify only one subject differently; one subject was randomized to treatment with levofloxacin but received amoxicillin/clavulanate due to errors in drug dispensing. The Modified Intent-to-Treat approach — grouping subjects by treatment received rather than by treatment assigned — should be more reflective of the relative efficacy of the comparative treatments and is therefore given greater attention than the Intent-to-Treat analysis. Consistent with this reasoning, the clinically evaluable analysis group is also determined by treatment actually received rather than by treatment assigned. The one incorrectly dosed subject who received amoxicillin/clavulanate instead of levofloxacin is included in the analyses based on the clinically evaluable group.

Reviewer's Note: In this application, the sponsor uses the phrase "modified intent-to-treat analysis" to mean an intent-to-treat analysis where patients are grouped according to the drug they actually received, rather than to the drug to which they were randomized. This should not be confused with the usual DAIDP definition of modified intent-to-treat analysis, which is an intent-to-treat analysis excluding patients with no valid admission pathogens (note: no microbiologic data was collected in this study).

Demographic and Baseline Characteristics

Six hundred fifteen subjects were enrolled in this study at 28 centers, including 306 who received levofloxacin and 309 who received amoxicillin/clavulanate (modified intent-to-treat group). The efficacy analyses focused mainly on the group of subjects considered clinically evaluable; the demographic and baseline characteristics for this group of 535 subjects are presented in Table 1 and are similar to the overall study group of 615 subjects. Overall, for the two clinically evaluable treatment groups, 63.6% of subjects were women and 76.1% were Caucasian.

Table 1. Demographic and Baseline Characteristics: Sponsor Clinically Evaluable Subjects

	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)				
Mean±SD	39.5±14.1		38.3±12.4	
Range	[redacted]		[redacted]	

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

Discontinuation/Completion Information

Of the 615 subjects enrolled in the study, 306 received levofloxacin and 309 received amoxicillin/ clavulanate (modified intent-to-treat group). Of the 293 subjects in the levofloxacin treatment group with known discontinuation/completion information, 21 (7.2%) discontinued therapy prematurely and 272 (92.8%) completed therapy. Of the 301 subjects in the amoxicillin/clavulanate group with known discontinuation/completion information, 27 (9.0%) discontinued therapy prematurely and 274 (91.0%) completed therapy. The most common reason for discontinuation in both treatment groups was an adverse event (Table 2).

Reviewer's Note: Thirteen (4.2%) of the 306 levofloxacin patients and 8 (2.6%) of the 309 amoxicillin/clavulanate patients had unknown discontinuation/completion information (i.e., were lost to follow-up). Thus, a total of 34 (11.1%) of the 306 levofloxacin patients were either discontinued or lost to follow-up. A total of 35 (11.3%) of the 309 amoxicillin/clavulanate patients were either discontinued or lost to follow-up.

Table 2. Reasons for Premature Discontinuation of Therapy: Sponsor Modified Intent-to-Treat Subjects

	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.

Efficacy Results

Reviewer's Note: Among patients considered clinically evaluable by FDA, 79% of levofloxacin patients and 74% of amoxicillin/clavulanate patients were cured at poststudy (see Table 3). The 95% confidence interval for the difference in cure rate at poststudy (amoxicillin/clavulanate minus levofloxacin) is $_{266,263}(-13.0, 2.2)_{74\%,79\%}$, suggesting that levofloxacin could be anywhere between 13% more effective and 2.2% less effective than amoxicillin/clavulanate.

Among the sponsor 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 (Table 4). Thirty-one (11.6%) subjects in the levofloxacin treatment group and 34 (12.7%) subjects in the amoxicillin/clavulanate treatment group failed treatment. Results similar to these, which indicate equivalence between treatment groups, were also observed across various sex, age, and race subgroups.

In the sponsor's modified-intent-to-treat group, levofloxacin treatment resulted in 54.2% cure, 30.4% improvement, and 11.1% failure; 4.2% of the 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.

Table 3: Poststudy Clinical Cure Rates and Confidence Intervals By Investigator: FDA Clinically Evaluable Subjects

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	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.

For sponsor clinically evaluable subjects, when the clinical response categories "cured" and "improved" were combined into a single category of "clinical success", 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-levofloxacin) in success rates. All of the treatment differences in this confidence interval lie below the upper bound of 15%, thereby establishing the therapeutic equivalence of the two treatments. Confidence intervals computed for each study center

with 10 or more evaluable subjects in each treatment group and for all other centers pooled demonstrate the consistency of results across centers.

Table 4. Clinical Response Rate at Posttherapy Evaluation for Each Study Center: Sponsor Clinically Evaluable Subjects

	Levofloxacin				Amoxicillin/Clavulanate				
Investigator	N	Cured[a]	Improved[a]	Failed[a]	N	Cured[a]	Improved[a]	Failed[a]	95% Confidence Interval[b]
Adelglass	16	11 (68.8)	3 (18.8)	2 (12.5)	18	9 (50.0)	7 (38.9)	2 (11.1)	(-23.5, 26.3)
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)	(-32.0, 27.9)
Deabate	34	26 (76.5)	7 (20.6)	1 (2.9)	32	27 (84.4)	4 (12.5)	1 (3.1)	(-10.0, 9.7)
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)	(-25.7, 47.2)
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)	(-3.1, 3.1)
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)	(-11.0, 26.3)
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)	(-41.8, 34.7)
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)	(-23.8, 13.8)
Nechtman	16	12 (75.0)	3 (18.8)	1 (6.3)	16	8 (50.0)	6 (37.5)	2 (12.5)	(-29.5, 17.0)
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)	(-34.0, 34.0)
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)	(-7.5, 70.8)
Stein	15	12 (80.0)	3 (20.0)	0 (0.0)	12	6 (50.0)	4 (33.3)	2 (16.7)	(-41.9, 8.6)
Wanderer	17	2 (11.8)	12 (70.6)	3 (17.6)	16	2 (12.5)	12 (75.0)	2 (12.5)	(-22.3, 32.6)
Winstead	0	0 –	0 –	0 –	2	2 (100.0)	0 (0.0)	0 (0.0)	–
Combined[c]	55	26 (47.3)	24 (43.6)	5 (9.1)	55	31 (56.4)	15 (27.3)	9 (16.4)	(-20.6, 6.0)
TOTAL	267	156 (58.4)	80 (30.0)	31 (11.6)	268	157 (58.6)	77 (28.7)	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) 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: Applgate, Bruner, Cass, Dworzak, Felicetta, Fiddes, Grossman, Hunter, Kerzner, Levine, Levy, Martin, Pearlman, Rudolph, and Winstead.

In the sponsor's modified-intent-to-treat group, the clinical success rates for treatment with levofloxacin and amoxicillin/clavulanate were 84.6% and 83.8%, respectively. The individual confidence intervals for all the analysis groups are centered below zero and are consistent with the therapeutic equivalence of the two treatments regarding clinical success rates.

Clinical response rates at the poststudy evaluation are summarized and cross-tabulated against clinical response rates at posttherapy for sponsor clinically evaluable subjects who had a poststudy assessment in Table 5. Of 233 levofloxacin-treated subjects who were cured or improved at the posttherapy evaluation two to five days after completing therapy

(3 others who were cured or improved did not have a poststudy assessment), only five had relapsed by the time of the poststudy evaluation approximately four weeks later, 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 *(again, 3 subjects who were cured or improved at posttherapy did not have a poststudy assessment)*.

Table 5. Clinical Response Rate at Poststudy Evaluation: Sponsor Clinically Evaluable Subjects

	Levofloxacin Poststudy (N=233)[a]				Amoxicillin/Clavulanate Poststudy (N=231)[a]			
Posttherapy	N	Cured	Improved	Relapse	N	Cured	Improved	Relapse
Cured	154	150 (97.4)	2 (1.3)	2 (1.3)	155	145 (93.5)	7 (4.5)	3 (1.9)
Improved	79	47 (59.5)	29 (36.7)	3 (3.8)	76	39 (51.3)	31 (40.8)	6 (7.9)

[a] Thirty-four subjects in the levofloxacin group and 37 subjects in the amoxicillin/clavulanate group either failed at th posttherapy evaluation or did not have a poststudy evaluation performed.
Numbers shown in parentheses are percentages for that category.

The proportions of clinically evaluable subjects with resolution, improvement, worsening of, or no change in abnormal admission radiographic findings at the posttherapy evaluation is presented in Table 6. 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 6. Summary of Radiographic Findings a at the Posttherapy Evaluation: Sponsor Clinically Evaluable Subjects

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.

Safety Results

Summary of All Adverse Events

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 potassium treatment group) were lost to follow-up with no postadmission information available and therefore were excluded from the safety analysis.

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 for the difference in adverse event rate, amoxicillin/clavulanate minus levofloxacin, is (1.7%, 18.2%) which 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. Adverse events in the other body systems occurred in fewer than 10.0% 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.

As shown in Table 7, 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.

Table 7. Incidence of Frequently Reported Adverse Events Summarized by Body System and Primary Term: Subjects Evaluable for Safety

	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.

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% or more 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% or more 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%).

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.

Deaths and Discontinuations Due to Adverse Events

No deaths occurred during the study. Twenty-seven subjects discontinued the study drug due to adverse events (Table 8), including 11 (3.7%) of the 297 subjects evaluable for safety in the levofloxacin treatment group and 16 (5.3%) of the 302 subjects evaluable for safety in the amoxicillin/clavulanate treatment group. In the levofloxacin group, the subjects who discontinued due to adverse events included four subjects with urticaria, rash, or pruritis, 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).

Table 8. Subjects Who Discontinued Therapy Due to Adverse Events

Subject Number	Age	Sex	Adverse Event (Primary Term)	Study Day Of Onset[a]	Severity	Relationship To Study Drug[b]	Duration Of Therapy (Days)
Levofloxacin							
	22	F	Asthenia, Dizziness	6	Moderate	Possible	7
	39	F	Constipation	1	Marked	Probable	7
	32	F	Abdominal Pain, Diarrhea	6	Marked	Probable	12
	52	M	Diarrhea, Nausea, Vomiting	2	Moderate	Possible	2
	21	F	Urticaria	1	Marked	Probable	1
	38	M	Nausea, Vomiting	1	Mild	Possible	2
			Abdominal pain	2	Mild	Possible	
	21	F	Influenza-Like Symptoms	3	Marked	None	4
	60	F	Pruritus (Arm), Pruritus (Foot)	2	Mild	Probable	2
	21	M	Pruritus, Rash	6	Moderate	Probable	6
	32	F	Nausea, Pruritus	2	Mild	Possible	10
	46	F	Urticaria	2	Moderate	Probable	2
Amoxicillin/Clavulanate							
	34	F	Nausea, Vomiting	3	Mild	Probable	4
	75	F	Fatigue	6	Mild	None	6
	35	M	Abdominal Pain	4	Moderate	Remote	10
	46	F	Nausea, Vomiting	1	Moderate	Probable	2
	56	F	Diarrhea	2	Mild	Definite	11
			Abdominal Pain	10	Mild	Possible	
	68	M	Diarrhea	2	Moderate	Probable	4
	62	M	Melena	5	Moderate	Probable	5
	27	F	Nausea	2	Moderate	Probable	3
			Vomiting	2	Moderate	Probable	
			Abdominal pain	3	Marked	Probable	
	44	F	Diarrhea, Nausea, Vomiting	2	Marked	Probable	4
	21	M	Pseudomembranous Colitis	3	Marked	Probable	5
	62	F	Nausea	1	Marked	Probable	1
	71	F	Abdominal Pain	1	Moderate	Possible	1
			Diarrhea	1	Mild	Possible	
	35	F	Abdominal Pain, Diarrhea	2	Moderate	Probable	3
			Nausea	2	Moderate	Possible	
			Dizziness	3	Moderate	Possible	
	20	F	Nausea, Pruritus, Vomiting	4	Marked	Probable	3
	43	M	Diarrhea	2	Moderate	Probable	3
	27	F	Abdominal Pain, Diarrhea, Flatulence	2	Marked	Definite	5

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

Serious or Potentially Serious Adverse Events

Two levofloxacin-treated subjects experienced a serious adverse event within one week after completing study therapy (anemia in one subject and two instances of chest pain in another). These adverse events are summarized in Table 9. Both of these adverse events resulted in hospitalization and neither was considered by the investigator to be related to study drug administration.

Table 9. Subjects Who Had Serious or Potentially Serious Adverse Events

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day Of Onset[a]	Severity	Relationship To Study Drug[b]	Duration Of Therapy (Days)
Levofloxacin							
	80	F	Anemia	20 (7PT)	Moderate	None	13
	57	M	Chest Pain	17 (3PT)	Moderate	Remote	14
			Chest Pain	20 (6PT)	Moderate	None	

[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.

Clinical Laboratory Tests

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for any laboratory analytes in either treatment group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group was low (≤1.1%) and similar across treatment groups (Table 10). As shown in Table 11, 16 subjects (six in the levofloxacin group and 10 in the amoxicillin/clavulanate group) had a total of 19 markedly abnormal treatment-emergent test results. Overall, five subjects had abnormal glucose levels: one subject in the levofloxacin group had increased glucose levels and two had decreased glucose levels; two subjects in the amoxicillin group had decreased levels. Five subjects (two in the levofloxacin group and three in the amoxicillin/clavulanate group) had elevations in SGPT or SGOT. Five subjects in the amoxicillin/ clavulanate group, but none in the levofloxacin group, had markedly abnormal hematologic tests.

Table 10. Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

	Levofloxacin		Amoxicillin/Clavulanate	
Laboratory Test	Proportion[a]	%	Proportion[a]	%
Blood Chemistry				
Elevated Glucose	1/285	0.4	0/285	0.0
Decreased Glucose	2/285	0.7	2/285	0.7
Decreased Phosphorous	0/282	0.0	1/286	0.3
Elevated Uric Acid	0/287	0.0	1/290	0.3
Elevated SGOT	1/287	0.3	1/290	0.3
Elevated SGPT	1/287	0.3	3/290	1.0
Elevated Bilirubin	1/282	0.4	0/287	0.0
Hematology				
Decreased Hemoglobin	0/281	0.0	1/280	0.4
Decreased Neutrophils	0/281	0.0	1/280	0.4
Decreased Lymphocytes	0/281	0.0	3/280	1.1

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

Table 11: Subjects Who Had 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[b]	Follow-up Value (Therapy Day)	Duration of Therapy (Days)
Levofloxacin								
41		F	Glucose (<70 or >200 mg/dL)	97.00	51.00	22 (8PT)	--	14
30		F	SGPT (>75 U/L)	31.00	79.00	18 (4PT)	62.00 (17PT)	14
74		F	SGOT (>75 U/L)	20.00	82.00	12 (2PT)	--	10
51		M	Glucose (<70 or >200 mg/dL)	92.00	216.00	15 (1PT)	--	14
56		M	Glucose (<70 or >200 mg/dL)	93.00	62.00	19 (5PT)	--	14
38		M	Total Bilirubin (>1.5 mg/dL)	0.90	2.60	19 (8PT)	--	11
Amoxicillin/Clavulanate								
39		M	Uric Acid (>10.0 mg/dL)	6.60	11.00	21 (9PT)	9.00 (15PT)	12
			SGPT (>75 U/L)	34.00	76.00	21 (9PT)	50.00 (15PT)	
22		F	Lymphocytes (<1.0 x 10^9/µL)	1.60	0.84	17 (3PT)	--	14
68		M	Glucose (<70 or >200 mg/dL)	119.00	63.00	7 (3PT)	--	4
42		M	Neutrophils (<1.0 x 10^9/µL)	2.20	0.94	21 (7PT)	--	14
38		M	SGOT (>75 U/L)	37.00	179.00	35 (21PT)	--	14
			SGPT (>75 U/L)	32.00	326.00	35 (21PT)		
26		F	Glucose (<70 or >200 mg/dL)	89.00	55.00	18 (3PT)	80.00 (30PT)	15
37		F	SGPT (>75 U/L)	41.00	96.00	14 (4PT)	--	10
42		F	Inorganic Phosphorus (<2.0 or >6.0 mg/dL)	3.20	1.90	16 (1PT)	--	15
			Hemoglobin (<12.0 g/dL)	12.90	9.80	16 (1PT)	14.00 (15PT)	
28		F	Lymphocytes (<1.0 x 10^9/µL)	1.40	0.93	9 (1PT)	--	8
45		F	Lymphocytes (<1.0 x 10^9/µL)	1.66	0.99	18 (3PT)	--	15

[a] Only range given in table. For complete criteria, see Attachment 18a.
[b] Relative to the start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy, relative to the last day of study drug administration.
[c] Subject also discontinued due to adverse event. (see Table 19)

Physical Examinations and Vital Signs

There were no clinically significant mean changes in vital signs from admission to posttherapy in the levofloxacin-treated or amoxicillin/clavulanate-treated subjects, with comparable results across the two groups. Similarly, there were no clinically significant treatment-emergent physical examination abnormalities.

Conclusions

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with acute bacterial sinusitis. The clinical response in the levofloxacin treatment group was therapeutically equivalent to that observed in the amoxicillin/clavulanate treatment group for patients considered clinically evaluable by FDA; 95% confidence interval for the difference (amoxicillin/clavulanate minus levofloxacin) in poststudy clinical cure rates (as defined by the reviewing medical officer) of $_{266,263}(-13.0, 2.2)_{74\%,79\%}$, suggesting that levofloxacin could be anywhere between 13% more effective and 2.2% less effective than amoxicillin/clavulanate. These data support the efficacy of levofloxacin for acute bacterial sinusitis.

Study N93-006

Title
A multicenter, noncomparative study to evaluate the safety and efficacy of oral levofloxacin in the treatment of acute sinusitis in adults.

Objectives
The objective of this study was to evaluate the safety and therapeutic efficacy of 500 mg levofloxacin administered orally once daily for 10 to 14 days in the treatment of acute bacterial sinusitis in adults.

Study Design
This was a noncomparative multicenter study. Subjects who met the entry criteria were treated with 500 mg of levofloxacin once daily for 10 to 14 days.

Efficacy evaluations were based on assessments of clinical signs and symptoms, radiographic signs, clinical response (evaluated posttherapy as cured, improved, failed, or unable to evaluate and poststudy as cured, improved, relapse, or unable to evaluate), and on microbiologic eradication of the suspected pathogen(s) isolated at admission and of the subject's infection considering all pathogens isolated. Clinical signs and symptoms were evaluated at admission, while on therapy (Days 3-6), at posttherapy (two to five days after completion of therapy), and at poststudy (28 to 32 days after completion of therapy) for subjects who were cured or improved at the posttherapy visit. Cultures, gram stains, and susceptibility testing of sinus aspirates collected by antral puncture or endoscope were performed at admission and posttherapy when clinically indicated (and at poststudy in cases of suspected relapse). Microbiologic response at posttherapy in the group of subjects evaluable for microbiologic efficacy (see below) was the primary efficacy variable. Clinical response at posttherapy in the group of subjects evaluable for clinical efficacy represented the secondary efficacy variable for this study. (Note: please see the medical officer's review for the definition of clinical and microbiologic evaluability, both for the sponsor and for FDA.)

Safety evaluations consisted of treatment-emergent adverse events collected at the posttherapy visit and of clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, and physical examinations performed at admission and posttherapy.

Reviewer's Note: Since this study is noncomparative, it is somewhat harder to interpret than the other sinusitis study. This is particularly true for clinical outcome, which is subjective. Microbiologic outcome, however, is an objective endpoint. Thus, if microbiologic outcome is considered satisfactory, and clinical outcome correlates with microbiologic outcome, this study should be able to confirm the findings of the other sinusitis study (M92-040) that levofloxacin is safe and effective.

The posttherapy visit was considered by the reviewing medical officer to be too early to assess outcome. Thus, clinical outcome at poststudy will be used for FDA analyses. Clinical outcome at poststudy will be defined as either cure or failure (note: earlier failures will be carried forward). Patients who are improved at poststudy will be considered failures.

Since little or no microbiologic data was collected at poststudy, for FDA analyses posttherapy data will be used with the following adjustment. All patients who are clinical failures (including relapses) at poststudy will have a microbiologic outcome at posttherapy of presumed persistence, even if the culture at posttherapy showed eradication (the idea being that at this early timepoint, any microbiologic infection would still be suppressed when cultured). This microbiologic endpoint will be referred to as "overall microbiologic outcome". In addition, Staphylococcus aureus will be considered a pathogen when isolated alone, but a contaminant when isolated as part of a polymicrobial infection.

Analysis Groups

The discussion and displays in this report focus mainly on the efficacy analyses based on (i) subjects classified by the sponsor and by FDA as microbiologically evaluable and (ii) subjects classified by the sponsor and by FDA as clinically evaluable. Supportive efficacy analyses are based on all subjects enrolled, i.e., intent-to-treat subjects, and subjects who had a pathogen isolated at admission, i.e., modified intent-to-treat subjects.

Demographic and Baseline Characteristics

Three hundred twenty-nine subjects (intent-to-treat group) were enrolled in this study at 24 centers. The sponsor's efficacy analyses focused mainly on the groups of subjects considered microbiologically or clinically evaluable; the demographic and baseline characteristics for these two groups are presented in Table 1 and were similar to those of the overall study group of 329 subjects. Among subjects who were considered microbiologically evaluable by the sponsor, 57.2% were women and 90.6% were Caucasian.

Table 1: Demographic and Baseline Characteristics:
Sponsor Clinically Evaluable and Sponsor Microbiologically Evaluable Subjects

	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)		
N	300	138
Mean±SD	41.4±12.7	39.0±12.2
Range	[redacted]	[redacted]

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

Discontinuation/Completion Information

All but one of the 329 subjects enrolled in the study were treated with levofloxacin p.o. 500 mg q24h (one subject took levofloxacin 500 mg q12h in error). Of the 329 subjects enrolled, 12 (3.6%) subjects discontinued therapy prematurely and 317 (96.4%) completed

therapy according to the regimen prescribed by the investigator. Reasons for premature discontinuation are summarized in Table 2. The most common reason for discontinuation was an adverse event (six subjects).

Table 2: Reasons for Premature Discontinuation of Therapy: Sponsor Intent-to-Treat Subjects

	Levofloxacin (N=329)	
Reason	No.	(%)
Adverse Event	6	(1.8)
Clinical Failure	2	(0.6)
Personal Reason	1	(0.3)
Other*	3	(0.9)
Total Discontinued	12	(3.6)

* Subject 2506 was discontinued for participation in another study (not revealed until after admission), Subject 2520 withdrew from the study because of perceived worsening of symptoms, and Subject 3902 was discontinued because of prior history of chronic sinusitis.

Efficacy Results

Clinical Response

Reviewer's Note: Among patients considered clinically evaluable by FDA, 71% were cured at poststudy (Table 3). This rate is somewhat lower than that observed for levofloxacin (79%) in the other sinusitis study (M92-040), but is similar to that observed for amoxicillin/clavulanate (74%) in that study.

Table 4 shows clinical cure at poststudy among FDA clinically evaluable subjects for the four admission pathogens that the sponsor is requesting in their label. Cure rates range from 90% for patients admitted with Streptococcus pneumoniae to 48% for patients admitted with Staphylococcus aureus.

The clinical response posttherapy for levofloxacin-treated subjects who were considered clinically evaluable by the sponsor is summarized by study center in Table 5. Among sponsor clinically evaluable subjects, 58.3% were cured, 30.0% were improved, and 11.7% failed treatment. When the clinical response categories "cured" and improved" were combined into a single category of "clinical success", levofloxacin treatment resulted in 88.3% clinical success.

Of the 264 sponsor clinically evaluable 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.

Table 3: Poststudy Clinical Cure Rates By Investigator:
FDA Clinically Evaluable Subjects

	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 (67)
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 4: Poststudy Clinical Cure Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects

Pathogen	Levofloxacin	
	N[a]	Cure[b]
Haemophilus influenzae	34	25 (74)
Moraxella (Branhamella) 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.

Table 5: Clinical Response Rate Posttherapy for Each Study Center: Sponsor Clinically Evaluable Subjects

Investigator	Levofloxacin					
	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)
Lioti	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] A window of 1-10 days posttherapy was used for determination of evaluability.

Microbiologic Response

Reviewer's Note: Overall microbiologic outcome for FDA microbiologically evaluable patients is summarized by pathogen category and pathogen in Table 6. The sponsor presents microbiologic results separately by collection method (antral puncture and endoscope). However, since results are very similar across collection methods, FDA results are presented for the combined data.

Note that overall eradication by subject is 73% and overall eradication by pathogen is 76%. Overall microbiologic eradication by subject (73%) is similar to clinical cure at poststudy (71%). Since microbiologic eradication is an objective endpoint, this suggests that even though this study is uncontrolled (and hence unblinded), clinical cure rates can probably be trusted.

Table 6: Overall Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects[a]

Pathogen Category/Pathogen	Levofloxacin	
	N[b]	Eradicated[c]
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 (Branhamella) 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.

Microbiologic eradication rates posttherapy summarized by pathogen category and pathogen are shown in Table 7 for sponsor microbiologically evaluable patients; in this display, the most prevalent pathogens (N≥5) are categorized by collection method (antral puncture or endoscope). The overall microbiologic eradication rate by pathogen was 91.3%; the eradication rates for pathogens identified by antral puncture (91.2%) and endoscope (92.0%) were similar. The overall microbiologic eradication rate by subject was 92.0%; this eradication rate was similar for subjects evaluated by antral puncture (92.2%) and endoscope (91.3%).

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 the cases (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.

Table 7: Microbiologic Eradication Rates Posttherapy Summarized by Pathogen Category, Pathogen, and Collection Method: Sponsor Microbiologically Evaluable Subjects

	Antral Puncture			Endoscope			Total		
Pathogen Category/Pathogen	N	Eradicated[2]		N	Eradicated[2]		N	Eradicated[2]	
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[3]									
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 parainfluenzae	5	5	(100.0)	1	1	(100.0)	6	6	(100.0)

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

Summary

Reviewer's Note: Overall success rates (defined as clinical cure at poststudy plus overall microbiologic eradication) are given in Table 8 for patients considered both clinically and microbiologically evaluable by FDA. The overall success rate in levofloxacin patients in this study was 72%.

Table 8: Overall Success Rates[a] By Study Center:
FDA Microbiologically AND Clinically Evaluable Subjects

Investigator	Levofloxacin	
	N	Overall Success[b]
Amsbaugh	2	0 (0)
Anthony	8	4 (50)
Dennington	8	1 (13)
Dyke	6	2 (33)
Edelstein	3	3 (100)
Follett	3	2 (67)
Kidder	3	2 (67)
Klein	1	0 (0)
Kopp	17	9 (53)
Lee	1	1 (100)
Littlejohn	11	9 (82)
McClean	7	5 (71)
Pulver	2	1 (50)
Scott	5	5 (100)
Sydnor	38	33 (87)
Weakley	12	12 (100)
Total	127	89 (70)

[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.

A summary of the sponsor's key efficacy results is presented in Table 9. In sponsor evaluable patients, comparable results were seen across analysis groups for both clinical and microbiologic endpoints. In addition, there was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency of these response measures.

Table 9: Summary of Sponsor's Key Efficacy Results

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

Response/Group	Clinical Success or Microbiologic Eradication Rates[b]	
Clinical Response		
Clinically Evaluable	265/300	(88.3)
Intent-to-Treat	265/329	(80.6)
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.

NOTES: 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. Numbers shown in parentheses are percentages for that category.

Safety Results

Summary of All Adverse Events

All 329 subjects enrolled in the study were evaluable for safety. One hundred twenty-nine (39.2%) subjects 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 was the gastrointestinal (GI) system in which 56 (17.0%) of the subjects reported an adverse event. Adverse events in other body systems occurred in fewer than 10% of the subjects, with insomnia (4.6% incidence) the second most common adverse event in this study. The most frequently reported adverse events were diarrhea (7.3%), insomnia (4.6%), nausea (4.3%), and

flatulence (2.7%) (Table 10). Twenty-nine (8.8%) subjects had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug. The three most common drug-related adverse events were diarrhea (2.7%), flatulence (1.8%), and nausea (1.2%). All other drug-related adverse events occurred at a rate of < 1.0%.

Table 10: Incidence of Frequently Reported (≥2.0%) Adverse Events Summarized by Primary Term: Subjects Evaluable for Safety

	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. Among the eight subjects with adverse events of marked severity, pruritus and erythematous rash in one subject and genital moniliasis in one subject were considered to be drug-related (i.e., definitely or probably related to study drug administration).

Deaths or Discontinuations Due to Adverse Events

No subject died during this study. Six (1.8%) of the subjects enrolled in the study discontinued due to adverse events (Table 11). Three subjects 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 of the three subjects with a treatment-limiting GI adverse event (nausea) also discontinued because of dizziness and lightheadedness.

Table 11: Subjects Who Discontinued Therapy Due to Adverse Events

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset[a]	Severity	Relationship To Study Drug[b]	Duration Of Therapy (Days)
Levofloxacin							
	30	M	Pruritus	2	Marked	Definite	2
			Erythematous Rash	2	Marked	Definite	
	30	F	Dizziness[c]	3	Mild	Possible	3
			Dizziness	3	Mild	Possible	
			Nausea	3	Mild	Possible	
	83	F	Edema	2	Mild	Probable	1
			Pruritus	2	Mild	Probable	
			Rash	2	Mild	Probable	
	52	F	Rash	5	Moderate	Probable	6
	83	F	Abdominal Pain	2	Mild	Possible	9
	26	M	Diarrhea	3	Moderate	Probable	7

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

Serious or Potentially Serious Adverse Events

One subject, a 65-year-old Caucasian woman with no reported history of cardiovascular disease, experienced a serious adverse event (myocardial infarction) 14 days after completing therapy. This adverse event was considered by the investigator to be unrelated to study drug administration.

Clinical Laboratory Tests

There were no clinically significant mean changes from admission to posttherapy for any laboratory analyte. The incidence of markedly abnormal test results for individual analytes was low (≤1%); only three subjects in the study experienced marked abnormalities. As shown in Table 12, two subjects had markedly abnormal blood chemistry values (one subject with elevated bilirubin and one with reduced glucose) and one had markedly abnormal hematology value (decreased lymphocytes).

Table 12: Subjects Who Had Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

Subject Number	Age	Sex	Lab Test (Markedly Abnormal Range)[a]	Admission Value	Abnormal Value	Study Day[b]	Follow-up Value (Therapy Day)	Duration of Therapy (Days)
Levofloxacin								
	23	F	Total Bilirubin (>1.5 mg/dL)	0.80	1.70	19 (PT 2)	–	17
	25	F	Glucose (<70 or >200 mg/dL)	96.00	54.00	17	67.00 (5PT)	21
	39	M	Lymphocytes (<1.0x10⁹/μL)	1.65	0.85	26 (PT 5)	–	21

[a] Only range given in table. For complete criteria, see Attachment 23a.
[b] Relative to the start of therapy (Day 1). NOTE: PT refers to the number of days posttherapy, relative to last day of study drug administration.

Physical Examination and Vital Signs

There were no clinically significant changes in vital signs from admission to posttherapy, and no clinically significant treatment-emergent pertinent physical examination abnormalities.

Conclusions

While this study is hard to interpret since it is uncontrolled, both clinical cure rate at poststudy and overall microbiologic eradication rate (by subject) were similar (71% and 73%, respectively) in patients considered evaluable by FDA. Efficacy for levofloxacin is somewhat less in this trial than in the other sinusitis trial, M92-040.

Study K90-070

Title
A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of oral levofloxacin versus cefaclor in the treatment of acute bacterial exacerbation of chronic bronchitis in adults.

Objectives
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.

Reviewer's Note: This study was originally designed to study 488 mg levofloxacin administered orally once daily for 7 to 14 days with that of 250 mg cefaclor administered orally three times daily for 7 to 14 days. The protocol was then later amended (after patients were already enrolled in the trial) to the dosing interval given above (5 to 7 days for levofloxacin and 7 to 10 days for cefaclor). Based on efficacy as explained below, FDA suggests that levofloxacin be administered for 7 to 10 days. To support such a dosing interval, FDA analyses include only levofloxacin patients who received levofloxacin for 7 to 10 days. FDA analyses include cefaclor patients who were dosed for 7 to 14 days, as originally planned.

Among FDA clinically evaluable subjects, 40, 4, 82, 8, 0, and 17 subjects received levofloxacin for 5, 6, 7, 8, 9, and 10 days, respectively. Clinical success rates (cured + improved) for these patients were 82.5%, 75%, 97.6%, 100%, N/A, and 100%, respectively. Thus, levofloxacin patients who received drug for 5 to 7 days had an overall clinical success rate of 92.1% (116 cured or improved of 126), while levofloxacin patients who received drug for 7 to 10 days had an overall clinical success rate of 98.1% (105 cured or improved of 107). No formal statistical test comparing overall clinical success rates between patients receiving 5-7 days of levofloxacin and patients receiving 7-10 days of levofloxacin was conducted, as patients receiving 7 days of levofloxacin are included in both groups (and hence a formal test is inappropriate). However, it was felt that 7 to 10 days of therapy with levofloxacin was more effective and is also more in line with other dosing regimens for this indication. Thus, FDA recommends that levofloxacin be given for 7 to 10 days if this indication is approved.

Study Design
This was a randomized, open-label (i.e., unblinded), active-control, multicenter study. Subjects who met the entry criteria were assigned randomly to receive either levofloxacin for 5 to 7 days or cefaclor for 7 to 10 days (*see above note*).

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 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 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. Clinical response in the group of subjects evaluable for clinical efficacy represented the secondary efficacy parameter for this study.

Reviewer's Note: As mentioned above, patients who received either 7 to 10 days of levofloxacin or 7 to 14 days of cefaclor were considered evaluable by FDA for clinical and microbiologic efficacy analyses (assuming they met other evaluability criteria). In addition, patients whose posttherapy visits were 4 to 8 days after the end of therapy were considered evaluable for clinical and microbiologic efficacy analyses. Finally, in this study the medical officer reviewed and changed data for individual pathogens; this information is incorporated in FDA analyses. Please see the medical officer's review for a more complete definition of patients considered evaluable for clinical and microbiologic efficacy analyses by both the sponsor and FDA.

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.

Analysis Groups

Treatment comparisons are based on several analysis groups to assess relative efficacy and consistency across different, standard approaches. The discussion and displays in the body of this report focus mainly on the efficacy analyses based on (i) subjects classified as clinically evaluable according to the sponsor and FDA and (ii) subjects classified as microbiologically evaluable according to the sponsor and FDA.

Supportive efficacy analyses include two types of analyses based on all subjects enrolled, i.e., randomized to a treatment group. One approach — Intent-to-Treat — adheres strictly to randomization; thus subjects are counted in their assigned treatment group regardless of any dosing or dispensing errors. An alternative approach — Modified Intent-to-Treat — takes into account the small number of drug dispensing errors that occurred by grouping subjects according to the drug actually received. These two approaches classify only two subjects differently; both were randomized to treatment with levofloxacin but received cefaclor. The Modified Intent-to-Treat approach — grouping subjects by treatment received rather than by treatment assigned — should be more reflective of the relative efficacy of the comparative treatments and is therefore given greater attention than the Intent-to-Treat analysis. Consistent with this reasoning, the clinically evaluable, microbiologically evaluable, and safety evaluable groups are also determined by treatment actually received rather than by treatment assigned. Supportive efficacy analyses also include an additional analysis group — Modified Intent-to-Treat Subjects with an Admission Pathogen — representing those subjects in the modified intent-to-treat group who had a pathogen isolated at admission.

Reviewer's Note: The sponsor's "modified intent-to-treat with an admission pathogen" group is what DAIDP usually terms "modified intent-to-treat". The sponsor's "modified intent-to-treat" group is actually an intent-to-treat group where patients were grouped according to

drug actually received (rather than to drug randomized).

Demographic and Baseline Characteristics

Three hundred seventy-three subjects were enrolled in the study at 20 centers, including 187 subjects who received levofloxacin treatment and 186 who received cefaclor (sponsor modified intent-to-treat group). The sponsor's efficacy analyses focused mainly on the groups of subjects considered clinically or microbiologically evaluable; the demographic and baseline characteristics for these two groups are presented in Table 1 and were comparable for the two treatment groups and were similar to that for the overall study group of 373 subjects. For the two treatment groups, approximately 60%of subjects were men, 95% Caucasian, and the majority (90%) had an admission diagnosis of chronic obstructive pulmonary disease (COPD).

Table 1. Demographic and Baseline Characteristics:
Sponsor Clinically Evaluable and Sponsor Microbiologically Evaluable Subjects

	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)				
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]
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.

Discontinuation/Completion Information

Of the 373 subjects enrolled in the study, 187 received levofloxacin and 186 received cefaclor (sponsor modified intent-to-treat group). Thirty (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. The most common reasons for discontinuation in the levofloxacin treatment group were an adverse event and absence of an admission pathogen. In the cefaclor group, the most common reason was clinical failure (Table 2).

Table 2. Reasons for Premature Discontinuation of Therapy: Sponsor Modified Intent-to-Treat Subjects

Reason	Levofloxacin (N=187) No.	(%)[a]	Cefaclor (N=186) 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 2202 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.

Efficacy Results

Clinical Response

Among sponsor 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 (Table 3a). Thirteen (8.4%) subjects in each treatment group failed treatment.

Table 3b summarizes clinical response rates for FDA clinically evaluable subjects. Among levofloxacin patients, the cure rate was 65%. Among cefaclor patients, the cure rate was 58%. This difference was considered therapeutically equivalent; the 95% confidence interval for the difference in cure rates, cefaclor minus levofloxacin patients, was $_{127,95}(-20.8, 6.8)_{58\%,65\%}$.

Table 3a. Clinical Response Rate By Study Center: Sponsor Clinically Evaluable Subjects

	Levofloxacin				Cefaclor				
Investigator	N	Cured[a]	Improved[a]	Failed[a]	N	Cured[a]	Improved[a]	Failed[a]	95% Confidence Interval[b]
Alwine	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)	(-1.8, 1.8)
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)	(-22.1, 13.9)
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)	(-12.2, 46.8)
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)	(-13.9, 37.1)
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[c]	57	40 (70.2)	16 (28.1)	1 (1.8)	64	35 (54.7)	23 (35.9)	6 (9.4)	(-16.4, 1.2)
Total	154	111 (72.1)	30 (19.5)	13 (8.4)	155	100 (64.5)	42 (27.1)	13 (8.4)	(-6.5, 6.6)

[a] Numbers shown in parentheses are percentages for that category.
[b] Two-sided 95% confidence interval around the difference (cefaclor minus levofloxacin) in clinical success rates (cure plus improved) calculated for study centers enrolling 10 or more clinically evaluable subjects in each treatment group.
[c] Combined = centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Alwine, Anthony, Brankston, Farber, Fogarty, Gilderman, Keller, Mestas, Padgett, Pollack, Scott, Stone, Stryker, Toney, and Wellman.

Table 3b. Clinical Response Rate By Study Center: 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".

For sponsor clinically evaluable subjects, when the clinical response categories "cured" and "improved" were combined into a single category of "clinical success", 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 for sponsor clinically evaluable patients (see Table 4a). The upper limit of this confidence interval lies below the confidence interval upper bound of 10%, thereby supporting clinical equivalence of the two treatments. Clinical response rates were generally comparable across analysis groups and centers.

Table 4b summarizes clinical success rates for FDA clinically evaluable subjects. Clinical success rates were considered therapeutically equivalent for levofloxacin and cefaclor.

Table 4a. Clinical Success/Failure Rates and Confidence Intervals by Study Center: Sponsor Clinically Evaluable Subjects

	Levofloxacin			Cefaclor			
Investigator	N	Success[a]	Failure[a]	N	Success[a]	Failure[a]	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.

Table 4b. Clinical Success/Failure Rates and Confidence Intervals by Study Center: 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.

Clinical response rates for sponsor clinically evaluable subjects infected with pathogens of interest alone or in combination with other pathogens are shown in Table 5a. Among the pathogens of interest, *H. influenzae, M. (Branhamella) catarrhalis*, and *H. parainfluenzae* were the most prevalent pathogens across the two treatment groups. *Clinical response rates for FDA clinically evaluable subjects infected with pathogens of interest alone or in combination with other pathogens are shown in Table 5b.*

Table 5a. Clinical Response Rates for Subjects With Pathogens of Primary Interest: Sponsor 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.

Table 5b. Clinical Response Rates for Subjects With Pathogens of Primary Interest: FDA Clinically Evaluable Subjects

	Levofloxacin				Cefaclor			
Pathogen	N*	Cure	Improve	Fail	N*	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 (Branhamella) 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.

*N = number of subjects who had that pathogen alone or in combination with other pathogens.

Microbiologic Response

The microbiologic eradication rates for subjects who were sponsor microbiologically evaluable are summarized by treatment group and study center in Table 6a. Among sponsor 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.

Microbiologic eradication rates for FDA microbiologically evaluable subjects are summarized by treatment group and study center in Table 6b. Microbiologic eradication rates are considered therapeutically equivalent for levofloxacin and cefaclor.

Table 6a. Microbiologic Eradication Rates and Confidence Intervals by Study Center: Sponsor Microbiologically Evaluable Subjects

	Levofloxacin			Cefaclor			95% Confidence Interval[b]	
Investigator	N	Eradicated[c]	Persisted	N	Eradicated	Persisted		
Alwine	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[d]	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 (cefaclor 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: Alwine, Anthony, Brankston, Farber, Fogarty, Gilderman, Keller, Mestas, Morowitz, Padgett, Pollack, Scott, Stone, Stryker, Toney, and Wellman.

Table 6b. Microbiologic Eradication Rates and Confidence Intervals by Study Center: 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.

Microbiologic eradication rates by pathogen and pathogen category for the sponsor's and FDA's analysis are in Tables 7a and 7b, respectively. The overall microbiologic eradication rates by pathogen in the levofloxacin and cefaclor treatment groups for the sponsor's analysis were 95.0% and 86.5%, respectively, with a 95% confidence interval of [-16.4, -0.4] for the difference between treatments (cefaclor minus levofloxacin) suggesting that levofloxacin is superior to cefaclor, assuming independence of multiple pathogens and multiple strains within a subject. *For the FDA analysis, microbiologic eradication rates by pathogen are considered therapeutically equivalent for levofloxacin and cefaclor, but superiority of levofloxacin is not established as it was in the sponsor's analysis.*

Table 7a. Microbiologic Eradication Rates Summarized by Pathogen Category and Pathogen: Sponsor Microbiologically Evaluable Subjects

Pathogen Category/Pathogen	Levofloxacin		Cefador		95% Confidence Interval[b]	
	N	Eradicated[a]	N	Eradicated[a]		
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						
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)	(-33.2,	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)	-	-

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

Table 7b. Microbiologic Eradication Rates Summarized by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects

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 (Branhamella) 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.

Among sponsor modified intent-to-treat subjects with an admission pathogen, the microbiologic eradication rates by subject for treatment with levofloxacin and cefaclor were 89.7% and 82.7%, respectively. The individual confidence intervals for all of the analysis groups are centered below zero and are consistent with therapeutic equivalence of treatments regarding microbiologic eradication rates.

Summary of Efficacy Results

A summary of sponsor key efficacy results is presented in Table 8a. Comparable results were seen across analysis groups for both clinical and microbiologic endpoints. In addition, there was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency of the clinical and microbiologic responses.

Overall success rates, defined as either clinical cure or clinical improvement with microbiologic eradication, are summarized for patients considered both clinically and microbiologically evaluable by FDA in Table 8b. The overall success rates were 92% for levofloxacin and 91% for cefaclor; 95% confidence interval of $_{64,61}(-12.7, 10.3)_{91\%,92\%}$. *Note that this confidence interval just misses showing therapeutic equivalence, however the study was not powered to address this specific question. No statistically significant difference is detected.*

Table 8a. Summary of Sponsor Key Efficacy Results

Clinical and Microbiologic Response					
	Levofloxacin		Cefaclor		
Response/Group	Clinical Success or Microbiologic Eradication Rates[a]		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				Cefaclor			
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 (cefaclor minus levofloxacin) in clinical success (cured plus improved) or microbiologic eradication rates.
[c] Based on microbiologically evaluable group.
[d] Cured, improved, or failed are clinical 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.

Table 8b. 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.

Safety Results

Summary of All Adverse Events

All but one of the 373 subjects enrolled were evaluated for safety. Of the 372 evaluable

subjects, 187 received levofloxacin and 185 received cefaclor. No data were available from one cefaclor-treated subject who was lost to follow-up with no postadmission data available and who was therefore excluded from the safety analysis.

Sixty-four (34.2%) of 187 evaluable subjects in the levofloxacin treatment group and 62 (33.5%) of 185 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. Body systems with the highest reported incidence of adverse events were the gastrointestinal (GI) system, the central and peripheral nervous system, and body as a whole. Gastrointestinal adverse events were the most common adverse events in both treatment groups (17.1% for levofloxacin and 15.1% for cefaclor). Although not statistically significantly different, a higher percentage of levofloxacin-treated subjects (5.9% and 9.1%) compared with cefaclor-treated subjects (3.8% and 5.4%) reported psychiatric or central and peripheral nervous system adverse events; adverse events in these body systems consisted primarily of reports of headache, dizziness, and insomnia.

The most commonly reported individual adverse events were nausea, diarrhea, headache, and abdominal pain (Table 9). The nature and frequency of individual 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.

Table 9. Incidence of Frequently Reported (≥2%) Adverse Events Summarized by Body System and Primary Term: Subjects Evaluable for Safety

	Levofloxacin (N=187)		Cefaclor (N=185)	
Body System/Primary Term	No.	(%)	No.	(%)
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 78.

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, i.e., probably or definitely related to study drug. Drug-related adverse events reported by ≥1.0% of levofloxacin-treated subjects were nausea (2.1%), flatulence (1.6%), insomnia (1.1%), abdominal pain (1.1%), and diarrhea (1.1%). Drug-related adverse events

reported by ≥1.0% of cefaclor-treated subjects were diarrhea (2.2%), vaginitis (1.3%), and abdominal pain (1.1%).

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 but no marked adverse event of a specific type was reported by more than one subject. 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. 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).

Deaths or Discontinuations Due to Adverse Events

Eighteen (4.8%) subjects discontinued study drug due to adverse events (Table 10), including 12 (6.4%) 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. One levofloxacin-treated subject [redacted] and one cefaclor-treated subject [redacted] died approximately three weeks after completing study therapy (see Table 10) due to progression of their underlying disease.

Table 10. Subjects Who Discontinued Therapy Due to Adverse Events

Subject Number	Age	Sex	Adverse Event (Primary Term)	Day of Onset*	Severity	Relationship to Study Drug†	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[‖]	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‡,[¶]	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

* Relative to start of therapy (Day 1).
† Based on investigator's assessment.
‡ An IND safety report was filed with the FDA for this subject.
‖ Chest tightening.
¶ Exacerbation of COPD.
‡Serious or potentially serious adverse event. (see Table VII)
**Subject also had a markedly abnormal laboratory value.

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 (Table 11). Of the 10 subjects with serious or potentially serious adverse events, three 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 many cases, appeared to be related to the subject's underlying respiratory condition.

Table 11. Subjects Who Had Serious or Potentially Serious Adverse Events

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
	64	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.

Clinical Laboratory Tests

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for any laboratory analytes in either treatment group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group was low (≤3.2% for all analytes except lymphocyte count) and comparable across treatment groups (Table 12). 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. Eight (5.1%) subjects in the levofloxacin group and 11 (7.2%) in the cefaclor group had markedly decreased lymphocytes. Nine subjects had markedly abnormal glucose levels: one levofloxacin-treated and two cefaclor-treated subjects had increased glucose levels and one levofloxacin-treated and five cefaclor-treated subjects had decreased glucose levels. Two subjects in each treatment group had markedly abnormal liver function tests (elevations in SGOT, SGPT, or alkaline phosphatase).

Table 12. Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

	Levofloxacin		Cefaclor	
Laboratory Test	Proportion[a]	%	Proportion[a]	%
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

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

Physical Examinations and Vital Signs

There were no clinically significant changes in vital signs from admission to posttherapy in levofloxacin-treated or cefaclor-treated subjects, with comparable results in the two groups. Similarly, there were no clinically significant treatment-emergent physical examination abnormalities.

Conclusions

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with acute bacterial exacerbation of chronic bronchitis. In both sponsor and FDA analyses, the microbiologic eradication rates in the levofloxacin treatment group were therapeutically equivalent to those observed in the cefaclor group, as were the clinical response rates.

Study M92-024

Title
A multicenter, randomized study to compare the safety and efficacy of oral levofloxacin with that of cefuroxime axetil in the treatment of acute bacterial exacerbation of chronic bronchitis in adults.

Objectives
The objective of this study was to compare the safety and efficacy of 500 mg levofloxacin administered orally once daily for 5 to 7 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.

Study Design
This was a randomized, open-label (i.e., unblinded), active-control, multicenter study. Subjects who met the entry criteria were assigned randomly to receive either levofloxacin for 5 to 7 days or cefuroxime axetil for 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 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 performed at admission and posttherapy. 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.

Reviewer's Note: To be consistent with FDA analyses in study K90-070, levofloxacin patients who received 7 to 10 days of study drug were considered evaluable for FDA clinical and microbiologic efficacy analyses. Since the majority of FDA clinically evaluable levofloxacin patients (212, to be exact) received 7 days of therapy with levofloxacin, changing the dosing interval from 5-7 (sponsor analysis) to 7-10 (FDA analysis) does not have a large effect in this study. For comparator patients, those dosed with 10-11 days of cefuroxime axetil were considered evaluable by FDA for clinical and microbiologic efficacy analyses. As in study K90-070, patients whose posttherapy visits were 4 to 8 days after the end of therapy were considered evaluable for FDA clinical and microbiologic efficacy analyses and individual pathogen data was reviewed and changed by the medical officer and incorporated in FDA analysis. Please see the medical officer's review for a more complete definition of patients evaluable for FDA and sponsor clinical and microbiologic efficacy analyses.

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 admission and posttherapy.

Analysis Groups

Treatment comparisons are based on several analysis groups to assess relative efficacy and consistency across different, standard approaches. The discussion and displays in the body of this report focus mainly on the efficacy analyses based on (i) subjects classified as clinically evaluable by the sponsor and FDA and (ii) subjects classified as microbiologically evaluable by the sponsor and FDA.

Supportive efficacy analyses are based on all subjects enrolled, i.e., randomized to a treatment group. These analyses are done in two ways. One approach — Intent-to-Treat — adheres strictly to randomization; thus subjects are counted in their assigned treatment group regardless of any dosing or dispensing errors. An alternative approach — Modified Intent-to-Treat — takes into account the small number of drug dispensing errors that occurred by grouping subjects according to the drug actually received. These two approaches classify only two subjects differently; both were randomized to treatment with cefuroxime axetil but received levofloxacin due to errors in drug dispensing. The Modified Intent-to-Treat approach — grouping subjects by treatment received rather than by treatment assigned — should be more reflective of the relative efficacy of the comparative treatments and is therefore given greater attention than the Intent-to-Treat analysis. Consistent with this reasoning, the clinically evaluable and microbiologically evaluable analysis groups are also determined by treatment actually received rather than by treatment assigned. Only one misdosed subject who received levofloxacin instead of cefuroxime axetil is included in the analyses based on the clinically and microbiologically evaluable groups.

Reviewer's Note: The sponsor's "modified intent-to-treat" approach is actually what DAIDP would term an intent-to-treat approach where patients are grouped according to drug actually received (rather than to drug randomized).

Demographic and Baseline Characteristics

Four hundred ninety-two subjects were enrolled in the study at 34 centers, including 248 subjects who received levofloxacin treatment and 244 who received cefuroxime axetil (modified intent-to-treat group). The efficacy analyses focused mainly on the groups of subjects considered clinically or microbiologically evaluable by the sponsor; the demographic and baseline characteristics for these two groups are presented in Table 1 and were comparable for the two treatment groups and were similar to that for the overall study group of 492 subjects. For the two treatment groups, approximately 54% of subjects were men, 73% Caucasian, and the majority (89%) had an admission diagnosis of chronic obstructive pulmonary disease (COPD).

Table 1. Demographic and Baseline Characteristics:
Sponsor Clinically Evaluable and Sponsor Microbiologically Evaluable Subjects

	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)				
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]
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.

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. Of the 238 subjects in the cefuroxime axetil group with known discontinuation/completion information, 13 (5.5%) discontinued therapy prematurely and 225 (94.5%) completed therapy. The most common reason for discontinuation in both treatment groups was an adverse event (Table 2).

Reviewer's Note: Nine levofloxacin and six cefuroxime axetil patients were lost to follow-up, thus the total number of patients discontinued or lost to follow-up in each arm was 18 (7.3%) for levofloxacin and 19 (7.8%) for cefuroxime axetil.

Table 2. Reasons for Premature Discontinuation of Therapy:
Sponsor Modified Intent-to-Treat Subjects

	Levofloxacin (N=248)		Cefuroxime Axetil (N=244)	
Reason	No.	(%)[a]	No.	(%)[a]
Adverse Event	7	(2.9)	8[b]	(3.4)
Clinical Failure	0	(0.0)	4	(1.7)
Other	2[c]	(0.8)	1[d]	(0.4)
Total Discontinued	9	(3.8)	13[b]	(5.5)
Total With Discontinuation/Completion Information	239	(100.0)	238	(100.0)
Total With Unknown Discontinuation/Completion Information	9		6	

[a] Percentages based on total number with discontinuation/completion information.
[b] Subject [redacted] was discontinued after receiving intravenous antibiotics for possible infiltrate present on admission chest X-ray. Subject [redacted] received three doses of levofloxacin and was dropped from the study after admission creatinine clearance results indicated renal insufficiency, an exclusion criterion for the study.
[c] Subject [redacted] was discontinued from the study after receiving antibiotics as treatment for a surgical wound present at admission.

Efficacy Results

Clinical Response

Among sponsor 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 (Table 3a). Twelve (5.4%) subjects in the levofloxacin treatment group and 17 (7.4%) subjects in the cefuroxime axetil treatment group failed treatment. In the sponsor 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.

Table 3b summarizes clinical response rates by center for FDA clinically evaluable subjects. Therapeutic equivalence between levofloxacin and cefuroxime axetil was established; 95% confidence interval for the difference in cure rates, cefuroxime axetil minus levofloxacin, of $_{203,196}(-10.5, 8.8)_{67\%,68\%}$.

Table 3a. Clinical Response Rate by Study Center: Sponsor Clinically Evaluable Subjects

	Levofloxacin				Cefuroxime axetil				
Investigator	N	Cured[a]	Improved[a]	Failed[a]	N	Cured[a]	Improved[a]	Failed[a]	95% Confidence Interval[b]
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)	(-10.9, 2.5)
Faris	16	13 (81.3)	3 (18.8)	0 (0.0)	18	12 (66.7)	6 (33.3)	0 (0.0)	(3.1, 34.1)
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)	(-18.9, 7.8)
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)	(-13.9, 14.3)
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)	(-17.9, 59.0)
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[c]	98	75 (76.5)	16 (16.3)	7 (7.1)	103	65 (63.1)	27 (26.2)	11 (10.7)	(-11.9, 4.3)
Total	222	173 (80.6)	31 (14.0)	12 (5.4)	229	173 (75.5)	39 (17.0)	17 (7.4)	(-6.8, 2.7)

[a] Numbers shown in parentheses are percentages for that category.
[b] Two-sided 95% confidence interval around the difference (cefuroxime axetil minus levofloxacin) in clinical success rate (cured plus improved) were calculated for study centers enrolling 10 or more clinically evaluable subjects in each treatment group.
[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.

Table 3b. Clinical Response Rate by Study Center: FDA Clinically Evaluable Subjects

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

For sponsor clinically evaluable subjects, when the clinical response categories "cured" and "improved" were combined into a single category of "clinical success," 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 (see Table 4a). All of the treatment differences in this confidence interval lie below the upper bound of 10%, thereby establishing therapeutic equivalence of the two treatments. In the sponsor modified intent-to-treat group, the clinical success rates for treatment with levofloxacin and cefuroxime axetil were 90.3% and 90.2%, respectively.

Table 4b summarizes clinical success rates for FDA clinically evaluable subjects. Levofloxacin and cefuroxime axetil are considered therapeutically equivalent in terms of success rates (as they were when cure rates were examined).

Table 4a. Clinical Success/Failure Rates and Confidence Intervals by Study Center : Sponsor Clinically Evaluable Subjects

	Levofloxacin					Cefuroxime axetil					
Investigator	N	Success[b]		Failure[b]		N	Success[b]		Failure[b]		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)	–
Interlano	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, 7.8)
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, 4.8)
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, Interlano, Kaye, Klaustermeyer, Korenblat, Littlejohn, Marbury, McAdoo, Memon Moyer, Nair, Nichols, Puopolo, Rice, Rosen, Smith, Sullivan, Summer, Thomas, Zervos, and Zorn.

Table 4b. Clinical Success/Failure Rates and Confidence Intervals by Study Center : FDA Clinically Evaluable Subjects

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)	96	82 (85)	(-17, 1)
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.

Clinical Response by Pathogen

Clinical response rates for sponsor clinically evaluable subjects infected with key pathogens alone or in combination with other pathogens are shown in Table 5a. *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.

Table 5b shows clinical response rates for FDA clinically evaluable subjects infected with key pathogens alone or in combination with other pathogens.

Table 5a. Clinical Response Rates for Subjects with Pathogens of Primary Interest: Sponsor Clinically Evaluable Subjects

Pathogen	Levofloxacin				Cefuroxime axetil			
	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.

* N=number of subjects who had that pathogen alone or in combination with other pathogens.

Table 5b. Clinical Response Rates for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects

Pathogen	Levofloxacin				Cefuroxime Axetil			
	N[a]	Cure	Improve	Fail	N[a]	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.
[a]N = number of subjects who had that pathogen alone or in combination with other pathogens.

Microbiologic Response

The microbiologic eradication rates for subjects who were sponsor and FDA microbiologically evaluable are summarized by treatment group and study center in Tables 6a and 6b, respectively. In both cases, levofloxacin was considered therapeutically equivalent to cefuroxime axetil in terms of eradication rates.

Table 6a. Microbiologic Eradication Rates and Confidence Intervals by Study Center: Sponsor Microbiologically Evaluable Subjects

Investigator	Levofloxacin					Cefuroxime axetil					95% Confidence Interval[b]	
	N	Eradicated[a]		Persisted[a]		N	Eradicated[a]		Persisted[a]			
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)	(-6.0,	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.

Table 6b. Microbiologic Eradication Rates and Confidence Intervals by Study Center: FDA Microbiologically Evaluable Subjects

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.

Microbiologic eradication rates for sponsor microbiologically evaluable patients are summarized by pathogen and pathogen category in Table 7a. 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. *Microbiologic eradication rates for FDA microbiologically evaluable patients are summarized by pathogen and pathogen category in Table 7b.*

Table 7a. Microbiologic Eradication Rates Summarized by Pathogen Category and Pathogen: Sponsor Microbiologically Evaluable Subjects

	Levofloxacin			Cefuroxime axetil			95% Confidence Interval[b]
Pathogen Category/Pathogen	N	Eradicated[a]		N	Eradicated[a]		
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)	(-6.6, 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)	(-6.7, 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.

Table 7b. Microbiologic Eradication Rates Summarized by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects

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.

Summary of Efficacy Results

A summary of sponsor key efficacy results is presented in Table 8a. Comparable results were seen across analysis groups for both clinical and microbiologic endpoints. In addition, there was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency of the clinical and microbiologic responses.

Table 8b summarizes overall success rate, defined as either clinical cure or clinical improvement with microbiologic eradication, by study center for patients considered both clinically and microbiologically evaluable by FDA. The 95% confidence interval for the difference in overall success rate, cefuroxime axetil minus levofloxacin, demonstrates therapeutic equivalence between levofloxacin and cefuroxime axetil.

Table 8a. Summary of Key Efficacy Results: Sponsor Analysis Groups

Clinical and Microbiologic Response			
	Levofloxacin	Cefuroxime Axetil	
ResponseGroup	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.

Table 8b. Overall Success Rates[a] and Confidence Intervals By Study Center: FDA Microbiologically AND Clinically Evaluable Subjects

	Levofloxacin		Cefuroxime Axetil		
Investigator	N[b]	Overall Success[c]	N	Overall Success	95% Confidence Interval[d]
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.

Safety Results

Summary of All Adverse Events

Four hundred eighty-four (98.4%) of 492 subjects enrolled were evaluated for safety. Of the 484 evaluable 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 postadmission data available and were therefore excluded from the safety analysis.

One-hundred twenty-seven (52.3%) of 243 evaluable subjects in the levofloxacin treatment group and 124 (51.5%) of 241 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 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%) (Table 9).

The two treatment groups were generally comparable with respect to the type and incidence of adverse events. 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%). 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 reported one or more adverse events of marked severity, including diarrhea and chest pain in two subjects each. 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).

Table 9. Incidence of Frequently Reported (≥2%) Adverse Events Summarized by Body System and Primary Term: Subjects Evaluable for Safety

	Levofloxacin (N=243)		Cefuroxime axetil (N=241)	
Body System/Primary Term[a]	No.	(%)[b]	No.	(%)
All Body Systems	127	(52.3)	124	(51.5)
Central & Peripheral Nervous System Disorders	32	(13.2)	24	(10.0)
Headache	17	(7.0)	9	(3.7)
Dizziness				
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				
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.

Deaths and Discontinuations Due to Adverse Events

Fifteen subjects discontinued study drug due to adverse events (Table 10), 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 dyspnea) and one cefuroxime-treated subject syncope). No deaths occurred during the study.

Table 10. Subjects Who Discontinued Therapy Due to Adverse Events

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
			Monilliasis	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
	60	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 VII)
** Subject also had a markedly abnormal laboratory value.

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 (Table 11). 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 11. Subjects Who Had Serious or Potentially Serious Adverse Events

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
	46	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
	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[c]	6	Marked	Remote	6
	65	M	Pneumonia	6	Marked	None	6
	78	M	Syncope	2	Marked	None	2
			Tachycardia[d]	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 posttherapy, relative to the last day of study drug administration.
[b] Based on investigator's assessment.
[c] These serious adverse events occurred after the scheduled posttherapy 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 VII)
[g] Subject also had markedly abnormal laboratory value.

Clinical Laboratory Tests

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for any laboratory analytes in either treatment group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group was low (≤2.2%) and comparable across treatment groups (Table 12). 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 12. Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

	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.

Physical Examination and Vital Signs

There were no clinically significant changes in vital signs from admission to posttherapy in levofloxacin-treated or cefuroxime axetil-treated subjects, with comparable results in the two groups. Similarly, there were no clinically significant treatment-emergent physical examination abnormalities.

Conclusions

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with acute bacterial exacerbation of chronic bronchitis. For both sponsor and FDA analyses, the clinical responses in the levofloxacin treatment group were therapeutically equivalent to those observed in the cefuroxime axetil group, as were the microbiologic eradication rates.

Study K90-071

Title
A multicenter, active-controlled, randomized study to evaluate the safety and efficacy of levofloxacin versus ceftriaxone sodium or cefuroxime axetil in the treatment of community-acquired pneumonia in adults.

Objectives
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. Data regarding the cost-effectiveness of the levofloxacin treatment regimen relative to the ceftriaxone sodium/cefuroxime axetil regimen in the treatment of community-acquired pneumonia were also collected but are not presented by the sponsor.

Study Design
This was a randomized, open-label (i.e., unblinded), active-control, multicenter study. Subjects who met the entry criteria were assigned randomly to receive either levofloxacin, cefuroxime axetil, or ceftriaxone sodium for 7 to 14 days.

Note: Levofloxacin dosage could be 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. Levofloxacin dosage was to be 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.

Efficacy evaluations were based on the assessments of clinical symptoms, chest examination, radiographic signs, clinical response (evaluated posttherapy as cured, improved, failed, or unable to evaluate and poststudy as cured, improved, relapsed, 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 signs and symptoms were monitored at admission, while on therapy (Days 2 to 4), five to seven days after the end of therapy (posttherapy -- *note: the sponsor actually accepted posttherapy visits which were 1 to 10 days after the end of therapy*), and 21 to 28 days after the end of therapy (poststudy) for subjects with a poststudy visit. Cultures, Gram stains, and susceptibility testing, serologic studies, and other diagnostic evaluations of respiratory specimens and blood samples were performed at admission, posttherapy and poststudy, if indicated. Clinical response at posttherapy in the group of subjects evaluable for clinical efficacy was the primary efficacy variable for this study. Microbiologic response

was the secondary efficacy variable and was based primarily on the group of subjects evaluable for microbiologic efficacy.

*Reviewer's Note: For both clinical and microbiologic efficacy analyses, FDA evaluated patients whose posttherapy visits were 5 to 10 days after the end of treatment based on their **posttherapy outcome**. Patients whose posttherapy visits were 0 to 4 days after the end of treatment were evaluated based on their **poststudy outcome**. In addition, evaluable patients with IgG titers equal to 1:512 for Chlamydia pneumoniae were included in FDA analyses (they were excluded in the sponsor's analyses). Finally, only patients dosed once a day were included in FDA analyses presented here (ie, patients receiving bid dosing were excluded). Please see the medical officer's review for a more complete definition of patients considered evaluable by the sponsor and FDA for clinical and microbiologic efficacy analyses (and for results for patients receiving bid dosing).*

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 admission and posttherapy.

Analysis Groups

Treatment comparisons are based on several analysis groups to assess relative efficacy and consistency across different, standard approaches. The discussion and displays in the body of this report focus mainly on the efficacy analyses based on (i) subjects classified as clinically evaluable by the sponsor and FDA and on (ii) subjects classified as microbiologically evaluable by the sponsor and FDA. Supportive efficacy analyses include all subjects enrolled, i.e., randomized to a treatment group.

Demographic and Baseline Characteristics

Five hundred ninety subjects were enrolled in the study at 40 centers, including 295 subjects who received levofloxacin treatment and 295 who received ceftriaxone/cefuroxime (intent-to-treat group). The sponsor's efficacy analyses focused mainly on the groups of subjects considered clinically or microbiologically evaluable; the demographic and baseline characteristics for these two groups are presented in Table 1 and were comparable for the two treatment groups. For the clinically evaluable group, approximately 55% of subjects were men, 65% Caucasian, and the majority (84%) had infections that were categorized as mild or moderate.

Table 1. Demographic and Baseline Characteristics:
Sponsor Clinically Evaluable and Sponsor Microbiologically Evaluable Subjects

	Levofloxacin		Ceftriaxone/Cefuroxime	
	Clinically Evaluable (N=225)	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	85	151	101
Black	74	41	75	42
Hispanic	5	1	2	1
Other	0	0	2	0
Age (Years)				
N	225	128	230	144
Mean±SD	49.1±17.5	50.0±17.9	50.1±18.5	50.6±17.7
Range	[redacted]	[redacted]	[redacted]	[redacted]
Weight (lbs.)				
N	215	120	219	136
Mean±SD	171.0±43.6	167.5±40.2	174.6±46.1	175.0±45.3
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.

Discontinuation/Completion Information

Of the 590 subjects enrolled in the study, 295 received levofloxacin and 295 received ceftriaxone/cefuroxime (intent-to-treat group). Twenty-eight (10.1%) of the 277 subjects in the levofloxacin group with known discontinuation/completion information discontinued therapy prematurely and 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. The most common single reasons for discontinuation in both treatment groups were adverse events and clinical failure (Table 2).

Table 2. Reasons for Premature Discontinuation of Therapy:
Sponsor Intent-to-Treat Subjects

	Levofloxacin		Ceftriaxone/Cefuroxime	
Reason	No.	(%)[a]	No.	(%)[a]
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	

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

Efficacy Results

Clinical Response

Sponsor Results

Among all sponsor clinically evaluable subjects in the levofloxacin treatment group, 72.1% were cured, 24.3% were improved and 3.5% failed at the posttherapy visit, compared with 69.1%, 21.3% and 9.6% in the ceftriaxone/cefuroxime treatment group (Table 3a). The data indicate that levofloxacin treatment was comparable in efficacy among subjects with severe infections and those with mild/moderate infections.

FDA Results

Table 3b summarizes clinical response rates by investigator for FDA clinically evaluable patients. The 95% confidence interval for the difference in cure rates (ceftriaxone/cefuroxime minus levofloxacin) is $_{226,207}(-25.6, -6.1)_{46\%,62\%}$ *suggesting that levofloxacin is superior to ceftriaxone/cefuroxime in terms of clinical cure.*

Table 3a. Posttherapy Clinical Response Rate By Study Center: Sponsor Clinically Evaluable Subjects

	Levofloxacin				Ceftriaxone/Cefuroxime				
Investigator	N	Cured	Improved	Failed	N	Cured	Improved	Failed	95% Confidence Interval[2]
Alessi	4	3 (75.0)	1 (25.0)	0 (0.0)	6	6 (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)	(-11.9, 14.3)
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)	(. , .)
Heuer	16	13 (81.3)	1 (6.3)	2 (12.5)	17	6 (35.3)	3 (17.6)	8 (47.1)	(-66.4, -2.7)
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)	(. , .)
Ismaiski	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)	(-3.1, 3.1)
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)	(-3.3, 3.3)
Plouffe	5	5 (100.0)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)	(. , .)
Ruf	4	3 (75.0)	1 (25.0)	0 (0.0)	3	1 (33.3)	1 (33.3)	1 (33.3)	(. , .)
Seggev	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[4]	150	110 (73.3)	35 (23.3)	5 (3.3)	160	105 (70.0)	32 (21.3)	13 (8.7)	(-11.0, 0.3)
Total	225	163 (72.4)	55 (24.3)	8 (3.5)	238	169 (69.1)	49 (21.3)	22 (9.6)	(-16.7, -1.3)

Numbers shown in parentheses are percentages for that category.

[1] A window of 1-10 days posttherapy was used for determination of evaluability.

[2] 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.

[4] Combined = centers that enrolled fewer than 10 clinically evaluable subjects in either treatment group: Alessi, Baird, Brankston, Budzak, Burford, Decker, Ellis, Ervin, Fite, Follett, Gardner, Geckler, Gombert, Gomes, Graham, Green J., Green S., Grunfeld, Habib, Havlichek, Holloway, Hunt, Ironside, Ismaiski, Joshi, Keller, Mandell, Moyer, Padgett, Parsons, Payne, Plouffe, Ruff, Seggev, Segreti, and Shankman.

Table 3b. Clinical Response Rate by Study Center: FDA Clinically Evaluable Subjects

	Levofloxacin						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.

When the clinical response categories "cured" and "improved" were combined into a single category of "clinical success" for sponsor clinically evaluable subjects (see Table 4a), levofloxacin treatment resulted in 96.5% clinical success and ceftriaxone/cefuroxime treatment resulted in 90.4% clinical success, with a 95% confidence interval of [-10.7, -1.3] for the difference (ceftriaxone/cefuroxime minus levofloxacin) in success rates, suggesting that levofloxacin is superior to ceftriaxone/cefuroxime. Clinical response rates were generally comparable across sponsor efficacy analysis groups and study centers.

Table 4b summarizes clinical success rates by investigator for FDA clinically evaluable patients. The 95% confidence interval for the difference in clinical success rates suggests that levofloxacin is superior to ceftriaxone/cefuroxime in terms of clinical success (clinical cure + improvement).

Table 4a. Posttherapy Clinical Success Rates and Confidence Intervals By Study Center: Sponsor 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	5	5 (100.0)	0 (0.0)	4	2 (50.0)	2 (50.0)	(. , .)
Brainston	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)	(. , .)
Geckler	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)	(. , .)
Heuer	16	14 (87.5)	2 (12.5)	17	9 (52.9)	8 (47.1)	(-55.4, -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)	(. , .)
Seggev	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)	150	137 (91.3)	13 (8.7)	(-11.0, 0.3)
Total	**235**	**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, Brainston, Budzak, Bufford, Decker, Ellis, Ervin, File, 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, Seggev, Segreti, and Shankman.

Table 4b. Clinical Success Rates and Confidence Intervals By Study Center: FDA Clinically Evaluable Subjects

Investigator	Levofloxacin		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.

[b]Two-sided confidence interval for the difference (ceftriaxone/cefuroxime minus levofloxacin) in clinical success rate.

Of the 205 sponsor clinically evaluable subjects in the levofloxacin treatment group who had a poststudy clinical evaluation and had a posttherapy clinical response of cured or improved, poststudy clinical responses were cure for 90.2%, improved for 5.9% and relapse for 2.9% of subjects. Of the 193 subjects in the ceftriaxone/cefuroxime group who met the aforementioned criteria, 92.2% had a poststudy response of cure, 5.7% improved, and 2.1% relapse. Poststudy clinical response ratings for the sponsor microbiologically evaluable and intent-to-treat subjects were consistent with the results of the clinically evaluable group.

Tables 5a and 5b summarize clinical response rates by pathogen for sponsor and FDA clinically evaluable patients, respectively. For Table 5a, pathogens are separated according to the method of evaluation (e.g., respiratory culture, blood culture, etc.).

Table 5a. Posttherapy Clinical Response for Subjects with Pathogens of Primary Interest: Sponsor Clinically Evaluable Subjects

	Levofloxacin				Ceftriaxone/Cefuroxime			
Method of Evaluation/Pathogen[b]	N[c]	Cured	Improved	Failed	N[c]	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.

97.9% to 100% of atypical pathogens detected by serology, as compared with eradication rates of 75.0% to 100% among ceftriaxone/cefuroxime-treated subjects.

FDA Results

Table 6b summarizes microbiologic eradication rates by pathogen category, pathogen, and subject, for FDA microbiologically evaluable patients. Both the confidence interval for the difference in eradication rates by pathogen and the confidence interval for the difference in eradication rate by subject suggest that levofloxacin is superior to ceftriaxone/cefuroxime.

Table 6a. Posttherapy Microbiologic Eradication Rates Summarized by Method of Evaluation, Pathogen, and Treatment Regimen: Sponsor Microbiologically Evaluable Subjects

	Levofloxacin						
	q24h and q48h Regimen (N=118)		All Regimens[b] (N=128)		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)	(. , .)
Klebsella 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)	(-2.6, 2.6)
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 118 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.

Table 6b. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects

Pathogen Category/Pathogen	Levofloxacin		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 (Branhamella) catarrhalis	7	6 (86)	6	5 (83)	N/A
Staphylococcus aureus	7	7 (100)	7	7 (100)	N/A
Streptococcus pneumoniae	35	34 (97)	42	38 (90)	(-19.7, 6.4)
Other Pathogens					
Chlamydia pneumoniae	57	55 (96)	90	78 (87)	(-19.8, 0.1)
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.

Microbiologic eradication rates, by subject and pathogen for sponsor microbiologically evaluable subjects, were 98.1% for subjects with mild/moderate infections and 100% for subjects with severe infections in the levofloxacin group; in the ceftriaxone/cefuroxime group, these rates were 87.9% for subjects with mild/moderate infections and 85.7% 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 as among those with mild/moderate infections and produced eradication rates as high or higher than ceftriaxone/cefuroxime treatment.

Summary

A summary of sponsor key efficacy results is presented in Table 7a. The clinical response rates are comparable among the efficacy 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 90.0% 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 88.0%. In addition, 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.

Table 7a. Summary of Sponsor Key Efficacy Results

Clinical and Microbiologic Response

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 Response					
Intent-to-Treat	257/295	(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]	146/166	(88.0)	139/181	(76.8)	(-19.4, -3.0)

Microbiologic Response Versus Clinical Response[d]

	Clinical Response: Levofloxacin					Ceftriaxone/Cefuroxime				
Microbiologic Response	N	Cured	Improved		Failed	N	Cured	Improved		Failed
Eradicated	126	93 (73.8)	32	(25.4)	1 (0.8)	125	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	126	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.

Table 7b summarizes "overall success rates" (defined by FDA as either clinical cure or improvement with microbiologic eradication) by investigator for patients considered both clinically and microbiologically evaluable by FDA. The 95% confidence interval for the overall difference in overall success rates suggests that levofloxacin is superior to ceftriaxone/cefuroxime.

Table 7b. Overall Success Rates[a] and Confidence Intervals By Study Center: FDA Microbiologically AND Clinically Evaluable Subjects

Investigator	Levofloxacin		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.

Safety Results

Summary of All Adverse Events

Five hundred eighty-four subjects of the 590 enrolled were evaluated for safety. Of the 584 evaluable subjects, 291 received levofloxacin and 293 received ceftriaxone/cefuroxime. Four levofloxacin-treated and two ceftriaxone/cefuroxime-treated subjects who were lost to follow-up with no postadmission data available were excluded from the safety analysis.

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 (Table 8). **All body systems had confidence intervals that included zero (indicating no statistically significant difference between treatments) with two exceptions: heart rate and rhythm disorders (reported by five levofloxacin-treated subjects and none of the ceftriaxone/cefuroxime-treated subjects) and urinary system disorders (reported by five ceftriaxone/cefuroxime-treated subjects and none of the levofloxacin-treated subjects).** Gastrointestinal adverse events were the most common adverse events in both treatment groups (22.3% for levofloxacin and 25.9% for ceftriaxone/cefuroxime). 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.

Table 8. Incidence of Frequently Reported (≥2.0%) Adverse Events 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[1]				
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)

[1] Primary term reported by ≥2.0% of subjects in either treatment group.
[2] 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.

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, 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 (1.4%) 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%).

The majority of adverse events were assessed as mild in severity. Twenty subjects in each of the levofloxacin and ceftriaxone/cefuroxime groups reported one or more events of marked severity. In the levofloxacin group, the most common of these events consisted of respiratory disorders (five subjects) and cardiac events (four subjects). In the ceftriaxone/cefuroxime group, the most common marked events consisted of respiratory disorders (eight subjects) and disorders of the body as a whole (four subjects).

Discontinuations Due to Adverse Events

Twenty-five subjects discontinued the study drug due to adverse events (Table 9), including 13 in the levofloxacin treatment group and 12 in the ceftriaxone/cefuroxime treatment group. In the levofloxacin group, all of the adverse events (with the exception of one case of diarrhea that occurred on Day 12) 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 ceftriaxone/cefuroxime group most frequently consisted of gastrointestinal complaints.

Table 9. Subjects Who Discontinued Therapy Due to Adverse Events

Subject Number	Age	Sex	Adverse Event (Primary Term)	Study Day Of Onset[a]	Severity	Relationship to Study Drug[b]	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
	59	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	
	76	F	Asthenia	2	Moderate	Definite	2
			Dizziness	2	Moderate	Definite	
			Rigors	2	Moderate	Definite	
			Vomiting	2	Moderate	Definite	
	25	M	WBC abnormal nos	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[c]	Marked	None	1
	67	F	Phlebitis	3	Mild	Possible	2

[a] Relative to start of therapy (Day 1).

[b] Based on investigator's assessment.

[c] 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 VII).

[††] Subject also had a markedly abnormal laboratory value (see Table 34).

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 reported a serious or potentially serious adverse

event during or up to approximately four weeks after completing study therapy (Table 10), including two deaths in the levofloxacin group and eight deaths in the ceftriaxone/cefuroxime group. Of the 47 subjects with serious or potentially serious adverse events, five withdrew from the study because of the adverse event. In the majority of 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 physical condition.

Table 10. Subjects Who Had Serious or Potentially Serious Adverse Events

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[c]	46	(PT 33)	Unknown	None	13
			Sepsis	46	(PT 33)	Marked	None	
			Myocardial infarction	47	(PT 34)	Marked	None	
	46	M	Convulsions	1		Marked	None	1
	52	M	Hyperglycemia	5		Marked	None	10
	75	M	Pneumonia[d]	31	(PT 21)	Unknown	Remote	10
	60	M	Pulmonary carcinoma	4		Marked	None	10
	73	F	Hyperkalemia	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[c]	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	
	35	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
	51	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	
			Hypoglycemia[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,g]	3	(PT 1)	Marked	Possible	2
			Dehydration[c]	7	(PT 5)	Unknown	Remote	
			Postural hypotension[c]	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	
[h]	55	M	Respiratory insufficiency	2	(PT 1)	Marked	None	1
			Fibrillation ventricular	9	(PT 8)	Marked	None	
	-		Acute renal failure[c]	Unknown		Unknown	Remote	
	60	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.
[h] Subject discontinued due to this adverse event (see Table VII).
[i] Subject also had markedly abnormal laboratory value (see Table 34).
[j] Subject died as a result of the serious adverse event(s). An IND Safety Report was submitted to FDA for Subject [redacted].

Table 10. Subjects Who Had Serious or Potentially Serious Adverse Events (Continued)

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[f]	44	(PT 29)	Unknown	None	15
			Dyspnea[f]	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[g]	19	(PT 9)	Unknown	Remote	10
	96	F	Respiratory insufficiency	7		Marked	None	8
			Fever	8		Marked	None	
	70	M	Pneumocystis carinii[h]	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[d]	0[i]		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	6		Marked	None	5
	72	F	Arrhythmia[e]	2	(PT 1)	Unknown	Remote	1
			Cardiac arrest[f]	2	(PT 1)	Unknown	Remote	
			Respiratory insufficiency[f]	2	(PT 1)	Unknown	Remote	
			Myocardial infarction[k]	2[k]		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 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 (see Table VII).
[k] Subject also had markedly abnormal laboratory value (see Table 34).
[l] Subject died as a result of the serious adverse event(s).

Clinical Laboratory Tests

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for any laboratory analytes in either treatment group, with comparable results in both groups. The incidence of markedly abnormal test results for individual analytes within a given treatment group was low (≤4.7%) and comparable across 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 11).

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. Seven subjects in the levofloxacin group and 11 in the ceftriaxone/cefuroxime group had markedly decreased lymphocytes. Twenty-five subjects had markedly abnormal glucose levels: three levofloxacin-treated and three ceftriaxone/cefuroxime-treated subjects had increased glucose levels and 11 levofloxacin-treated and eight ceftriaxone/cefuroxime-treated subjects had decreased glucose levels. Four subjects in the levofloxacin group and 15 subjects in the ceftriaxone/cefuroxime treatment group had markedly abnormal liver function tests (elevations in SGOT, SGPT, or alkaline phosphatase).

Table 11. 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.

Physical Examinations and Vital Signs

There were no clinically significant changes from admission to posttherapy in levofloxacin-treated or ceftriaxone/cefuroxime-treated subjects, with comparable results in the two groups.

Conclusions

Levofloxacin was safe, well-tolerated, and effective in the treatment of subjects with community-acquired pneumonia. Clinical success rate, microbiologic eradication rate (by pathogen and subject), and overall success rate in the levofloxacin treatment group were each statistically significantly different (i.e., higher) than those observed in the ceftriaxone/cefuroxime group in FDA analyses.

Study M92-075

Title
A multicenter, noncomparative study to evaluate the safety and efficacy of levofloxacin in the treatment of community-acquired pneumonia in adults.

Objectives
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.

Study Design
This was a noncomparative multicenter study. Subjects who met the entry criteria were treated with 500 mg of levofloxacin intravenously or orally once daily for 7 to 14 days.

Efficacy evaluations were based on assessments of clinical symptoms, chest examination and radiographic signs, clinical response (evaluated posttherapy as cured, improved, failed, or unable to evaluate and poststudy as cured, improved, relapse, 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 signs (chest examination) and symptoms were monitored at admission, while on therapy (Days 2 to 4), at the posttherapy (posttherapy days 5-7 -- *note: the sponsor actually accepted posttherapy visits which were 1 to 10 days after the end of therapy*) visit, and at post-study (posttherapy days 21-28) for subjects who had a poststudy visit. Cultures, Gram stains, susceptibility testing, serologic studies, and other diagnostic evaluations of respiratory secretions and blood samples were performed at admission and repeated at the posttherapy visit and, if appropriate, poststudy. Microbiologic response at posttherapy in the group of subjects evaluable for microbiologic efficacy represented the primary efficacy variable for this study. Clinical response was a secondary efficacy variable and was based primarily on the groups of subjects evaluable for clinical and microbiologic efficacy.

*Reviewer's Note: For both clinical and microbiologic efficacy analyses, FDA evaluated patients whose posttherapy visits were 5 to 10 days after the end of treatment based on their **posttherapy outcome**. Patients whose posttherapy visits were 0 to 4 days after the end of treatment were evaluated based on their **poststudy outcome**. In addition, evaluable patients with IgG titers equal to 1:512 for Chlamydia pneumoniae were included in FDA analyses (they were excluded in the sponsor's analyses). Finally, only patients dosed once a day were included in FDA analyses presented here (ie, patients receiving bid dosing were excluded). Please see the medical officer's review for a more complete definition of patients considered evaluable by the sponsor and FDA for clinical and microbiologic efficacy analyses (and also for results for patients dosed bid).*

Safety evaluations consisted of treatment-emergent adverse events collected throughout the study and of clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, and physical examinations performed at admission and posttherapy.

Analysis Groups

The discussion and displays in the body of this report focus mainly on the efficacy analyses based on (i) subjects classified as microbiologically evaluable according to the sponsor and FDA, and (ii) subjects classified as clinically evaluable according to the sponsor and FDA. Supportive efficacy analyses are based on all subjects enrolled, i.e., intent-to-treat population, and subjects who had a pathogen isolated at admission, i.e., modified intent-to-treat subjects with an admission pathogen.

Demographic and Baseline Characteristics

Two hundred sixty-four subjects (intent-to-treat group) were enrolled in the study at 18 centers. The sponsor's efficacy analyses focused mainly on the groups of subjects considered microbiologically or clinically evaluable; the demographic and baseline characteristics for these two groups are presented in Table 1 and were similar to those of the overall study group of 264 subjects. Among subjects who were microbiologically evaluable, 56.4% were men, 79.8% were Caucasian, 77.9% had mild/moderate infections, and 55.8% were treated as outpatients.

Table 1. Demographic and Baseline Characteristics:
Sponsor Clinically Evaluable and Sponsor Microbiologically Evaluable Subjects

	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)		
N	234	163
Mean±SD	52.2±17.8	53.0±18.1
Range	[redacted]	[redacted]
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.

Discontinuation/Completion Information

All 264 subjects enrolled in the study received levofloxacin treatment; 248 (93.9%) subjects were treated with q24h or q48h dosing regimens throughout their entire course of therapy, and 16 (6.1%) subjects received one or more days of q12h dosing. Of the 256 subjects with known discontinuation/completion information, 23 (9.0%) subjects discontinued therapy prematurely and 233 (91.0%) completed levofloxacin therapy according to the regimen prescribed by the investigator. Discontinuation/completion information is unknown for an additional eight subjects who did not return for the final visit. Reasons for premature

discontinuation are summarized in Table 2. The most common reasons for discontinuation were an adverse event or clinical failure.

Table 2. Reasons for Premature Discontinuation of Therapy: Sponsor Intent-to-Treat Subjects

Reason	Levofloxacin (N=264) 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 609 and 2302 required treatment with additional antibiotics and were withdrawn from the study after receiving levofloxacin treatment for three and 10 days, respectively. Subject 205 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 2806 was withdrawn after seven days of levofloxacin treatment because of persistent pre-existing diarrhea.

Efficacy Results

Clinical Response

Sponsor Results

The clinical response posttherapy for levofloxacin-treated subjects considered clinically evaluable by the sponsor is summarized by study center in Table 3a. Among sponsor clinically evaluable subjects, 77.8% were cured, 17.1% improved, and 5.1% failed treatment. For the sponsor 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.

FDA Results

Table 3b summarizes clinical response rates by investigator for FDA clinically evaluable patients. The overall cure rate for levofloxacin was 52%.

Table 3a. Posttherapy Clinical Response Rate By Study Center: Sponsor Clinically Evaluable Subjects

	Levofloxacin						
Investigator	N	Cured		Improved		Failed	
Alvine	4	4	(100.0)	0	(0.0)	0	(0.0)
Carroll	9	7	(77.8)	2	(22.2)	0	(0.0)
Chatman	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.

Table 3b. Clinical Response Rate by Study Center: FDA Clinically Evaluable Subjects

	Levofloxacin						
Investigator	N	Cure		Improve		Fail	
Chattman	18	11	(61)	6	(33)	1	(6)
Fogarty	50	19	(38)	31	(62)	0	(0)
Gaman	10	5	(50)	5	(50)	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	59	26	(44)	22	(37)	11	(19)
Total	203	105	(52)	83	(41)	15	(7)

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.

For sponsor clinically evaluable subjects, when the clinical response categories "cured" and "improved" were combined into a single category of "clinical success", levofloxacin treatment resulted in 94.9% clinical success (see Table 4a). Clinical success rates were similar for subjects with mild/moderate (94.3%) and severe (97.5%) infections. 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.

Table 4b summarizes clinical success rates by investigator for FDA clinically evaluable patients. The overall success rate for levofloxacin was 93%.

Table 4a. Posttherapy Clinical Success Rates By Study Center: Sponsor Clinically Evaluable Subjects

	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.

Table 4b. Clinical Success Rates By Study Center: FDA Clinically Evaluable Subjects

	Levofloxacin	
Investigator	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)

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.

Tables 5a and 5b summarize clinical response rates by pathogen for sponsor and FDA clinically evaluable patients, respectively. For Table 5a, pathogens are separated according to the method of evaluation (e.g., respiratory culture, blood culture, etc.).

Table 5a. Posttherapy Clinical Response for Subjects with Pathogens of Primary Interest: Sponsor Clinically Evaluable Subjects

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.

Table 5b. Clinical Response for Subjects with Pathogens of Primary Interest: FDA Clinically Evaluable Subjects

Pathogen	Levofloxacin							
	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	49	15	(31)	30	(61)	4	(8)
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.

Table 5c presents clinical response by severity of infection for FDA clinically evaluable subjects.

Table 5c. Clinical Response by Severity of Infection:
FDA Clinically Evaluable Subjects

	Levofloxacin							
Severity	N	Cure		Improve		Fail		
Mild/Moderate	167	94	(56)	61	(37)	12	(7)	
Severe	36	11	(31)	22	(61)	3	(8)	

Numbers shown in parentheses are percentages for that category

Microbiologic Response

Sponsor Results

Posttherapy microbiologic eradication rates are summarized by investigator in Table 6a for sponsor microbiologically evaluable patients. The overall microbiologic eradication rate was 95%.

FDA Results

Table 6b summarizes microbiologic eradication rates by investigator for FDA microbiologically evaluable patients. The overall eradication rate in this analysis was 94%.

Table 6a. Posttherapy Microbiologic Eradication Rates By Study Center:
Sponsor Microbiologically Evaluable Subjects

	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)	
Kemodle	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.

Table 6b. Microbiologic Eradication Rates By Study Center:
FDA Microbiologically Evaluable Subjects

	Levofloxacin	
Investigator	N	Eradicated[a]
Chattman	13	12 (92)
Fogarty	47	47 (100)
Rodman	10	10 (100)
Sullivan	35	35 (100)
Other	56	47 (84)
Total	161	151 (94)

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

Sponsor Results

Posttherapy microbiologic eradication rates are summarized by pathogen in Table 7a for sponsor microbiologically evaluable patients; in this display, the most prevalent pathogens ($N \geq 5$) are categorized based on the method used to evaluate microbiologic response (i.e., respiratory cultures, blood cultures, or serology and other diagnostic procedures). The overall microbiologic eradication rate for sponsor microbiologically evaluable subjects was 95.1%. Eradication rates ranged from 83.3% to 100.0% for prevalent pathogens detected in cultures of respiratory secretions. Levofloxacin treatment eradicated 100% of *S. pneumoniae* detected in blood cultures, and from 80.0% to 100.0% of atypical pathogens diagnosed by serology or other diagnostic procedures. Microbiologic results were comparable across analysis groups and were similar for subjects with mild/moderate and severe infections.

FDA Results

Table 7b summarizes microbiologic eradication rates by pathogen category, pathogen, and subject, for FDA microbiologically evaluable patients.

Table 7a. Posttherapy Microbiologic Eradication Rates Summarized by Method of Evaluation, Pathogen, and Levofloxacin Regimen: Sponsor Microbiologically Evaluable Subjects

	Levofloxacin					
	q24h and q48 Regimens (N=155)			All Regimens[2] (N=163)		
Method of Evaluation/Pathogen[3]	N[4]	Eradicated[5]		N[4]	Eradicated[5]	
Respiratory Cultures						
Haemophilus influenzae	36	35	(97.2)	39	38	(97.4)
Streptococcus pneumoniae	32	31	(96.9)	34	33	(97.1)
Staphylococcus aureus	12	10	(83.3)	12	10	(83.3)
Moraxella (Branhamella) catarrhalis	11	11	(100.0)	11	11	(100.0)
Haemophilus parainfluenzae	9	8	(88.9)	9	8	(88.9)
Klebsiella pneumoniae	7	7	(100.0)	7	7	(100.0)
Escherichia coli	5	5	(100.0)	5	5	(100.0)
Blood Cultures						
Streptococcus pneumoniae	9	9	(100.0)	10	10	(100.0)
Serology/Other Diagnostic Procedures						
Chlamydia pneumoniae	70	66	(94.3)	75	71	(94.7)
Mycoplasma pneumoniae	9	9	(100.0)	10	10	(100.0)
Legionella pneumophila	4	3	(75.0)	5	4	(80.0)

[1] A window of 1-10 days posttherapy was used for determination of evaluability.
[2] Includes the 155 microbiologically evaluable subjects who received q24h or q48 levofloxacin dosing for the entire course of therapy, and the eight subjects who received one or more days of b.i.d. levofloxacin treatment.
[3] The most prevalent pathogens (N≥5) are presented in this summary for each method of evaluation.
[4] Denominator represents total number of pathogens, including pathogens for which the microbiologic response is unknown.
[5] Numbers shown in parentheses are percentages for that category.

Table 7b. Microbiologic Eradication Rates by Pathogen Category and Pathogen: FDA Microbiologically Evaluable Subjects

	Levofloxacin	
Pathogen Category/Pathogen	N	Eradicated[a]
Pathogen Category		
Gram-positive aerobic pathogens	75	70 (93)
Gram-negative aerobic pathogens	84	79 (94)
Other	95	91 (96)
Total by pathogen	254	240 (94)
Total by subject	161	151 (94)
Routine Bacterial Pathogens		
Haemophilus influenzae	28	27 (96)
Haemophilus parainfluenzae	10	9 (90)
Klebsiella pneumoniae	5	5 (100)
Moraxella (Branhamella) catarrhalis	11	11 (100)
Staphylococcus aureus	10	8 (80)
Streptococcus pneumoniae	48	45 (94)
Other Pathogens		
Chlamydia pneumoniae	103	98 (95)
Legionella pneumophila	4	3 (75)
Mycoplasma pneumoniae	6	6 (100)

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

Summary

Sponsor Results

A summary of sponsor key efficacy results is presented in Table 8a. Comparable results were seen across analysis groups for both clinical and microbiologic endpoints. In addition, there was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency of the clinical and microbiologic responses.

FDA Results

Table 8b summarizes "overall success rates" (defined by FDA as either clinical cure or improvement with microbiologic eradication) by investigator for patients considered both clinically and microbiologically evaluable by FDA. The overall success rate for levofloxacin was 94%.

Table 8a. Summary of Sponsor Key Efficacy Results

Clinical and Microbiologic Response 5 to 7 Days Posttherapy	
	Levofloxacin
Response/Group	Clinical Success or Microbiologic Eradication Rate (Posttherapy)
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 5-7 Days Posttherapy[1]				
		Clinical Response		
Microbiologic Response	N	Cured[4]	Improved[4]	Failed[4]
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.

[1] A window of 1-10 days posttherapy was used for determination of evaluability.
[2] Denominator for clinical success = cured + improved + failed + unable to evaluate. Denominator for microbiologic eradication rate = eradicated + persistence + unknown.
[3] Based on microbiologically evaluable subgroup.
[4] Cured, improved, or failed are clinical response outcomes.

Table 8b. Overall Success Rates[a] By Study Center:
FDA Microbiologically AND Clinically Evaluable Subjects

Investigator	Levofloxacin	
	N	Overall Success[b]
Chattman	13	12 (92)
Fogarty	47	47 (100)
Rodman	10	10 (100)
Sullivan	35	35 (100)
Other	56	47 (84)
Total	161	151 (94)

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.

Safety Results

Summary of All Adverse Events

Two-hundred sixty-three (99.6%) of 264 subjects enrolled were evaluated for safety. One subject was lost to follow-up with no postadmission data available and was therefore excluded from the safety analysis.

One hundred twenty-five (47.5%) of 263 evaluable subjects reported at least one treatment-emergent adverse event during the study, including events considered by the investigators as related or unrelated to the study drug. Body systems with the highest reported incidence of adverse events were gastrointestinal system (22.1% incidence), followed by the central and peripheral nervous system, respiratory system, and body as a whole, each with an incidence of approximately 8%. The most frequently reported adverse events were nausea (10.3%), diarrhea (6.5%), headache (4.2%), insomnia (3.4%), and dizziness (3.0%) (Table 9).

Table 9. Incidence of Frequently Reported (≥2.0%) Adverse Events Summarized by Body System and Primary Term: Subjects Evaluable for Safety

	Levofloxacin (N=263)	
Body System/Primary Term	No. Subjects	% Subjects
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 ≥ 2.0 % of subjects.

Fourteen (5.3%) subjects 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 subjects were diarrhea (1.5%) and nausea (1.1%).

The majority of adverse events were assessed as mild or moderate in severity. Twenty-six (9.9%) subjects reported one or more adverse events of marked severity, including dyspnea in three subjects and nausea, headache, supraventricular tachycardia, cardiac arrest, and myocardial infarction in two subjects each. No other adverse events of marked severity occurred in more than one subject, and only one case of marked nausea was considered by the investigator as having a probable relationship to the study drug.

Discontinuations Due to Adverse Events

Nine subjects discontinued levofloxacin therapy due to adverse events (Table 10), including three subjects with rash, two with respiratory depression, and one each with abnormal hepatic function tests, nausea, cardiac arrest, and tinnitus. The treatment-limiting adverse events were considered serious or potentially serious in three subjects ([redacted]-respiratory depression, [redacted]-respiratory insufficiency, [redacted]-cardiac arrest), who died as a result of these adverse events after therapy was discontinued, and probably related to levofloxacin treatment in two subjects ([redacted]-nausea, [redacted]-rash).

Table 10. Subjects Who Discontinued Therapy Due to Adverse Events

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‡
	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.
‡ Only one 500-mg dose administered during this period.
‡ Subject also had markedly abnormal laboratory values.
‡‡ Subject died as a result of the adverse event.
† Serious or potentially serious adverse event (see Table VII).

Serious or Potentially Serious Adverse Events, Including Death

Twenty-two subjects reported a serious or potentially serious adverse event, mostly respiratory or cardiovascular events, and seven of these subjects died, during the study or up to approximately one month after completing study therapy (Table 11). Three of the subjects with serious or potentially serious adverse events withdrew from the study because of the adverse event(s). None of the serious or potentially serious adverse events were considered by the investigator to be definitely or probably related to levofloxacin administration, and, in most cases, the adverse events were attributed 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 11. Subjects Who Had Serious or Potentially Serious Adverse Events

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[e]	3		–	Remote	
			Abscess[d]	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		–	–	
	61	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[d]	26	(12PT)	–	Remote	
			Cardiac Failure[e]	26	(12PT)	–	Remote	
			Acidosis[e]	26	(12PT)	–	Remote	
			Circulatory Failure[e]	26	(12PT)	–	Remote	
			Pulmonary Collapse[e]	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 partio the 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 VII).
**Subject also had treatment-emergent, markedly abnormal laboratory value(s).

Clinical Laboratory Tests

There were no clinically significant treatment-emergent mean changes from admission to posttherapy for laboratory tests. The incidence of markedly abnormal test results for individual analytes was low (≤5.3%) (Table 12). 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 test results (elevations in SGOT, SGPT, alkaline phosphatase, or LDH). Some abnormalities were related to the underlying disease state of the subject or to concomitant therapy.

Table 12. Incidence of Treatment-Emergent Markedly Abnormal Laboratory Values: Subjects Evaluable for Safety

	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 posttherapy data available) for that analyte.

Physical Examination and Vital Signs

One subject [redacted] who discontinued from the study because of marked respiratory depression and subsequently died, had clinically significant hypotension. There were no other clinically significant changes in vital signs from admission to posttherapy, and there were no clinically significant treatment-emergent physical examination abnormalities.

Conclusions

Levofloxacin, administered in i.v. or oral doses of 500 mg once-daily, was safe, well-tolerated, and effective in the treatment of subjects with mild-to-moderate or severe community-acquired pneumonia. The effectiveness of levofloxacin treatment was demonstrated by both the clinical and microbiologic results.

Statistical Review and Evaluation

NDA #: 20-634 MAY 6 1996

Applicant: The R.W. Johnson Pharmaceutical Research Ins.

Name of Drug: Elequin (levofloxacin) Tablets

Types of Review: Animal Carcinogenicity

Documents Reviewed:

1. NDA submission volume 1.033, "Review Summary of 2-year Dietary Oncogenicity Study in Rats with DR-3355 (Levofloxacin), August 18, 1995, Document ID: 339457:1, Date of Document, Jan., 1996.

2. NDA submission volumes 1-2, "Statistical Analysis for Levofloxacin Oncogenicity Study in Rats", Date of Documents, Jan. 19, 1996.

I. Background

One rat carcinogenicity study was included in this NDA submission. The purpose of this study was to evaluate the oncogenic potential of levofloxacin when administered in the diet to Fischer 344 rats for 104 weeks. Dr. Sewa Ram Joshi, HFD-520, who is the reviewing pharmacologist of this NDA, requested the Division of Biometrics IV to perform the statistical review and evaluation of this study.

II. The Rat Study

II. a. Design

In this study, 200 male and 200 female Charles River CDF (F-344)/CrlBR rats were randomly assigned to one of three dose groups or control group (50/sex/group). Animals in treated groups received DR-3355 in the diet for at least 104 weeks at dose levels of 10, 30, and 100 mg/kg/day, respectively. Parameters evaluated for treatment-related effects included survival, clinical signs, weekly body weights and total body weight change, weekly food consumption and total food consumption, hematology parameters, as well as necropsy and histopathology findings. Necropsies were conducted on all unscheduled deaths and on all animals killed at

study termination. Tissues were examined microscopically from all unscheduled deaths, as well as all animals in the control and high-dose groups that were killed at study termination. In this study, the treatment commenced on May 9, 1990, and ended on May 13, 1992.

II. b. Sponsor's Analyses

In the low and medium dose groups, a complete histopathological examination was conducted only on animals that were found dead or were sacrificed moribund before the scheduled terminal sacrifice (as per the protocol). Therefore, the statistical analysis was performed only on the control group and the high dose groups, in these groups a complete histopathological examination was conducted on all the animals.

Survival data and tumor data were analyzed using the computer program TUMOSTAT

VAX-VMS version 1.05, 1991). Survival analyses included in this program are the regression model/life table method of Cox and the generalized Kruskal-Wallis method of Gehan, Breslow, and Wilcoxon. Based on the above analyses, the sponsor indicated that no statistically significant difference between the control and high dose groups in mortality was detected in either female or male rats.

The survival rates for control, low, medium, and high dose groups at week 104 are 60%, 68%, 74%, and 60% for males, and 73%, 84%, 90%, and 70% for females, respectively. The sponsor indicated that there were no statistically significant effects on survival for the male treated groups. Survival in females significantly increased in a medium dose group compared to the respective control group. Appendix 1 listed the mortality by weeks across treatment groups for male and female rats. For the tumor data analysis, the prevalence method and the death-rate method described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used in the computer program TUMOSTAT. When there were less than three tumor occurrences, an

exact test analog of the asymptotic test was applied. The time intervals used in this program are 0-82, 83-104 weeks and terminal sacrifice (>105 weeks). The results of the above analyses showed that no statistical significance in tumor incidence rates were found in the incidental/possible incidental, the fatal/possible fatal and the mortality-independent contexts. Appendix 2 listed the tumor incidences for organ/tumor types for male and female rats, respectively. Noted that the sponsor incorrectly coded 50/sex/group as the total number of animals examined in Appendix 2. Appendix 3 listed the statistical analysis summary of individual tumors within organs.

Based on the above analyses, the sponsor concluded that "there was no evidence of toxic or oncogenic potential for DR-3355 when administered in the diet to male and female rats at dose levels of 10, 30, and 100 mg/kg/day. In male and female rats, the no-effect-level (NOEL) of DR-3355 for toxicity and for oncogenicity was 100 mg/kg/day"

II.c. Reviewer's analyses and Comments

The reviewer independently performed analyses on the survival and tumor data. In the survival data analysis, the methods described in the papers of Cox (Regression Models and Life Tables, Journal of The Royal Statistical Society, B, 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon Test for Comparing Arbitrarily Singly Censored Samples, Biometrika, 52, 203-223, 1965) were used. The death rate method described in the paper of Peto et al. (1980) was also applied. The tumor data analyses were performed using the Peto's methods and the method of exact permutation trend test. The data used in the reviewer's analysis were provided by the sponsor on floppy diskettes.

Survival analysis: The intercurrent mortality rates for both male and female rats (see Table 1) were tested for linear trend according to the Peto death rate method using the time intervals 0-50, 51-80, and 81-104 weeks. The actual dose levels 0, 10, 30, and 100 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in either sex (male: $p = 0.1888$; female: $p = 0.0918$).

The homogeneity of survival distributions of all four groups was tested separately for male and female rats using the Cox and the generalized Wilcoxon tests. The p-values of the Cox test were 0.5111 and 0.0381 for males and females, respectively. Hence, there was no statistically significant difference (at 0.05 level) in survival distribution in male rats. However, there was a statistically significant difference in survival distribution in female rats. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.4246 and 0.0364 for males and females, respectively.

The pairwise comparisons of survival distributions among four groups showed that there was no statistically significant difference in survival distributions between control and treated groups in males rats. However, there were significant differences in survival distribution between control and medium dose females, and between medium and high dose females. Tables 2 and 3 list the above results. The plots of Kaplan-Meier estimates of the survival distributions of the control and treated groups for female and male rats are given in Figures 1-2, respectively.

Tumor data analysis: The sponsor classified the tumor types as 'cause of death', 'not cause of death', and 'undetermined'. Following Peto et al. (1980), the reviewer applied the 'death rate method' to the first tumor type and the 'prevalence method' to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories, a combined test was performed. In the analysis, the actual dose levels 0, 10, 30 and 100 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The time intervals used were 0-50, 51-80, and 81-104 weeks, and terminal sacrifice for both sexes.

In the low and medium dose groups, a complete histopathological examination was conducted only on animals that were found dead or were sacrificed moribund before the scheduled terminal sacrifice. Complete histopathological examination was done on all the animals in the control and high dose groups. Therefore, due to the incomplete histopathological examination on low and medium dose groups, two sets of statistical analyses were performed on tumor data. First, the age-adjusted Peto methods were performed on the tumor data of the control and high dose groups. The results of the analyses are consistent with the sponsor's findings. No

statistically significant difference in tumor incidence rates was found in either sex. Second, the age-unadjusted exact permutation trend test was performed on the tumor data of control, low, medium, and high dose groups. This analysis included only the animals which were histopathologically examined. The results of the second analyses showed that no statistically significant dose related trend was detected in either sex. The following table lists some tumors with relatively higher incidence rates in control and treated groups. Note that there are more male rats than female rats dead before the scheduled terminal sacrifice.

Tumor/organ	Incidence of tumors/no. of an. Examined				P-value
Males:					
Thyroid c cell carcinoma	3/50	0/16	0/17	4/50	0.2416
Females:					
Mammary Gland Fibroadenoma	7/47	1/8	0/5	8/46	0.3566
Thyroid c cell adenoma	4/50	0/9	1/5	6/50	0.2097
Uterus Endometrial Stromal Polyp	9/50	2/9	1/5	8/50	0.3896

In order to reduce the overall false positive rate, the following decision rule was used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor.

Evaluation of the validity of the experiment: The following two issues are important in determining the validity of an experiment: (1) The numbers of animals alive over the course of the study to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors. (2) If the doses are high enough to present a reasonable tumor challenge to the animals.

With regard to the first issue, the following criteria or rules of thumb have been proposed by some experts in the field:

(A) Haseman proposes (through personal communication with Dr. Karl Lin) that a 50% survival rate of the 50 initial animals in the high dose group between weeks 80-90 will be considered as a sufficient number and an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex is larger or smaller than 50 as long as there will be between 20 and 30 animals still alive during these weeks.

(B) Chu, Ceuto, and Ward ("Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", Journal of Toxicology and Environmental Health, 8, 1981, pp. 251-280) propose that an experiment that has not shown a chemical to be carcinogenic should have (high dose) groups of animals with greater than 50% survival at one year (52 weeks).

In this study, the survival rates of the high dose rats at one-year were 96% and 100% for males and females, respectively. These one-year survival rates satisfy the criterion of Chu et al. (1981). The survival rates of the control, low, medium, and high dose rats in the terminal sacrifice were 60%, 68%, 66%, and 56%, respectively, for males, and 72%, 82%, 90%, and 68%, respectively, for females. There were sufficient male and female rats in the treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition.

With regard to the second issue, in the paper of Chu, Ceuto and Ward (1981), the following criteria for dose adequacy are mentioned.

(A) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(B) "The administered dose is also considered an MTD (Maximum Tolerated Dose) if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

© "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Figure 3 plots the mean body weight versus time in weeks for males and females, respectively. In Tables 4-5, summaries of mean body weight data of the male and female rats are given. All treated male rats gained more body weight than the control group. The weight gains in the male low, medium, and high dose groups are 4.61%, 6.43%, and 5.99%, respectively, more than that of the male control group. However, the weight gains in the female low, medium, and high dose groups are 1.76%, 2.05%, and 6.84%, respectively, less than that of the female control group. Based on the above body weight gain data, it seems that the high dose is below MTD for the male rats. The relevance of this is to be determined by clinician or/and pharmacologist.

III. Summary

Applying Peto's method to test the positive linear trend in intercurrent mortality rates, the results of the analyses showed that no significant (at 0.05 level) linear trend in the intercurrent mortality rate was detected in either sex.

The test results also showed that there was no statistically significant difference (at 0.05 level) in survival distribution in male rats. However, there was a statistically significant difference in survival distribution in female rats.

In the low and medium dose groups, a complete histopathological examination was conducted only on animals that were found dead or were sacrificed moribund before the scheduled terminal sacrifice. Hence, two sets of statistical analyses were performed on tumor data. First, the age-adjusted Peto methods were performed on the tumor data of the control and high dose groups. Second, the age-unadjusted exact permutation trend test was performed on the tumor data of control, low, medium, and high dose groups. This analysis included only the animals which were histopathologically examined. Results of first tumor data analyses showed that there was no statistically significant difference in tumor incidence rates between control and high dose groups. Results of second tumor data analyses showed that there was no dose related trend in male or female rats.

The results of mortality analyses showed that there were sufficient male and female rats in the treated group living long

enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors. The analysis of weight gain data showed that the high dose was below MTD for male rats. The relevance of this is to be determined by clinician or/and pharmacologist.

Daphne Lin 5/6/96

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Chron.
This review contains 28 pages, 5 Tables, and 3 Figures.
WordPerfect6.1/Eleq.wp6/4-26-96

Table 1: Intercurrent Mortality Rates

Male Rats

Weeks	Control			Low			Medium			High		
	D	S	%	D	S	%	D	S	%	D	S	%
0-50	1	50	2	0	50	0	0	50	0	2	50	4
51-80	4	49	8.1	3	50	6	1	50	2	2	48	4.1
81-104	15	45	33.3	13	47	27.6	16	49	32.6	18	46	39.1
> 105	30			34			33			28		

Peto Test: p = 0.1888

Female Rats

Weeks	Control			Low			Medium			High		
	D	S	%	D	S	%	D	S	%	D	S	%
0-50	0	50	0	0	50	0	0	50	0	0	50	0
51-80	3	50	6	1	50	2	0	50	0	3	50	6
81-104	11	47	23.4	8	49	16.3	5	45	10	13	47	27.6
> 105	36			41			45			34		

Peto Test: p = 0.0918

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 3: Pairwise Comparisons for Homogeneity of Survival

Male Rats

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.3906	NEG	.3323	.3322		.4620	.4619	
	PROB	.2661	.5320		.5643	.5644		.4967	.4967	
0 VS. 2	CHISQ		.7033	NEG	.9358	.9350		1.3650	1.3640	
	PROB	.2009	.4017		.3334	.3336		.2427	.2428	
0 VS. 3	CHISQ		.0000	POS	.0019	.0019		.1353	.1352	
	PROB	.5808	1.0000		.9651	.9651		.7130	.7131	
1 VS. 2	CHISQ		.0000	NEG	.0289	.0289		.1717	.1716	
	PROB	.5000	1.0000		.8650	.8650		.6786	.6787	
1 VS. 3	CHISQ		.3906	POS	.5996	.5991		1.0936	1.0927	
	PROB	.2661	.5320		.4387	.4389		.2957	.2959	
2 VS. 3	CHISQ		.7033	POS	1.3458	1.3440		2.3342	2.3309	
	PROB	.2009	.4017		.2460	.2463		.1266	.1268	

Table 4: Summary of Mean Body Weight and standard deviation (grams)
The Male Rats Study

Dose Group	Week 0	Week 104	Gain in Wt.	Gain rel. to Control
Control	134.9 (6.36)	360.2 (27.9)	225.3	-
Low	135.5 (7.88)	371.2 (29.26)	235.7	4.61%
Medium	134.8 (6.01)	374.6 (36.79)	239.8	6.43%
High	135 (7.72)	373.8 (27.1)	238.8	5.99%

Table 5: Summary of Mean Body Weight and standard deviation (grams)
The Female Rats Study

Dose Group	Week 0	Week 104	Gain in Wt.	Gain rel. to Control
Control	95.2 (4.36)	270.6 (17.6)	175.4	-
Low	94.9 (3.72)	267.2 (31.2)	172.3	- 1.76%
Medium	93.6 (3.9)	265.4 (25.3)	171.8	- 2.05%
High	94.4 (3.82)	257.8 (33.7)	163.4	- 6.84%

Note: (*) A negative sign stands for decrease in weight gain relative to control.

Figure 1: The Plots of Kaplan-Meier Estimates of the Survival Distributions

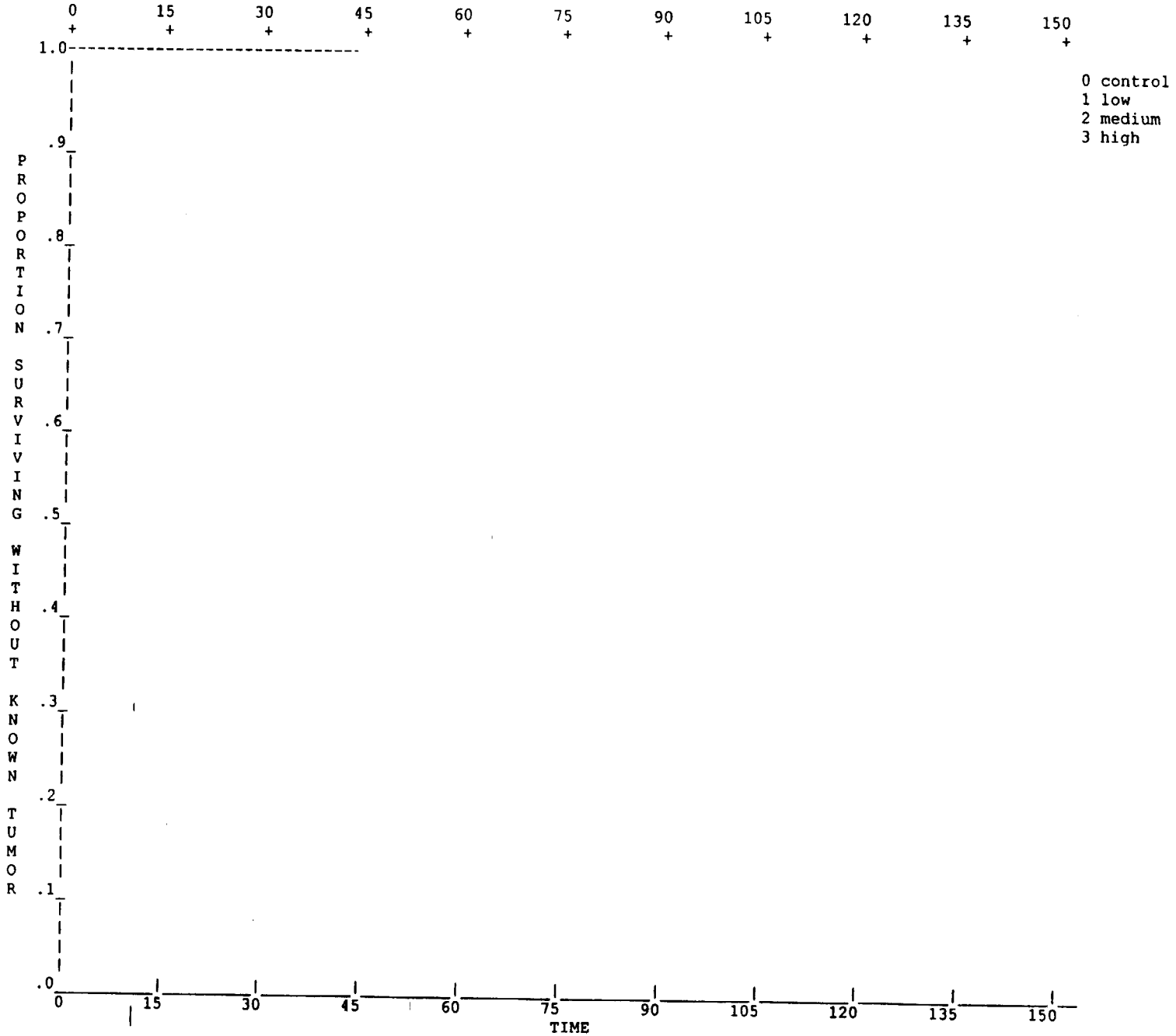


Figure 2: The Plots of Kaplan-Meier Estimates of the Survival Distributions

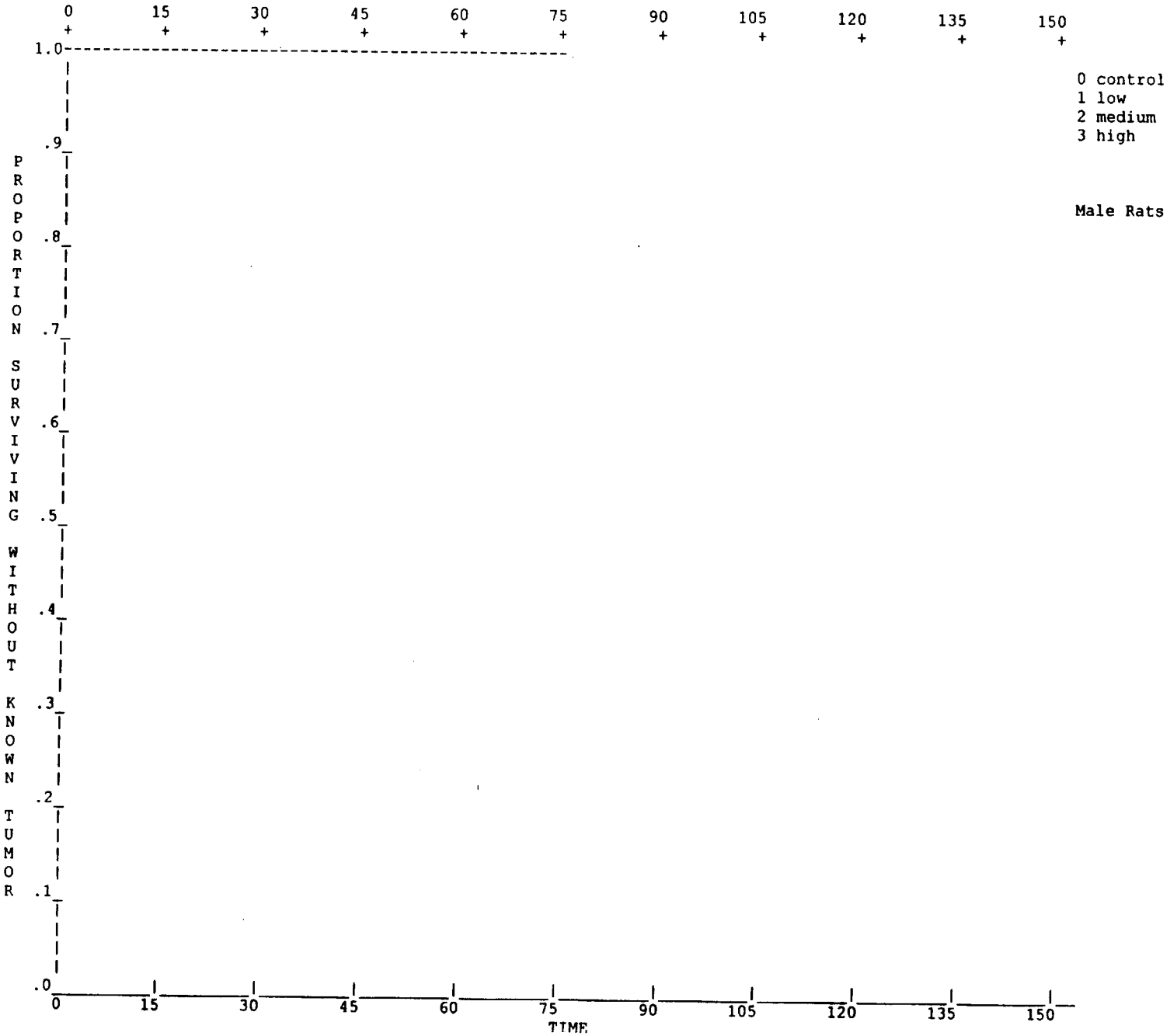
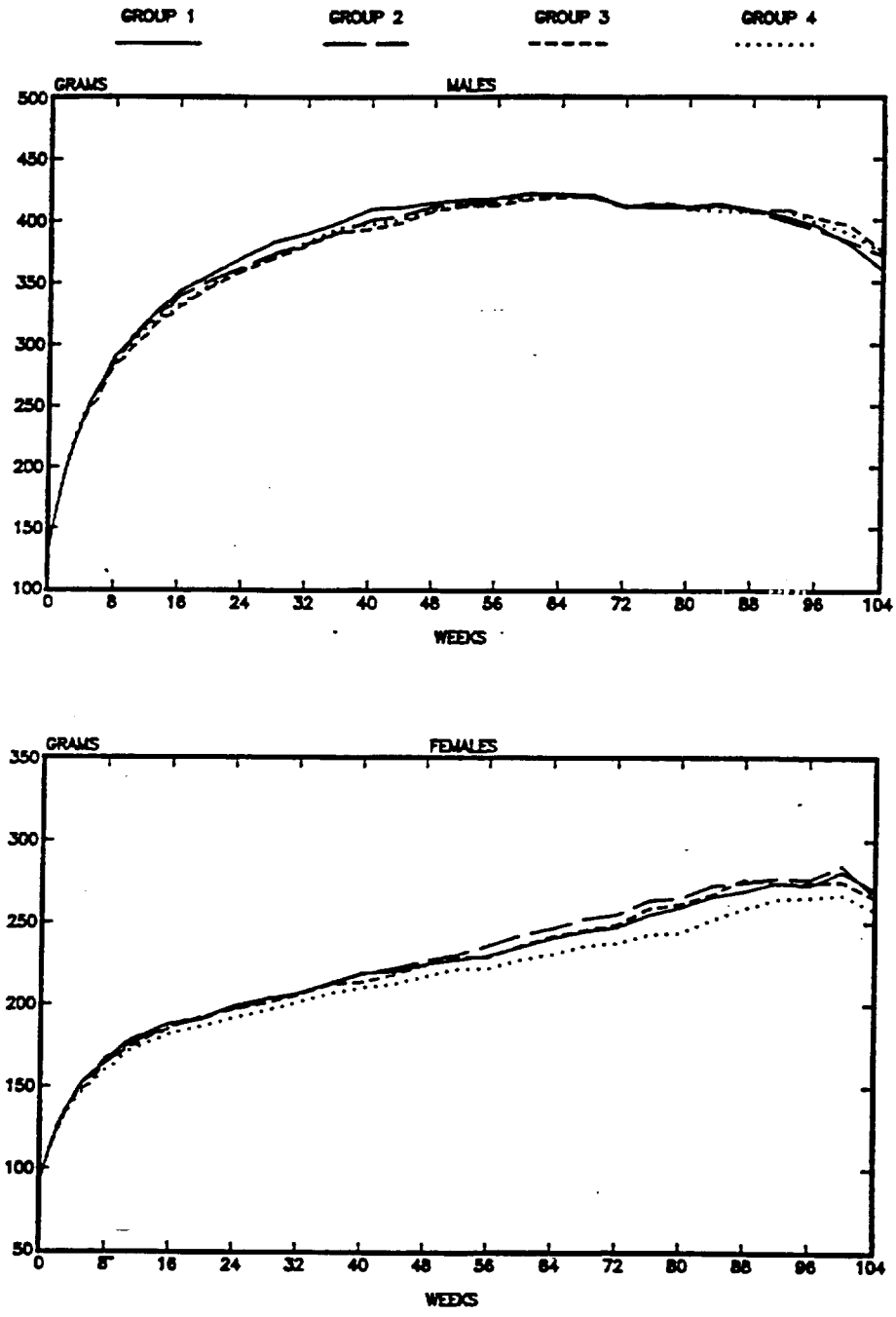


FIGURE 3 – MEAN BODY WEIGHTS



REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

MORTALITY BY WEEKS ACROSS TREATMENT GROUPS - MALE
NUMBER OF ANIMALS

	GROUP 0					GROUP 1					GROUP 2					GROUP 3				
WEEKS	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N
34	50	0	0	0	0	50	0	0	0	0	50	0	0	0	0	50	1	0	0	1
39	50	1	0	0	1	50	0	0	0	0	50	0	0	0	0	49	0	0	0	0
46	49	0	0	0	0	50	0	0	0	0	50	0	0	0	0	49	1	0	0	1
53	49	0	0	0	0	50	0	0	0	0	50	0	0	0	0	48	1	0	0	1
58	49	0	0	0	0	50	0	0	0	0	50	0	0	0	0	47	1	0	0	1
68	49	0	0	0	0	50	1	0	0	1	50	0	0	0	0	46	0	0	0	0
71	49	0	0	0	0	49	1	0	0	1	50	0	0	0	0	46	0	0	0	0
73	49	1	0	0	1	48	0	0	0	0	50	0	0	0	0	46	0	0	0	0
77	48	1	0	0	1	48	1	0	0	1	50	1	0	0	1	46	0	0	0	0
78	47	2	0	0	2	47	0	0	0	0	49	0	0	0	0	46	0	0	0	0
81	45	0	0	0	0	47	1	0	0	1	49	1	0	0	1	46	0	0	0	0
82	45	0	0	0	0	46	1	0	0	1	48	0	0	0	0	46	1	0	0	1
83	45	0	0	0	0	45	0	0	0	0	48	0	0	0	0	45	1	0	0	1
84	45	0	0	0	0	45	0	0	0	0	48	0	0	0	0	44	1	0	0	1
85	45	1	0	0	1	45	0	0	0	0	48	0	0	0	0	43	0	0	0	0
86	44	1	0	0	1	45	0	0	0	0	48	0	0	0	0	43	0	0	0	0

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: D=DIED S=SCHEDULED SACRIFICE M=MORIBUND SACRIFICE N=NECROPSIED
START=NO. ANIMALS ALIVE AT START OF TIME PERIOD *=SCHEDULED AND TERMINAL SACRIFICES

Appendix 1 (4 pages)

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

MORTALITY BY WEEKS ACROSS TREATMENT GROUPS - MALE (CONTINUED)
NUMBER OF ANIMALS

	GROUP 0					GROUP 1					GROUP 2					GROUP 3				
WEEKS	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N
87	43	0	0	0	0	45	0	0	0	0	48	0	0	0	0	43	3	0	0	3
88	43	0	0	0	0	45	0	0	0	0	48	0	0	0	0	40	1	0	0	1
89	43	0	0	0	0	45	0	0	0	0	48	4	0	0	4	39	2	0	0	2
92	43	1	0	0	1	45	0	0	0	0	44	0	0	0	0	37	0	0	0	0
93	42	0	0	0	0	45	2	0	0	2	44	1	0	0	1	37	0	0	0	0
95	42	3	0	0	3	43	1	0	0	1	43	0	0	0	0	37	1	0	0	1
97	39	0	0	0	0	42	1	0	0	1	43	0	0	0	0	36	1	0	0	1
98	39	0	0	0	0	41	1	0	0	1	43	1	0	0	1	35	0	0	0	0
99	39	1	0	0	1	40	0	0	0	0	42	0	0	0	0	35	0	0	0	0
100	38	0	0	0	0	40	2	0	0	2	42	0	0	0	0	35	0	0	0	0
101	38	2	0	0	2	38	2	0	0	2	42	3	0	0	3	35	3	0	0	3
102	36	3	0	0	3	36	1	0	0	1	39	0	0	0	0	32	1	0	0	1
103	33	1	0	0	1	35	1	0	0	1	39	0	0	0	0	31	1	0	0	1
104	32	2	0	0	2	34	0	0	0	0	39	4	0	0	4	30	0	0	0	0
*TERM	30	0	30	0	30	34	0	34	0	34	35	2	33	0	35	30	2	28	0	30

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: D=DIED S=SCHEDULED SACRIFICE M=MORIBUND SACRIFICE N=NECROPSIED
START=NO. ANIMALS ALIVE AT START OF TIME PERIOD *=SCHEDULED AND TERMINAL SACRIFICES

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

MORTALITY BY WEEKS ACROSS TREATMENT GROUPS - FEMALE
NUMBER OF ANIMALS

	GROUP 0					GROUP 1					GROUP 2					GROUP 3				
WEEKS	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N
51	50	0	0	0	0	50	1	0	0	1	50	0	0	0	0	50	0	0	0	0
65	50	0	0	0	0	49	0	0	0	0	50	0	0	0	0	50	1	0	0	1
69	50	1	0	0	1	49	0	0	0	0	50	0	0	0	0	49	0	0	0	0
70	49	1	0	0	1	49	0	0	0	0	50	0	0	0	0	49	0	0	0	0
76	48	1	0	0	1	49	0	0	0	0	50	0	0	0	0	49	1	0	0	1
80	47	0	0	0	0	49	0	0	0	0	50	0	0	0	0	48	1	0	0	1
82	47	1	0	0	1	49	0	0	0	0	50	0	0	0	0	47	1	0	0	1
85	46	0	0	0	0	49	1	0	0	1	50	0	0	0	0	46	0	0	0	0
86	46	0	0	0	0	48	0	0	0	0	50	0	0	0	0	46	1	0	0	1
87	46	1	0	0	1	48	0	0	0	0	50	0	0	0	0	45	0	0	0	0
89	45	0	0	0	0	48	1	0	0	1	50	1	0	0	1	45	1	0	0	1
93	45	0	0	0	0	47	1	0	0	1	49	0	0	0	0	44	0	0	0	0
95	45	1	0	0	1	46	0	0	0	0	49	1	0	0	1	44	1	0	0	1
97	44	2	0	0	2	46	0	0	0	0	48	0	0	0	0	43	1	0	0	1
98	42	1	0	0	1	46	0	0	0	0	48	1	0	0	1	42	0	0	0	0
99	41	1	0	0	1	46	1	0	0	1	47	0	0	0	0	42	2	0	0	2

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: D=DIED S=SCHEDULED SACRIFICE M=MORIBUND SACRIFICE N=NECROPSIED
START=NO. ANIMALS ALIVE AT START OF TIME PERIOD *=SCHEDULED AND TERMINAL SACRIFICES

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

MORTALITY BY WEEKS ACROSS TREATMENT GROUPS - FEMALE (CONTINUED)
NUMBER OF ANIMALS

	GROUP 0					GROUP 1					GROUP 2					GROUP 3				
WEEKS	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N	START	D	S	M	N
100	40	2	0	0	2	45	0	0	0	0	47	1	0	0	1	40	0	0	0	0
101	38	0	0	0	0	45	0	0	0	0	46	1	0	0	1	40	1	0	0	1
102	38	1	0	0	1	45	0	0	0	0	45	0	0	0	0	39	2	0	0	2
104	37	1	0	0	1	45	3	0	0	3	45	0	0	0	0	37	2	0	0	2
*TERM	36	0	36	0	36	42	1	41	0	42	45	0	45	0	45	35	1	34	0	35

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: D=DIED S=SCHEDULED SACRIFICE M=MORIBUND SACRIFICE N=NECROPSIED
START=NO. ANIMALS ALIVE AT START OF TIME PERIOD *=SCHEDULED AND TERMINAL SACRIFICES

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

TUMOR SUMMARY - MALE

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS			
	GRP 0	GRP 1	GRP 2	GRP 3
NUMBER EXAMINED	50	50	50	50
*BRAIN W/STEM GLIOMA	0	0	1	0
*CORD, THORACIC GLIOMA	0	0	0	1
PITUITARY ADENOMA	22	10	8	15
*PITUITARY NEUROFIBROSARCOMA	0	0	0	1
*PITUITARY CARCINOMA	2	0	0	0
ADRENAL, CORTEX ADENOMA	0	0	0	1
ADRENAL, MEDULLA PHEOCHROMOCYTOMA	2	1	0	3
*ADRENAL, MEDULLA PHEOCHROMOCYTOMA	0	0	0	0
THYROID C CELL ADENOMA	12	1	1	4
*THYROID C CELL CARCINOMA	3	0	0	4
PARATHYROID ADENOMA	1	0	1	0
*SPLEEN HEMANGIOSARCOMA	0	0	0	0
*LIVER HEPATOCELLULAR CARCINOMA	1	0	0	0
KIDNEY LIPOMA	0	0	0	1
*KIDNEY TUBULE CELL CARCINOMA	0	1	0	0
*STOMACH, NONGL SQUAMOUS CELL CARCINOMA	2	0	0	0
*STOMACH, GL FIBROSARCOMA	0	0	0	1
ILEUM FIBROMA	0	1	0	0
PANCREAS ISLET CELL ADENOMA	5	0	1	5
*PANCREAS ISLET CELL CARCINOMA	3	0	0	0
PANCREAS ACINAR CELL ADENOMA	1	0	0	0
TESTIS INTERSTITIAL CELL TUMOR	43	11	17	44
*TESTIS CARCINOMA, NOS	0	0	1	0
*MAND SALIVARY GL NEUROFIBROSARCOMA	0	0	0	1
*PREPUTIAL GLAND CARCINOMA	0	1	1	1
MAMMARY GLAND FIBROADENOMA	0	0	0	1
*MAMMARY GLAND CARCINOMA	0	0	0	0
MAMMARY GLAND ADENOMA	1	0	0	0
*HEMATO NEOPLASIA LGL LYMPHOMA	29	12	12	24
*HEMATO NEOPLASIA FIBROUS HISTIOCYTOMA	0	0	0	0
SKIN, OTHER KERATOACANTHOMA	1	0	1	0
SKIN, OTHER SQUAMOUS CELL PAPILLOMA	1	0	0	0
*SKIN, OTHER SQUAMOUS CELL CARCINOMA	1	0	0	0
SKIN, OTHER SEBACEOUS GLAND ADENOMA	0	0	0	1
*CAVITY, ABDOM MESOTHELIOMA	2	0	0	0

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: * DENOTES A MALIGNANT TUMOR; ? DENOTES TUMOR MALIGNANCY STATUS UNKNOWN; OTHERWISE BENIGN

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

TUMOR SUMMARY - MALE (CONTINUED)

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS			
	GRP 0	GRP 1	GRP 2	GRP 3
NUMBER EXAMINED	50	50	50	50
SUBCUTANEOUS TIS FIBROMA	2	1	1	0
SUBCUTANEOUS TIS LIPOMA	0	1	0	0
*SUBCUTANEOUS TIS NEUROFIBROSARCOMA	0	0	0	1
*SUBCUTANEOUS TIS HEMANGIOSARCOMA	1	0	0	0
SUBCUTANEOUS TIS NEUROFIBROMA	0	0	0	0
*SUBCUTANEOUS TIS LIPOSARCOMA	0	0	0	1
*ZYMBAL'S GLAND SQUAMOUS CELL CARCINOMA	0	0	0	1

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: * DENOTES A MALIGNANT TUMOR; ? DENOTES TUMOR MALIGNANCY STATUS UNKNOWN; OTHERWISE BENIGN

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

TUMOR SUMMARY - FEMALE

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS			
	GRP 0	GRP 1	GRP 2	GRP 3
NUMBER EXAMINED	50	50	50	50
*BRAIN W/STEM GLIOMA	1	0	1	0
*CORD, THORACIC GLIOMA	0	0	0	1
PITUITARY ADENOMA	20	3	3	13
*PITUITARY NEUROFIBROSARCOMA	0	0	0	1
*PITUITARY CARCINOMA	0	0	0	0
ADRENAL, CORTEX ADENOMA	2	0	1	3
ADRENAL, MEDULLA PHEOCHROMOCYTOMA	0	0	0	1
*ADRENAL, MEDULLA PHEOCHROMOCYTOMA	0	0	0	1
THYROID C CELL ADENOMA	4	0	1	6
*THYROID C CELL CARCINOMA	3	0	0	0
PARATHYROID ADENOMA	0	0	0	0
*SPLEEN HEMANGIOSARCOMA	0	0	1	0
*LIVER HEPATOCELLULAR CARCINOMA	0	0	0	0
KIDNEY LIPOMA	0	0	0	0
*KIDNEY TUBULE CELL CARCINOMA	0	0	0	0
*STOMACH, NONGL SQUAMOUS CELL CARCINOMA	0	0	0	0
*STOMACH, GL FIBROSARCOMA	0	0	0	0
ILEUM FIBROMA	0	0	0	0
PANCREAS ISLET CELL ADENOMA	0	0	0	1
*PANCREAS ISLET CELL CARCINOMA	0	0	0	0
PANCREAS ACINAR CELL ADENOMA	1	0	0	0
*OVARY CARCINOMA	1	0	0	0
UTERUS ENDOMETRIAL STROMAL POLYP	9	2	1	8
*UTERUS CARCINOMA	4	0	0	0
*MAND SALIVARY GL NEUROFIBROSARCOMA	0	0	0	0
*CLITORAL GLAND CARCINOMA	1	0	0	0
*PREPUTIAL GLAND CARCINOMA	0	0	0	0
MAMMARY GLAND FIBROADENOMA	7	1	0	8
*MAMMARY GLAND CARCINOMA	3	0	0	0
MAMMARY GLAND ADENOMA	0	0	0	1
*HEMATO NEOPLASIA LGL LYMPHOMA	16	3	1	13
*HEMATO NEOPLASIA FIBROUS HISTIOCYTOMA	1	0	0	0
SKIN, OTHER KERATOACANTHOMA	0	0	0	0
SKIN, OTHER SQUAMOUS CELL PAPILLOMA	1	0	0	0
*SKIN, OTHER SQUAMOUS CELL CARCINOMA	0	0	0	0

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: * DENOTES A MALIGNANT TUMOR; ? DENOTES TUMOR MALIGNANCY STATUS UNKNOWN; OTHERWISE BENIGN

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

TUMOR SUMMARY - FEMALE (CONTINUED)

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS			
	GRP 0	GRP 1	GRP 2	GRP 3
NUMBER EXAMINED	50	50	50	50
SKIN, OTHER SEBACEOUS GLAND ADENOMA	0	0	0	0
*CAVITY, ABDOM MESOTHELIOMA	0	0	0	0
SUBCUTANEOUS TIS FIBROMA	0	0	1	0
SUBCUTANEOUS TIS LIPOMA	1	0	0	0
*SUBCUTANEOUS TIS NEUROFIBROSARCOMA	0	0	0	0
*SUBCUTANEOUS TIS HEMANGIOSARCOMA	0	0	0	0
SUBCUTANEOUS TIS NEUROFIBROMA	1	0	0	0
*SUBCUTANEOUS TIS LIPOSARCOMA	0	0	0	0
*ZYMBAL'S GLAND SQUAMOUS CELL CARCINOMA	0	1	0	1

GROUP: #0: 0 MG/KG/DAY, Control
#1: 10 MG/KG/DAY, Low
#2: 30 MG/KG/DAY, Mid
#3: 100 MG/KG/DAY, High
NOTE: * DENOTES A MALIGNANT TUMOR; ? DENOTES TUMOR MALIGNANCY STATUS UNKNOWN; OTHERWISE BENIGN

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

ANALYSIS SUMMARY OF INDIVIDUAL TUMORS WITHIN ORGAN - INCIDENTAL AND FATAL TUMORS

ORGAN	TUMOR	SEX	PREVALENCE ANALYSIS OVERALL COMPARISON	DEATH-RATE ANALYSIS OVERALL COMPARISON	POOLED ANALYSIS OVERALL COMPARISON
BRAIN W/STEM	GLIOMA	FEMALE B	1.0000 E		1.0000 E
CORD, THORACIC	GLIOMA	MALE A		0.4948 E	0.4948 E
		FEMALE A		0.5060 E	0.5060 E
PITUITARY	ADENOMA	MALE A		0.8275	0.8275
		MALE B	0.8797		0.8797
		FEMALE A		0.2870	0.2870
		FEMALE B	0.9549		0.9549
		BOTH A		0.6352	0.6352
		BOTH B	0.9784		0.9784
	NEUROFIBROSARCOMA	MALE A		0.5000 E	0.5000 E
		FEMALE A	0.5238 E		0.5238 E
		FEMALE B		0.5000 E	0.5000 E
	CARCINOMA	MALE B	1.0000 E		1.0000 E
ADRENAL, CORTEX	ADENOMA	MALE B	0.5000 E		0.5000 E
		FEMALE B	0.3110		0.3110
ADRENAL, MEDULLA	PHEOCHROMOCYTOMA	MALE B	0.3245		0.3245
		FEMALE B	0.4930 E		0.4930 E
	PHEOCHROMOCYTOMA	FEMALE B	0.5000 E		0.5000 E
THYROID	C CELL ADENOMA	MALE B	0.9863		0.9863
		FEMALE B	0.2437		0.2437
		BOTH B	0.8960		0.8960

NOTE: THERE WERE NO SIGNIFICANT PAIRWISE COMPARISONS FOR PREVALENCE , DEATH-RATE AND POOLED ANALYSES
E: P-VALUE IS FROM EXACT TEST
A: PREVALENCE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH
B: DEATH-RATE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

ANALYSIS SUMMARY OF INDIVIDUAL TUMORS WITHIN ORGAN - INCIDENTAL AND FATAL TUMORS

ORGAN	TUMOR	SEX	PREVALENCE ANALYSIS OVERALL COMPARISON	DEATH-RATE ANALYSIS OVERALL COMPARISON	POOLED ANALYSIS OVERALL COMPARISON
THYROID	C CELL CARCINOMA	MALE	B 0.3473		0.3473
		FEMALE	B 0.9584		0.9584
		BOTH	B 0.7384		0.7384
PARATHYROID	ADENOMA	MALE	B 1.0000 E		1.0000 E
LIVER	HEPATOCELLULAR CARCINOMA	MALE	B 1.0000 E		1.0000 E
KIDNEY	LIPOMA	MALE	B 0.5000 E		0.5000 E
STOMACH, NONGL	SQUAMOUS CELL CARCINOMA	MALE	B 1.0000 E		1.0000 E
STOMACH, GL	FIBROSARCOMA	MALE	B 0.5000 E		0.5000 E
PANCREAS	ISLET CELL ADENOMA	MALE	B 0.5000		0.5000
		FEMALE	B 0.4930 E		0.4930 E
	ISLET CELL CARCINOMA	MALE	B 0.9592		0.9592
	ACINAR CELL ADENOMA	MALE	B 1.0000 E		1.0000 E
		FEMALE	B 1.0000 E		1.0000 E
OVARY	CARCINOMA	FEMALE	A	1.0000 E	1.0000 E
UTERUS	ENDOMETRIAL STROMAL POLYP	FEMALE	A 0.6057		0.6057
		FEMALE	B 0.6890	0.5000 E	
	CARCINOMA	FEMALE	A	1.0000 E	1.0000 E
		FEMALE	B 0.9584		0.9584

NOTE: THERE WERE NO SIGNIFICANT PAIRWISE COMPARISONS FOR PREVALENCE , DEATH-RATE AND POOLED ANALYSES
E: P-VALUE IS FROM EXACT TEST
A: PREVALENCE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH
B: DEATH-RATE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

ANALYSIS SUMMARY OF INDIVIDUAL TUMORS WITHIN ORGAN - INCIDENTAL AND FATAL TUMORS

ORGAN	TUMOR	SEX	PREVALENCE ANALYSIS OVERALL COMPARISON	DEATH-RATE ANALYSIS OVERALL COMPARISON	POOLED ANALYSIS OVERALL COMPARISON
TESTIS	INTERSTITIAL CELL TUMOR	MALE	A 0.3618		0.3618
		MALE	B 0.3627	0.6395	0.4785
MAND SALIVARY GL	NEUROFIBROSARCOMA	MALE	A	0.4756 E	0.4756 E
CLITORAL GLAND	CARCINOMA	FEMALE	A	1.0000 E	1.0000 E
PREPUTIAL GLAND	CARCINOMA	MALE	A	0.4800 E	0.4800 E
MAMMARY GLAND	FIBROADENOMA	MALE	B 0.5000 E		0.5000 E
		FEMALE	A	0.5065 E	0.5065 E
		FEMALE	B 0.4806		0.4806
	CARCINOMA	FEMALE	A	1.0000 E	1.0000 E
		FEMALE	B 1.0000 E		1.0000 E
	ADENOMA	MALE	B 1.0000 E		1.0000 E
		FEMALE	B 0.5238 E		0.5238 E
HEMATO NEOPLASIA	LGL LYMPHOMA	MALE	A 0.7793	0.6092	0.7650
		MALE	B 0.7663	0.6027	0.7477
		FEMALE	A	0.3879	0.3879
		FEMALE	B 0.8787		0.8787
		BOTH	A	0.5179	0.5179
		BOTH	B 0.9061		0.9061
	FIBROUS HISTIOCYTOMA	FEMALE	A	1.0000 E	1.0000 E
SKIN, OTHER	KERATOACANTHOMA	MALE	B 1.0000 E		1.0000 E
	SQUAMOUS CELL PAPILLOMA	MALE	B 1.0000 E		1.0000 E
		FEMALE	B 1.0000 E		1.0000 E

NOTE: THERE WERE NO SIGNIFICANT PAIRWISE COMPARISONS FOR PREVALENCE , DEATH-RATE AND POOLED ANALYSES
E: P-VALUE IS FROM EXACT TEST
A: PREVALENCE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH
B: DEATH-RATE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

ANALYSIS SUMMARY OF INDIVIDUAL TUMORS WITHIN ORGAN - INCIDENTAL AND FATAL TUMORS

ORGAN	TUMOR	SEX	PREVALENCE ANALYSIS OVERALL COMPARISON	DEATH-RATE ANALYSIS OVERALL COMPARISON	POOLED ANALYSIS OVERALL COMPARISON
SKIN, OTHER	SQUAMOUS CELL CARCINOMA	MALE	A	1.0000 E	1.0000 E
	SEBACEOUS GLAND ADENOMA	MALE	B 0.5000 E		0.5000 E
CAVITY, ABDOM	MESOTHELIOMA	MALE	B 1.0000 E		1.0000 E
SUBCUTANEOUS TIS	FIBROMA	MALE	B 1.0000 E		1.0000 E
	LIPOMA	FEMALE	B 1.0000 E		1.0000 E
	NEUROFIBROSARCOMA	MALE	A	0.4706 E	0.4706 E
	HEMANGIOSARCOMA	MALE	B 1.0000 E		1.0000 E
	NEUROFIBROMA	FEMALE	B 1.0000 E		1.0000 E
	LIPOSARCOMA	MALE	A	0.5000 E	0.5000 E
ZYMBAL'S GLAND	SQUAMOUS CELL CARCINOMA	MALE	A	0.4844 E	0.4844 E
		FEMALE	A	0.5065 E	0.5065 E

NOTE: THERE WERE NO SIGNIFICANT PAIRWISE COMPARISONS FOR PREVALENCE , DEATH-RATE AND POOLED ANALYSES
E: P-VALUE IS FROM EXACT TEST
A: PREVALENCE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH
B: DEATH-RATE ANALYSIS INCLUDES TUMORS WITH UNDETERMINED CAUSE OF DEATH

REVIEW SUMMARY OF 2-YEAR DIETARY ONCOGENICITY STUDY IN RATS WITH DR-3355
(RWJ-25213-097, LEVOFLOXACIN)

ANALYSIS SUMMARY OF INDIVIDUAL TUMORS WITHIN ORGAN - MORTALITY INDEPENDENT TUMORS

ORGAN	TUMOR	SEX	ONSET-RATE ANALYSIS OVERALL COMPARISON	
MAND SALIVARY GL	NEUROFIBROSARCOMA	MALE	0.5000	E
CLITORAL GLAND	CARCINOMA	FEMALE	1.0000	E
PREPUTIAL GLAND	CARCINOMA	MALE	0.4894	E
MAMMARY GLAND	FIBROADENOMA	FEMALE	0.3692	
	CARCINOMA	FEMALE	0.9573	
	ADENOMA	FEMALE	0.4944	E
SKIN, OTHER	SQUAMOUS CELL PAPILLOMA	MALE	1.0000	E
		FEMALE	1.0000	E
	SQUAMOUS CELL CARCINOMA	MALE	1.0000	E
	SEBACEOUS GLAND ADENOMA	MALE	0.4684	E
SUBCUTANEOUS TIS	FIBROMA	MALE	1.0000	E
	LIPOMA	FEMALE	1.0000	E
	NEUROFIBROSARCOMA	MALE	0.4684	E
	HEMANGIOSARCOMA	MALE	1.0000	E
	NEUROFIBROMA	FEMALE	1.0000	E
	LIPOSARCOMA	MALE	0.5000	E
ZYMBAL'S GLAND	SQUAMOUS CELL CARCINOMA	MALE	0.5000	E
		FEMALE	0.5052	E

NOTE: THERE WERE NO SIGNIFICANT PAIRWISE COMPARISONS FOR ONSET-RATE ANALYSES
E: P-VALUE IS FROM EXACT TEST

micro

NDA 20-634
NDA 20-635
R.W.Johnson

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #1

NDA #'s 20-634 & 20-635 **DATE COMPLETED: 17 July, 1996**

APPLICANT(NDA):

R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

CHEM/THER. TYPE:
fluoroquinolone

SUBMISSION REVIEWED: Original NDA
PROVIDING FOR: Treatment of the following Clinical infections: Sinusitis, bronchitis, pneumonia, skin and skin structure infections, urinary tract and kidney infections,

PRODUCT NAMES(S):
Proprietary: **Levaquin**

Non-Proprietary/USAN: levofloxacin

Compendia: levofloxacin

CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. WT.
(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate

DOSAGE FORMS(S): Tablet or Injection

STRENGTHS: 250 & 500 milligrams

ROUTE(S) OF ADMINISTRATION: oral or parenteral

PHARMACOLOGICAL CATEGORY: Antiinfective

DISPENSED: __X__ Rx _____ OTC

INITIAL SUBMISSION:
Received by CDER: 22 December, 1995
Received by Reviewer: 3 January, 1996
Review Completed: 17 July, 1996

AMENDMENT(S)
Received by CDER: N/A
Received by Reviewer:
Review Completed:

RELATED DOCUMENTS:
IND's

REMARK(S):

[Revision Note: This review was significantly revised in response to Microbiology Team Leader's comments. Most of the comments related to the proposed draft Microbiology portion of the package insert. The proposed draft portion has been replaced by adaptations of model labeling suggested by the Team Leader. Therefore, the previous comments from the Team Leader are no longer applicable to the currently proposed Microbiology portion of the package insert.

The remaining comments by the Team Leader related to document format concerns rather than to substantive issues. Revised: 11/13/96]

[Second Revision Note: Since the first revision, the proposed package insert has undergone several drafts. The currently proposed package insert incorporates comments on the text of the package insert from the package insert discussions. No additional substantive issues are of significant concern based on pending FDA policies on

allowable advertising.
Revised 12/16/96]

[Editorial Note: This NDA was simultaneously submitted as a CANDA. The Microbiology summary was submitted on a separate disk as well as the other clinical portions of the NDA. NDA table numbering was intentionally maintained in the Microbiology Review Appendices I and II. Within those appendices, the names of specific organisms can be located by searching electronically for the name of the desired organism. At the Team Leader's option, Appendices I and II could be maintained only in the electronic files of this review without reduction to hard copy. The full electronic copy will be maintained on the CDER computer server under m:\nda20634.$k4]

1.

Technically, levofloxacin injection is a terminally sterilized product. Therefore, the format for a terminally sterilized product will be used for the CMC portion of this review. However, the terminal sterilization begins with an aseptically filled product; although the aseptically filled product may be sterile, the terminal sterilization provides a much higher probability for the sterility of the product. The terminal sterilization process begins after the Levofloxacin Injection is aseptically filtered and filled in a Class 100 environment. This dual process is discussed below.

Levofloxacin injection will be aseptically filled and terminally sterilized in two types of packaging. The first type of packaging includes glass vials with stoppers; the second type includes flexible plastic bags with two alternative fill volumes. The glass vials will be filled and sterilized according to procedures reviewed below. However, the plastic bags will be filled and sterilized by separate procedures administered by according to commitments described in DMF This DMF contains sterilization procedures and conditions which are not consistent with sterilization of the glass vials. The sterilization procedures and conditions for the bags should be reviewed using expertise and policies which are currently outside the scope of the responsibilities of Microbiologists within DAIDP. The required policies are currently established by and administered by Microbiologists in the

Office of New Drug Chemistry. For the final evaluation of the DMF commitments, DAIDP Project Management Staff should request a consultative review of the levofloxacin Abbott DMF sterilization commitments from the Office of New Drug Chemistry Microbiologists; the review notes included below deal effectively with the sterilization procedures and conditions applied to levofloxacin injection in glass vials.

2.
This application is quite confusing from the clinical microbiology perspective. The confusion arises because pre-NDA discussions with the applicant suggested quite strongly that levofloxacin is conceptually identical to ofloxacin. For ofloxacin, the dominant active drug substance is its l-isomer, which is levofloxacin. Conceptually, this premise should lead to microbiological labeling essentially identical to ofloxacin. The microbiological labeling initially proposed by the applicant for levofloxacin varied significantly from ofloxacin in the microbiological spectrum listed; this variation is troubling because the proposed levofloxacin microbiological labeling implies significant medical superiority of levofloxacin over ofloxacin whose activity is purported to be almost entirely due to its levofloxacin content.

The confusion was further exacerbated when the applicant provided various basic studies in support of levofloxacin that had been actually performed using ofloxacin instead of levofloxacin. Particularly, some of the studies on mechanisms of action and the related resistance mechanisms were recapitulated from ofloxacin data rather than being generated anew for levofloxacin. Theoretically, levofloxacin should stand alone with respect to NDA submissions; however, this commingling of levofloxacin and ofloxacin data in support of levofloxacin leaves major portions of the NDA without supporting data derived from studies using levofloxacin only. Although adequate supporting data were not supplied for levofloxacin alone in parts of the NDA, logic almost dictates that the conceptual extrapolations from ofloxacin microbiological data are valid when applied to levofloxacin, the active principal of ofloxacin.

Unfortunately, additional confusion arose during the review of the quality control parameters used for antimicrobial susceptibility testing with levofloxacin. The proposed quality control parameters differed significantly from those currently approved for ofloxacin, whose activity is

purported to be due almost exclusively to its levofloxacin content. Some of the proposed quality control parameters simply do not make sense when viewed from the perspective of ofloxacin. These concerns will be addressed in portions of the review dealing with QC parameters.

CONCLUSIONS and/or RECOMMENDATIONS:

1. Comments on Microbiological Manufacturing and Controls issues.

From the DAIDP microbiological perspective, this application is approvable only if the product is marketed as sterile in glass vial packaging. Alternate packaging of the product in plastic bags should be reviewed by microbiologists in the Office of New Drug Chemistry; DAIDP Project Management should request a consultative review of the terminal sterilization procedures for the product packaged in plastic bags.

2. Comments on Clinical Microbiology issues

From the microbiological perspective, this application is approvable pending final negotiation of an appropriate Microbiology section of a proposed package insert. The following package insert text represents the FDA-proposed labeling for the Microbiology section pertaining to this NDA. The labeling contains proposed lists of microorganisms recommended for approval as well as the clinical microbiology breakpoints which qualify the listing of those organisms.

Additional Phase IV studies should be performed to look for trends in clinical failure of levofloxacin to treat subjects with infections due to microorganisms which demonstrate susceptibility to levofloxacin and simultaneously demonstrate intermediate or resistant status for ofloxacin.

MICROBIOLOGY

The microbiology section of the package insert should, therefore, be revised to read as follows:

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of DNA gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, transcription, repair and recombination.

Levofloxacin has in vitro activity against a wide range of gram-negative and gram-positive

microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones differ in chemical structure and mode of action from β-lactam antibiotics. Fluoroquinolones may, therefore, be active against bacteria resistant to β-lactam antibiotics.

Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorgansims resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis
Staphylococcus aureus

Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following in vitro data are available, **but their clinical significance is unknown.**

Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC's) of 2μg/mL or less against most strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms
Staphylococcus epidermidis
Streptococcus (Group C/F)

Streptococcus (Group G)
Staphylococcus saprophyticus
Streptococcus agalactiae
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter anitratus
Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter lwoffii
Bordetella pertussis
Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Serratia marcescens

Anaerobic gram-positive microorganisms
Clostridium perfringens

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity. However, until levofloxacin susceptibility testing is available, the susceptibility of the organism to ofloxacin may be used to predict susceptibility to levofloxacin. While ofloxacin susceptible organisms will be susceptible to levofloxacin, ofloxacin intermediate or resistant organisms may be susceptible to levofloxacin.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorgansims other than *Haemophilus influenzae, Haemophilus parainfluenzae,* and *Streptococcus pneumoniae:*

MIC
(μg/mL)

Interpretation	
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[a]

MIC (μg/mL)	Interpretation
≤2	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenza* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*:[b]

MIC (μg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Muller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard levofloxacin powder should give the following MIC values:

Microorganism		MIC (μg/mL)
Enterococcus faecalis	ATCC 29212	0.25 - 2
Escherichia coli	ATCC 25922	0.008 - 0.06
Escherichia coli	ATCC 35218	0.015 - 0.06
Pseudomonas aeruginosa	ATCC 27853	0.5 - 4
Staphylococcus aureus	ATCC 29213	0.06 - 0.5

Haemophilus influenzae	ATCC 49247[c]	0.008 - 0.03
Streptococcus pneumoniae	ATCC 49619[d]	0.5 - 2

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-μg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-μg levofloxacin disk should be interpreted according to the following criteria:

For aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae,* and *Streptococcus pneumoniae:*

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

For *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[e]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)

[e] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenza* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus pneumoniae*:[f]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

[f] These zone diameter standards for *Streptococcus pneumoniae* apply only to tests performed

using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg levofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29 - 37
Pseudomonas aeruginosa	ATCC 27853	19 - 26
Staphylococcus aureus	ATCC 25923	25 - 30
Haemophilus influenzae	ATCC 49247[g]	32 - 40
Streptococcus pneumoniae	ATCC 49619[h]	20 - 25

[g] This quality control range is applicable to only *H. Influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM).[2]

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically–Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests–Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

1.

Description of the building and facilities including the number of filling areas and layout of critical and control area, a brief description of the water systems and air-handling.

The buildings used in the manufacturing, processing, packaging and holding of drug product were designed and constructed in accordance with the requirements of 21CFR§211.42. The manufacturing facilities include the following buildings:

Building No.	Operation(s)
1	Aseptic Fill Facility, Weighmaster and Compounding Areas, Technical Support, Quality Assurance Offices, Quality Control Laboratories, Cafeteria
2	Manufacturing Operations for Sterile Ophthalmic Products
3	Engineering Department
5	Executive and General Offices, Human Resources, Management Information Systems (MIS) and Weighmaster

Bioburden
Both washed and unwashed stoppers were tested for bioburden. All samples showed zero (0) colonies/5 washed stoppers and conformed to the established limits of the validation protocol: <25 colonies/5 washed stoppers.

Sterilization
Three runs were conducted by processing a full load of stoppers (15,000) at one-half exposure cycles. Only the sterilization part of the cycle was conducted. Ten thermocouples and ten biological indicators of *Bacillus stearothermophilus* impregnated with 10^6 spores/ strip were distributed within each load. No growth was exhibited by sterilized BIs.

(3) Vials
The drug product is filled on the Strunck Filling line. The conventional Cozzoli line may be used as an alternate. Vials that will be filled on the Strunck line are depyrogenated in the Strunck Sterilization Tunnel. Those filled on the Cozzoli line will be sterilized and depyrogenated using the Gruenberg oven. The following

validation studies were conducted.

Strunck B Tunnel

The Strunck Vial Washer with Depyrogenation Tunnel and Filler is the equipment used to automatically wash, depyrogenate and then fill the vials. Vials filled with water are first transported to a water bath and onto an ultrasonic vibratory plate. The vials are inverted and moved to a cleaning station. For internal cleaning, the vials are sprayed with recirculated Water for Injection (WFI) followed by fresh WFI and then oil-less dry compressed air via sanitary stainless steel piping.

Following the cleaning procedure, the vials continue their transport to the sterilization tunnel. The vials are dried and sterilized in this tunnel by dry heat at 300 °C ± 5 °C. Validation studies were conducted in triplicate according to protocol SAI-VA-032 entitled "Validation Protocol For The Strunck B Sterilization Tunnel" to evaluate the Strunck B Sterilization Tunnel in sterilizing 20 mL vials.

Five (5) 20 mL vials spiked with 6300 EU/mL of endotoxin were placed in each area of the tunnel representing the leading, middle and trailing edge of the product container load. The vials were placed across the conveyor belt at positions of 0%, 25%, 50%, 75% and 100% of the width of the belt. One calibrated thermocouple was positioned inside a container next to each of the endotoxin spiked vials. A complete load of washed stoppers was then supplied to the tunnel and operated as normal. The vials containing the endotoxin were then tested.

The validation protocol, which includes an exhibit of the thermocouple and challenge locations, was provided. The overall endotoxin challenge test results are summarized in the following table.

Table 1: Endotoxin Data

Run No.	Amount of Endotoxin Added (EU/mL)	Amount of Endotoxin Recovered (EU/mL)	Log Reduction
1	6300	1.0	3.7993
2	6300	0.25	4.4014
3	6300	-- 0.25	4.4014

The minimum endotoxin log reduction achieved for the three

runs was 3.8, which meets the acceptance criteria of a reduction in recoverable endotoxin of 3 log or greater. Based on these data, a set point of 300 °C is acceptable for the depyrogenation of the vials. With respect to heat distribution studies, the accumulated lethality indicates that the least kill is obtained at the trailing edge of the container load.

Gruenberg Oven

Prior to depyrogenation on the Gruenberg oven, the vials are washed on the Cozzoli Washer. Vials are placed over the hollow needles of the cleaning manifold plate which is fed clean steam, WFI, and oil-free compressed air via sanitary stainless steel piping. Following the cleaning procedure, the vials are transferred to the Gruenberg oven for depyrogenation. Depyrogenation occurs according to an established validated procedure which includes: 227°C for three (3) hours. This cycle was validated under Validation Protocol SAI-VA-027 entitled "Validation of the Tray Depyrogenation Cycles Using Bracket Loads - Building. 1". Validation included a thermal mapping study to identify the hot and cold zones for tray loads of the vials. Additionally, heat distribution and heat penetration/endotoxin challenge were performed for three validation runs to assure that the slowest to heat locations were consistently exposed to sufficient heat lethality. The findings of these studies showed that the minimum endotoxin log reduction achieved in all validation runs was 4.0. Based on the temperature reached during heat exposure and the three logarithmic reduction of all endotoxin challenge, the depyrogenation cycle is acceptable.

3. A description of the sterilization processes used for the finished drug product. A description of the validation of these processes should be provided including, for example, heat distribution/penetration summaries, biological studies (biological indicators and endotoxin), routine monitoring procedures, etc. Information and data demonstrating distribution and penetration of the sterilant and efficacy of each process should be submitted.

Autoclave Process and Performance Specifications

A Finn Aqua Steam Sterilizer, Model No. 151824-DP (Serial No. 35933), is utilized for terminal sterilization of the drug product using saturated steam as its source of heat. The chamber temperature is controlled to maintain a temperature of 121.0 ± 0.5 °C for the required exposure time. The product is terminally sterilized for 15 ± 1 minutes or to an equivalent F_o of 12 minutes or greater, as identified in the manufacturing batch record.

The autoclave cycle consists of five pre-vacuum cycles where the chamber is evacuated and refilled with steam. The chamber is then heated to the setpoint temperature (121.0 °C) with saturated steam, pressure is maintained at 30 psi, and temperature control is maintained for a duration of 15 minutes exposure time. The pressure in the chamber is released at the end of the cycle by means of slow exhaust.

Autoclave Loading Patterns

A representative autoclave loading pattern includes a maximum of five carts (or layers) with one located in the middle. A total of 30 trays are distributed throughout the five carts and each tray contains 154 vials (20 mL, 26 mm O.D.). Consequently, a maximum total of 4620 vials can be placed in the autoclave.

Methods and Controls to Monitor Production Cycles

Routine production cycles are controlled by monitoring the temperature in the drain of the autoclave. Feedback from this temperature sensor controls the autoclave inlet steam valve which in turn regulates the amount of saturated steam entering the chamber. Temperatures are monitored within the chamber during production cycles. Additionally, six (6) biological indicators (10^6 of *Bacillus stearothermophilus*) are placed throughout each autoclave load during the production cycle. At the end of the cycle, a seven day incubation period follows to confirm that no microbiological growth was observed.

Requalification of Production Autoclaves

Revalidation of the Finn Aqua Steam Sterilizer is conducted annually according to a standard operating procedure.

Reprocessing

The R. W. Johnson Pharmaceutical Research Institute does not have procedures in place at present to reprocess any batch of Levofloxacin Injection, 25 mg/mL that does not meet regulatory specifications. Current standard operating procedures and validated programs at
do not provide for any additional thermal processing and/or reprocessing of product.

4. Summaries of recent validation methods and results for the same container/closure type and size class that is used for the product. All results obtained, including failures, should be supplied. These data should be obtained using the same filling line(s) that are to be used for the product in question.

Heat Distribution/Penetration Studies

The validation of the terminal sterilization process for Levofloxacin Injection, 25 mg/mL was conducted according to Protocol No. SAI-VA-029 and consisted of the following two phases: 1) Thermal mapping characterization study for the maximum and minimum load configurations; and 2) Validation studies for the worst case sterilization load from studies in the first phase, i.e., the load with the lowest F_o value.

The objective of the first phase was to compare the thermal and lethality characteristics of different tray load and mass considerations in order to establish the rationale for conducting the validation of the levofloxacin terminal sterilization loads in the Finn Aqua autoclave. The 20 mL vials that were used in the development of Levofloxacin Injection, 25 mg/mL, include the 26 mm O.D. vial that is proposed as the container for commercial product in this NDA. It also includes the 29 mm O.D. vial that was used in filling some early batches of this formulation and in generating some supporting stability data for this NDA. General information on these two types of vials follows:

Table 2: Summary of the Phase 1 Sterilization Levofloxacin Loads Evaluated

Vial Size	Volume (mL)	No. of Units per Tray	No. of Trays	Mass of Glass, Stopper and Cap (g)	Mass of Liquid (g)	No. of Units per Load	Total Units Mass (kg)
26 mm	20	154	30	18.91	20.14	4,620	180.41
29 mm	20	120	37	20.64	20.14	4,440	181.0

The second phase included the validation of the worst load configuration by the execution of three additional runs. The sterilization parameters used in both phases include:

Table 3: Operating Parameters and Settings for Sterilization Validation

Operating Parameters	Setting
Exposure Temperature	121 ° ± 0.5 °C
Exposure Duration	Fifteen ± 1 minute
Pre-vacuums	Five pulses at not less than 3 psia
Cycle Mode	Slow Exhaust
Chamber Pressure	30 ± 2 psia during exposure

Details of the experiments conducted and the data generated are provided in a report entitled "Validation Report for the Levofloxacin Terminal Sterilization Cycles", which was provided. A summary of this report follows.

Phase 1 : Water for Injection, USP was used in the Phase 1 studies. Since the 29 mm O.D. vial presentation load represents the worst case condition because of its mass, it was the only vial selected for evaluation. Three loaded chamber heat distribution/ penetration and microbiological challenge mapping studies were conducted for each maximum and minimum configuration.

Minimum load configuration: one cart located in the middle of the sterilizer chamber with one tray containing one hundred and twenty (120) units.

Maximum load configuration: five carts with one located in

the middle of the sterilization chamber. A total of 37 trays are distributed throughout the five carts and each tray contains 120 units for a maximum total of 4420 units.

No growth was observed in either configuration with the biological indicators included in the microbiological challenge studies. All loads behave almost identically during the cycles of exposure and cool down periods. The main difference was observed in the accumulated F_o of the slowest to heat location (maximum configuration required 21.96 minutes and the minimum configuration needed 28.62 minutes). As a result of these data, the maximum configuration was selected for Phase 2 studies.

Phase 2: The three additional runs with the maximum configuration load yielded an F_o greater than 12 minutes and no microbiological growth of biological indicators was observed. These results conform to the validation protocol acceptance criteria.

Thermal Monitors

The terminal sterilization validation procedure for Levofloxacin Injection, 25 mg/mL includes the use of twelve thermocouples to monitor each run. Two thermocouples are used to monitor the chamber distribution and the remaining ten are used as penetration probes. The thermocouples are placed inside the filled containers at the previously determined slowest-to-heat point, i.e., the middle of the fill volume. Information pertaining to the placement and patterns of thermocouples and biological indicators is provided in the validation report for the Levofloxacin Injection terminal sterilization cycle.

3. The Effects of Loading on Thermal Input
Three loaded chamber heat distribution/penetration and microbiological challenge thermal mapping studies with an exposure time of 15 minutes were conducted for each maximum and minimum configuration. The results of the studies are presented below.

Table 4: Results of the Thermal Mapping Studies: Maximum and Minimum Validation Runs

Parameter	Maximum Configuration	Minimum Configuration
Results		

Average air-removal time	68 minutes	45 minutes
Average come-up time	18 minutes	18 minutes
Average penetration temperature during exposure time	120.5 °C	120.8 °C
Exposure temperature (distribution)	120.0 -120.9	119.6 -121.4
Exposure time (all six runs)	15 minutes	15 minutes
Average cool-down time	76 minutes	76 minutes
Average slowest to heat accumulated F_0	21.96 minutes	28.62 minutes
Average chamber pressure (psia)	29.6	29.8
Microbial growth during the seven day samples incubation period of each run	none	none

After these studies, the maximum configuration load was validated by executing three additional runs. The thermocouples and biological challenge were concentrated around the slowest to heat locations which were identified in the Phase 1 study. The data generated are presented below.

Table 5: Results for the Three Validation Runs (Maximum Configuration)

Parameter	Result
Average air-removal time	65 minutes
Average come-up time	16 minutes
Average penetration temperature during exposure time	120.6 °C
Exposure time (all three runs)	15 minutes

12 log reduction in population of *B. stearothermophilus* concentration.

5. A description of sterility testing methods and release criteria. Methods should include the protocol for the selection of representative units from the filling line during production.

Sterility testing is performed by according to the current USP using the Membrane Filtration Technique as provided in SOP 31-032-00. Every lot of Levofloxacin Injection, 25 mg/mL that is manufactured for commercial use must be tested for Sterility according to the USP requirements.

7. Information concerning methods and results of container/closure integrity testing for both end-product release testing and the procedure used for the stability protocol.

A Broth Immersion Test was performed on a recent lot of media fill (Lot No. TTSB-069) from to assess the integrity of the container/closure system for the drug product. Sixty vials of media were sealed with minimum seal force and sterilized at 121 °C for 15 minutes (maximum exposure). The vials were then heated at 52 °C for 24 hours, inverted and challenged with 6.3 X 10^9/mL of *Pseudomonas diminuta* (ATCC 19146) for 72 hours. Incubation followed for 10 days at 35 °C. The vials were inspected for growth. Each of the 60 vials was negative (sterile), the five negative controls were negative and the five positive controls were positive. The results demonstrated that no growth was exhibited for all vials tested.

Integrity over Product Shelf Life

Both sterility and bacterial endotoxins testing will be conducted as part of the marketing stability protocol at the beginning of the stability period and at the expiration date.

At this time, all primary stability batches for Levofloxacin Injection, 25 mg/mL have been tested for sterility and bacterial endotoxins over 12 months according to the designated stability program of this NDA. All data generated conform to the corresponding specifications.

Average cool down time	81 minutes
Average slowest to heat accumulated F_0	25.41 minutes
Average chamber pressure (psia)	29.6
Microbial growth during the seven day samples incubation period of each validation run	none

These data provide a high degree of assurance that the levofloxacin terminal sterilization process will consistently provide a sterile product.

Terminal sterilization validation of the drug product includes the placement of a *Bacillus stearothermophilus* 10^6 population suspension biological indicator (BI) close to each heat penetration thermocouple. This microbiological challenge was performed on both the maximum and minimum loading patterns. A sterility assurance of greater than 10^{-6} was demonstrated for the terminal sterilization process.

Levofloxacin Injection, 25 mg/mL bulk solution is sterile filtered and aseptically filled prior to terminal sterilization. As demonstrated by media fills, this aseptic process is effective in maintaining the sterile conditions of the product prior to further terminal sterilization. Media fills for Levofloxacin Injection, 25 mg/mL in the commercial container/closure system have been conducted using both the Strunck Tunnel and the Cozzoli Vial Filling Machine at in accordance with the current established media fill SOP No. 24-002 entitled "Process Validation Media Fills". The procedure involves conducting three successful media fills for initial qualification and subsequent semiannual media fills to assure a continuing state of control.

Identification and Characterization of Bioburden Organisms

Three successful media fills (STSB062, STSB063 and STSB064) were conducted in June 1994 using the Strunck Tunnel. The corresponding environmental monitoring and media fill results were included.

Table 6: Media Fill Results; Strunck Tunnel

Media Lot No.	Size/Fill Volume (mL)	Date Filled	Room No.	Units Filled	Units Incubated	Quantity ~~Positive~~	% Positive
STSB062	20/20 ± 1	6/09/94	111	4,567	4,406	0	0
STSB063	20/20 ±1	6/10/94	111	4,541	4,347	0	0
STSB064	20/20 ±1	6/14/94	111	4,593	4,411	0	0

Action Concerning Product When Media Fill Fails

Action Limits : An acceptance level of no more than 0.1% contaminated units has been established for the Process Validation Media Fills.

Out of Limits: When the acceptance level is exceeded, investigative action includes a review of environmental data and identification of contaminating microorganisms in units filled with media. If the investigation shows an attributable cause to the failure which is not a flaw in the design of the filling process, one media fill will be performed and production will resume if successful media results are obtained.

If the problem is not identified, three additional media fills are scheduled. Products filled during the incubation period of the media fill in the same size components as used in the failed media fill will not be released until the success of the repeated media fill is confirmed. In addition, the process which used the particular filling equipment, container/closure and filling room, will cease production until the required number of successful media fills are performed.

Specifications for Bioburden

Prior to filtration, the bioburden content for Levofloxacin Injection, 25 mg/mL is obtained. The action limit is 100 CFU/ 100 mL. Additionally, the three successful media fills for initial qualification are followed by subsequent semiannual fills to assure a continuing state of control.

Identification, Resistance and Stability of Biological

Indicators

The biological indicator used in the validation of the cycles was *Bacillus stearothermophilus* (ATCC 7953) supplied by NAMSA Sportrol, Lot No. S43305. Samples of this lot of spores were used to determine the time required to reduce the number of *Bacillus stearothermophilus* spores by 90%, (referred to as the D-value) in the presence of Levofloxacin Injection, 25 mg/mL using a fractional sterilization exposure.

The D-value was 0.58 minutes (Z=10). This value indicates that to obtain a 12-log reduction of *Bacillus stearothermophilus* spores at 121 °C, a $F_o \geq 7$ minutes is required (i.e., 12 X 0.58 minutes = 7). Consequently, the minimum acceptable F_o of 12 minutes specified in the manufacturing directions of the drug product adequately meets this requirement.

The Resistance of the Biological Indicator Relative to that of Bioburden

No measurable bioburden is present at the point of terminal sterilization. The product is sterile filtered and aseptically filled. D-values of *Bacillus stearothermophilus* were determined in both Levofloxacin Injection, 25 mg/mL and water. It was determined that the D-value of the Bacillus spores in water was 1.9 minutes while the D-value in Levofloxacin Injection, 25 mg/mL was 0.58 minutes.

Microbiological Challenge Studies

The efficacy of the worst load configuration (i.e., maximum load configuration) was validated by the execution of three additional runs to demonstrate the required sterility assurance for the product. Each load consisted of five carts with a total of thirty-seven (37) trays distributed throughout the carts. Thermocouples were placed inside the filled containers at their previously determined slowest-to-heat point (middle of the fill volume). The complete sterilization cycle was then conducted (121 °C for 15 minutes with five vacuum pulses of at least 3 psia each). In all cases, the average accumulated F_o (minutes) for the three runs of the slowest-to-heat was 25.41 minutes, which exceeds the minimum acceptable F_o of 12 minutes. Additionally, it also exceeds the minimum theoretical F_o value of ≥ 7 at a temperature of 121 °C necessary to cause a

8. A description of the microbiological monitoring program used during routine production. Include the frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded. These descriptions should include air, surface, personnel, and water monitoring programs. Descriptions of the bioburden monitoring program should also be provided, including specifications.

During the filling of the qualification media fills, areas related to the manufacture of Levofloxacin Injection, 25 mg/mL were monitored for environmental microbial contamination. Monitoring included RODAC plates and swabs of personnel, equipment and room surfaces. Also included were fall out plates, slit to agar monitoring and biotest sampling of air. Table 7 provides a summary of the location of bacteria identified during the qualification media fills conducted on the Strunck Tunnel.

Table 7: Media Fill Environmental Monitoring: Colony Forming Units (CFUs) per Plate

Sample Source	Lot No. STSB062	Lot No. STSB063	Lot No. STSB064
Surface	0	1 (Floor)	0
Personnel Gown Monitoring	2,1	3	3

For the media fill conducted using the Cozzoli filling process, only one (1) CFU per plate was identified and isolated during the run (personnel mask).

The corresponding type of bacteria isolated during the three qualification media fills conducted on the Strunck Tunnel and the one on the Cozzoli are provided in Table 8. All bacteria isolated were gram positive cocci belonging to the *Micrococcus* and *Staphylococcus* genera or gram positive rods belonging to the *Bacillus* species.

Table 8: Bacteria Isolated During Qualification Media Fills

Lot Number	Count (CFU/plate)	Position	Identification
STSB062	2	Group Leader's Front	*Micrococcus sp. and Staphylococcus sp.*
STSB062	1	Mechanic's Front	*Staphylococcus sp.*
STSB063	1	Floor Before Filling	*Bacillus sp.*
STSB063	3*	Mechanic's Front	*Staphylococcus sp.*
STSB064	2	Mechanic's Mask	*Staphylococcus sp.*
STSB064	1	Mechanic's Front	*Staphylococcus sp.*
RTSB064	1	Group Leader's Mask	*Staphylococcus sp.*

Alert limit is 3 CFU/plate, action limit is 7 CFU/plate.

In summary, the data demonstrate that the aseptic processing associated with the filtration and filling of Levofloxacin Injection, 25 mg/mL is under control and appropriate for this sterile product when using either the Strunck Tunnel or the Cozzoli Filling Machine for the filling process.

Anaerobic microorganisms are monitored during media fills using centrifugal air samplers, fall-out plates and swabs:

- Centrifugal Air Sample Strips and Fall-Out Plates are incubated in the anaerobic jar at 30-35 °C for not less than 5 days.

- The applicators of the swabs are added to 30 mL of sterile Fluid Thioglycolate Medium and then incubated for not less than 5 days at 30-35 °C. Following incubation, tubes with growth are

streaked to individual TSA Plates. These are then incubated again in the anaerobic jar at 30-35 °C for not less than 5 days.

All growth observed is identified. The limit is no anaerobes recovered. When action limits are exceeded, the supervisor of the affected area is notified through a Non-Conformance Report. Sanitization of the affected area is performed and documented. The contaminants are identified. The area is then retested.

9. Evidence should be provided that there are formal, written procedures describing the above elements and that these procedures are followed.

The Technical Department of [redacted] is responsible for maintaining standard operating procedures and ensuring that they are followed. The extensive list of written procedures governing the manufacturing and quality control operations was provided.

Microbiological Review Notes:

TABLE OF CONTENTS

INTRODUCTION

Levofloxacin is the L-isomer of a racemic mixture, ofloxacin; ofloxacin is a currently marketed quinolone antibacterial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer which exerts its mechanism of action through inhibition of DNA gyrase (bacterial topoisomerase II); this gyrase is required for DNA replication, transcription, repair and recombination. Overall, levofloxacin rapidly and specifically inhibits bacterial DNA synthesis. Levofloxacin has in vitro activity against a broad spectrum of gram-positive and gram-negative aerobic and anaerobic bacteria.

PRECLINICAL EFFICACY

In vitro

Mechanism(s) of Action.

Levofloxacin is purported to inhibit bacteria through its action on the subunit A (Gyr A) of the DNA gyrase holoenzyme, a topoisomerase II. In general, quinolones are purported to interfere with the DNA breakage-rejoining step by forming a ternary complex with DNA and gyrase. Overall, the mechanism of action of the quinolones resides within biochemical pathways involved in DNA synthesis. However, a complete detailed understanding of the process has not been elucidated yet, although several strong candidate pathways have been identified.

Antimicrobial Spectrum of Activity.

[Editorial Note: This NDA was simultaneously submitted as a CANDA. The Microbiology summary was submitted on a separate disk as well as the other clinical portions of the NDA. NDA table numbering was intentionally maintained in the Microbiology Review Appendix I. Within the tables, references were numerically cited by the applicant; additional reports were used for purposes of labeling review of microorganism lists in the package insert.]

Data in the accompanying tables shown in Review Appendix I (Tables 2-9 as numbered in the NDA) illustrate the broad spectrum of antibacterial activity of levofloxacin and compare that activity with several other quinolones currently in clinical use in the United States: ofloxacin, ciprofloxacin, enoxacin, norfloxacin, and lomefloxacin, or nonquinolones. Appendix I was transcribed electronically directly from the NDA application; all literature citations in or around the tables represent accompanying citations appropriately listed in the NDA. Within these tables

concluded that the alterations conferring moderate to high levofloxacin resistance to clinical isolates are likely to involve alterations of the Gyr A subunit of DNA gyrase, similar to resistant mutants observed for other quinolones.

The secondary alterations accompanying the *gyrA* mutations which are found among many quinolone-resistant clinical isolates are not fully defined, but generally affect cell permeability (porin channels, lipopolysaccharide), uptake, or efflux of the antimicrobials. These mutations are believed to be the first ones selected, providing the low level of resistance to quinolones that warrants residual growth in the presence of the drug. This allows much rarer *gyrA* mutations (which in *S. aureus* is preceded by a topoisomerase IV mutation) to appear as a later event.

Any interpretation of the supporting data could be significantly flawed where levofloxacin characteristics are inferred from ofloxacin data. The package insert will only contain claims clearly derived from studies of levofloxacin rather than extrapolated data from studies of ofloxacin.

In vivo

Pharmacokinetics/Bioavailability
(Human and animal).

This portion of the review collates information supplied by the applicant. This information provides a background for evaluations associated with the determination of susceptibility testing breakpoints. The applicant characterized the pharmacokinetics and bioavailability of levofloxacin in humans. In summary, the pharmacokinetics of levofloxacin are linear, predictable, and essentially identical to the pharmacokinetics of ofloxacin.

I. BIOAVAILABILITY

Levofloxacin is readily absorbed after oral administration. Average peak plasma concentrations of 2.80 and 5.09 µg/mL occur at approximately 1.6 and 1.3 hours following single oral doses of the 250- and 500-mg proposed market tablets, respectively. The absolute bioavailability of a 500-mg oral dose of levofloxacin is approximately 99% compared to a 500-mg i.v. infusion dose.

There is no statistically significant effect of food on the

extent of absorption of levofloxacin from the 500-mg tablet. Administration with food slightly prolongs the absorption of levofloxacin (T_{max} changes from ~1.5 to 2.4 hours) and decreases the peak plasma concentration (C_{max} changes from ~5.93 to 5.09 μgmL). These differences are not considered to be clinically significant, therefore levofloxacin tablets can be administered without regard to food.

As expected, due to the slightly shorter delivery period when levofloxacin is given via a 1-hour i.v. infusion versus oral administration (T_{max} ~1 to 2 hours), a slightly higher mean peak plasma concentration of 6.18 μg/mL is achieved after i.v. administration as compared with 5.09 μg/mL after oral administration. The plasma levofloxacin concentration profiles for i.v. and oral administrations are nearly superimposable in the post-peak, distribution-elimination phase. The two routes of administration are equivalent in the extent of absorption. Therefore, the oral and i.v. routes of levofloxacin administration can be considered interchangeable.

METABOLISM

Levofloxacin is stereochemically stable in human body fluids (serum and urine) and does not invert metabolically to its enantiomer, D-ofloxacin. Three metabolites of levofloxacin have been identified at low concentrations in rats, dogs, monkeys, and/or humans. These metabolites are: (S)-1-[9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylate]β-D-Glucopyranuronic acid (**M1**: levofloxacin-β-D-glucuronide), (S)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-10-(1-piperazinyl)-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (**M2**: desmethyl-levofloxacin), and 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 N-oxide (**M3**: levofloxacin N-oxide). Only the **M2** and **M3** metabolites have been identified in humans.

ELIMINATION

Levofloxacin is eliminated mainly in the urine and mainly as unchanged drug.

PROTEIN BINDING

Over the clinically relevant serum/plasma levofloxacin

concentration range of [redacted] µg/mL, and as determined by equilibrium dialysis, approximately 24 to 38% of levofloxacin is bound to serum proteins across all species studied. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Animal Prophylactic and Therapeutic Studies.

The application contains a very thorough and lengthy analysis of various animal models for a plethora of infectious processes including studies with a large range of pathogenic bacteria. The studies appear to be well thought out in relation to similarities with human infections; the studies go well beyond simple dosing of animals which had been injected intraperitoneally with test organisms. The studies provide reasonably accurate models of infectious processes. In all cases, summary data clearly show that levofloxacin is reasonably similar to ofloxacin. The summary data are included as Appendix II.

CLINICAL EFFICACY

Clinical Microbiology

Isolates/relevance to approved indications.

The applicant prepared the NDA based on a very large database of clinical isolates. The data were provided in aggregate by the applicant. These data are included in this review as Appendix I. Clearly, all relevant clinically important microorganisms have been included in the database. The database was generated using the following microbiological methods during the clinical trials.

For all clinical trials with levofloxacin, the same susceptibility testing procedures were employed. The procedures adhered to the guidelines established by the NCCLS, Document M2-A3, Performance Standards for Antimicrobial Disk Susceptibility Tests - 3rd edition, 1984, of the National Committee for Clinical Laboratory Standards. In later trials, the 4th edition, 1990, Vol 10, No. 7. was used. Depending on the indication, the comparator drugs were varied as appropriate, but all susceptibility testing procedures followed NCCLS guidelines.

Generally, a 5-μg levofloxacin disk was used for susceptibility testing. When levofloxacin disks were not available in early clinical trials, a 5-μg ofloxacin disk was substituted. For both the levofloxacin and ofloxacin disks, the following criteria were employed (the approved ofloxacin susceptibility criteria were used for the tentative levofloxacin criteria):

Inhibition Zone Diameter	Interpretation
≥16 mm	Susceptible
13-15 mm	Moderately susceptible
≤12 mm	Resistant

MICs of levofloxacin and the comparator drugs were obtained for all pathogens at the reference laboratory, according to NCCLS guidelines NCCLS document M7-A3 (Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard, 3rd edition, NCCLS), and NCCLS document M11-A3 (Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria, Approved Standard, 3rd edition, NCCLS). The following interpretive criteria were used for levofloxacin:

MIC (μg/mL)	Interpretation
≤2	Susceptible
4	Moderately susceptible
≥8	Resistant

At broth microdilution is used for aerobic organisms other than *N. gonorrheae*, as described in NCCLS document M7-A3. Quality control was performed on the following ATCC strains: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, and *S. pneumoniae* ATCC 49619 and 49136.

As noted above, many of the clinical isolates were initially

tested against ofloxacin disks instead of levofloxacin disks but reported as susceptible or resistant to levofloxacin. This condition leads to concerns about whether separate levofloxacin susceptibility testing methods are needed. At best, the applicant's justification for a separate susceptibility testing method is marginal. If a separate susceptibility testing method is necessary, then consideration should be given to retrospectively validating the levofloxacin susceptibility of isolates included in those clinical studies which were initiated on the basis of ofloxacin susceptibility testing rather than using levofloxacin. Nevertheless, the database of isolates is sufficiently large to support the list of microorganisms proposed for the labeling detailed above in the Conclusions section.

Inoculum density studies

No pivotal inoculum density studies were provided. There is no basis for evaluation of the presence or absence of heteroresistance as well as the ruggedness of the susceptibility testing methods.

Disk content Studies.

The five microgram disk content was chosen on the basis of confirmatory disk content studies provided by the applicant. The applicant appropriately concluded from these abbreviated studies that a 5-microgram levofloxacin disk content reasonably closely approximates the MIC responses associated with the currently approved 5-microgram ofloxacin disk. These zone diameter responses continue to fall within an acceptable range which is large enough to be reasonably sensitive while not being so large that the test would consistently interfere with susceptibility tests for other antimicrobials. Overall, the FDA concurs with the proposed disk content of 5 micrograms subject to confirmation of reliability by testing under Phase IV studies proposed above in the Conclusions section.

MIC broth/agar dilution comparisons.

The applicant provided a study performed at the
The study was designed to differentiate among the three principal methods for determining levofloxacin MIC's of clinical isolates.

The study included broth macrodilution, broth microdilution, and agar dilution methods. The broth microdilution method was individually compared against both broth macrodilution and agar dilution tests. These test results were presented both as line data and as regression lines. The regression lines were indistinguishable when either of the MIC vs. MIC analyses were performed. The applicant has reasonably concluded that these three MIC testing methods are equivalent.

MIC/Disk diffusion Correlation Studies.

The applicant provided numerous studies demonstrating the correlation of MIC's to zone diameters from disk diffusion measurements. Each of these studies suffered at least somewhat from a paucity of data in and around the Intermediate ranges for both dilution and diffusion testing methods. In fact, these studies were individually marginal for determining MIC correlates for disk diffusion susceptibility testing. However, the studies had been aggregated for presentation by the applicant to the NCCLS Subcommittee on Antimicrobial Susceptibility Testing. These aggregate data were presented to the Subcommittee at a public meeting of the Subcommittee, and the data were explicitly noted as data from the NDA; the data were contained in the applicant's NCCLS documentation as Figure 7 on page 69 of a report titled "Levofloxacin NCCLS Presentation January 1996."

The data displayed in Figure 7 have ranges of zone diameters of 45 mm down to the diameter of the paper disk while ranges of MIC's cover 0.0078 to 32 mcg/mL; inspection of regression data in Figure 7 strongly suggests an approximately bimodal distribution of isolates into two groups. One group, the susceptible group, generally has zone diameters 17 mm or larger and MIC's 1 mcg/mL or less while the other group, the resistant group, generally has zone diameters 13 mm or smaller and MIC's of 8 or higher. The largest group is likely to contain susceptible isolates while the isolates in the smaller group are likely to be resistant; these groups appear to be reasonably split by the proposed breakpoint boundary lines superimposed on the aggregate regression data in Figure 7. The proposed breakpoint boundary lines appear to minimize the number of isolates which fall into ranges between either presumed susceptible or presumed resistant isolates. These data strongly suggest that the applicant's proposed breakpoint boundary lines should be established by

the FDA as the official susceptibility breakpoints in the proposed product package insert until the proposed Phase IV monitoring is completed.

Tentative Breakpoints and Interpretative Criteria for Levofloxacin for Organisms Other than *Haemophilus influenzae and Streptococcus pneumoniae*

	Zone (5-μg disk)	MIC
Susceptible	≥17 mm	≤2 μg/mL
Intermediate	14 -16 mm	4 μg/mL
Resistant	≤13 mm	≥8 μg/mL

The proposed breakpoint boundaries are based purely on *in vitro* population analyses. Further analyses will be directed toward understanding how these proposed breakpoints relate to the FDA-approved clinical efficacy of individual taxons and other related species when the FDA-proposed list of Indications with their attendant organisms has been completed. Further evaluation will be done in preparation for review of draft labeling when a preliminary medical review is complete. Overall, when a preliminary medical officer's review is complete, then adjustments in the breakpoints will be effected to accommodate exclusion for treatment of any group of organisms which might be included as falsely susceptible. If necessary, these issues will be addressed in a later review pertaining to labeling considerations.

Quality Control Studies (MIC and Disk diffusion).

Summary statistical data were provided for a number of QC studies distributed throughout the application. All of the pertinent QC studies were done with methods proposed for clinical susceptibility testing of levofloxacin in the U.S.A. These proposed methods will require the use of QC strains as a basis of comparison of consistency and reliability; the applicant has evaluated several appropriate QC organisms for both the disk diffusion test as well as dilution susceptibility testing. The applicant's proposed QC organisms and their limits are shown in the table below.

Quality Control Ranges for Levofloxacin

Organism (strain)	Zone diameter (mm)	MIC(μg/mL)

E. coli (ATCC 25922)	29-37	0.008-0.06
E. coli (ATCC 35218)	ND	0.015-0.06
S. aureus (ATCC 29213)	ND	0.06-0.5
S. aureus (ATCC 25923)	25-30	ND
P. aeruginosa (ATCC 27853)	19-26	0.5-4
E. faecalis (ATCC 29212)	ND	0.25-2
H. influenzae (ATCC 49247)	32-40	0.008-0.03
S. pneumoniae (ATCC 49619)	20-25	0.5-2

ND = not determined

Some disturbing concerns emerged from evaluation of the QC ranges associated with the 5-microgram susceptibility testing disks for levofloxacin. A significant concern arises because at least two of the QC zone diameter limits are disproportionately larger for levofloxacin than for ofloxacin. In particular, the QC ranges for *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) are 29-37 and 19-26, respectively. These proposed QC ranges were supported by an appropriate typical multicenter QC study; no obvious underlying bias in the data could be easily observed. Nevertheless, the proposed ranges will tend to bias disk susceptibility testing toward producing susceptible readings when an isolate may be truly resistant (i.e. a false susceptible result). Given this uncertainty about the QC breakpoints in the face of conclusions from appropriate QC validation studies, the rate of clinical failures after approval should be monitored for isolates which show susceptible readings by diffusion testing. Overall, Phase IV monitoring should be performed to define the clinical failure rate for susceptible isolates when compared with ofloxacin by diffusion testing.

Cross Resistance/Cross Susceptibility Studies.

Levofloxacin-resistant organisms were almost universally resistant to other quinolones but not to unrelated antibiotics.

Anaerobic Studies.

Considerations of activity against anaerobic species were included in discussion of Isolates/relevance to approved indications as noted above. The summary of supporting data is provided in Appendix I.

Haemophilus and *Neisseria* Studies.

Considerations of activity against Haemophilus and Neisseria species were included in discussion of Isolates/relevance to approved indications as noted above. The summary of supporting data is provided in Appendix I.

Bacteriological Efficacy

Correlation of Test Results with Outcome Statistics.

At the time of this microbiology review, the medical review of clinical efficacy has not been concluded; thus, the determination of clinical outcomes has not been completed, and outcome data are not available in the Microbiology volumes of the NDA for comparison with *in vitro* susceptiblilty data. When the clinical outcomes are known, then the proposed susceptibility testing breakpoints may be further refined to include or exclude appropriate species; any exclusions will be built into product labeling which is pertinent to clinical microbiologists.

Package Insert.

Isolates Approved

See text of package insert in Remarks section.

Interpretative Criteria Established.

See text of package insert in Remarks section.

James R. King 12/17/96

James R. King, Ph.D.

Microbiologist, HFD-520

SMicro/ASheldon
RD1 init 10/29/96 ATP

AD 12.17.96

DepDir/LGavrilovich 12/17/96

cc: Orig. NDA # 20-634
NDA # 20-635
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon
HFD-502
HFD-520
HFD-520/Micro/King
HFD-520/MO/Frank and Hopkins
HFD-520/Pharm/Joshi
HFD-520/Chem/Shetty
HFD-520/CSO/LeSane

Printed for signatures without Appendices on 12/17/96

Chem

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 11, 1996

FROM: Frances V. LeSane
Project Manager
DAIDP/HFD-520
301-827-2125
301-827-2325/2327 FAX

SUBJECT: Evaluation of NDA -MVP for Levaquin Tablets and Levofloxacin Drug Substance, NDA 20-634.

TO: Heather L. Jordan
Associate Director
Regulatory Affairs
The R.W. Johnson PHARMACEUTICAL RESEARCH INSTITUTE
908-704-4607
908-722-5113 FAX

The methods tested are suitable for control and regulatory purposes.

Following are comments on the methods:

Elequin Tablets - There is a mistake in the preparation of the extracting solution on page 04 00395. The method says to prepare a solution of
it should read

Levofloxacin Drug Substance - We did not have a
in the enantiomeric purity method. I used only the column with satisfactory results.

If you have any questions, please call me at the above number and I will arrange a telecon with the reviewer.

cc:
Orig. NDA 20-634
20-635
HFD-520/Div. Files
HFD-520/PM/FVLeSane/10-11-96

cc Francis Legare
BVS 9/18/96
Please send to firm for making correction in assay.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Analysis
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel (314) 539-2168
FAX Tel (314) 539-2113

NDA 20-634

Date: August 20, 1996

From: Henry D. Drew, Ph.D., Deputy Director, Chemistry II (HFD-920)

Subject: **Evaluation of NDA - MVP for Elequin Tablets and Levofloxacin Drug Substance (NDA: 20-634) Submitted by R.W. Johnson Pharmaceutical Research Institute, Raritan NJ**

To: B.V. Shetty, Ph.D., NDE Review Chemist (HFD-520)

The evaluation of the Elequin Tablets and Levofloxacin Drug Substance NDA - MVP has been completed and all methods are acceptable with minor modification for quality control and regulatory purposes. Please refer to specific comments from the evaluating chemist, James F. Brower,

As per program requirements, we are forwarding the original worksheets. We shall **retain the reserve sample for 90-days before disposal of remaining sample**. If you feel that the reserve sample should be held longer, please contact DDA.

Henry D. Drew

Henry D. Drew, Ph.D.
Deputy Director, Chemistry II

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Drug Analysis
St. Louis, MO
Tel. (314) 539-2011
Ext. 119
FAX Tel. (314) 539-2113

DATE : August 8, 1996

FROM : James F. Brower, Chemist, HFD-920

SUBJECT: NDA 20-634 Elequin (levofloxacin) Tablets

TO : B.V. Shetty, Ph.D., Reviewing Chemist
CDER HFD-520
Phone: (301) 827-2187

The methods tested are suitable for control and regulatory purposes.

Following are comments on the methods:

Elequin Tablets - There is a mistake in the preparation of the extracting solution on page 04 00395. The method says to prepare a solution of
it should read

Levofloxacin Drug Substance - We did not have a
in the enantiomeric purity method. I used only the column with satisfactory results.

James F. Brower
James F. Brower

Consult #677 (HFD-520)

LEVAQUIN levofloxacin tablets and injection

The Committee found no look-alike/sound-alike conflicts nor any misleading and fanciful aspects with the proposed proprietary name.

The LNC has no reason to find the proposed name unacceptable.

D Boring 10/18/96, Chair
CDER Labeling and Nomenclature Committee

cc Frances Informed the firm
BVS Send a copy to them
10/28/96

(613)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-540)

From: Division of New Drug Chemistry III HFD-830/520
Attention: Dr. Vithal Shetty Phone: 827-2187

Date: May 13, 1996

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: LEVAQUIN NDA/~~ANDA~~# 20-634

Company Name: R.W. Johnson Pharmaceutical Research Institute

Established name, including dosage form: Levofloxacin 250 mg and 500 mg tablets

Other trademarks by the same firm for companion products: ELEQUIN I.V (25mg/mL and 5mg/mL (NDA 20-635) (Levofloxacin Injection)

Indications for Use (may be a summary if proposed statement is lengthly): Antibacterial (Quinolone)

Initial comments from the submitter (concerns, observations, etc.): The firm had submitted ELEQUIN as their trade name earlier. This was submitted to Trade name committee on 1/24/96. It was found unacceptable. The firm is proposing LEVAQUIN as an alternate trade name

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev May.94

Consult #613 (HFD-520)

LEVAQUIN (levofloxacin tablets)

The LNC found no look alike/sound alike conflicts nor misleading aspects in the proprietary name.

The LNC has no reason to find the proposed proprietary name unacceptable.

D V Boring 6/20/96, Chair
CDER Labeling and Nomenclature Committee

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: **Division of Anti-Infective Drug Products**		**HFD-520**
Attention: Frances LeSane	**Phone:** 301-827-2125(301) 827-2120	
Date: May 8, 1996		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: LEVAQUIN	**NDA/ANDA#** NDA 20-634	
Established name, including dosage form: Levofloxacin Tablets		
Other trademarks by the same firm for companion products: ELEQUIN		
Indications for Use (may be a summary if proposed statement is lengthy):		
Initial Comments from the submitter (concerns, observations, etc.):		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-634; HFD-520/division file; HFD-520/; HFD-520/

Rev. December 95

Shetty

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#	CHEM. REVIEW#:	REVIEW DATE:
20-634	1	1/17/96 Revision: 9/23/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL Original Submission	12/21/95	12/27/95	

NAME & ADDRESS OF APPLICANT: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300, Raritan, NJ. 08869

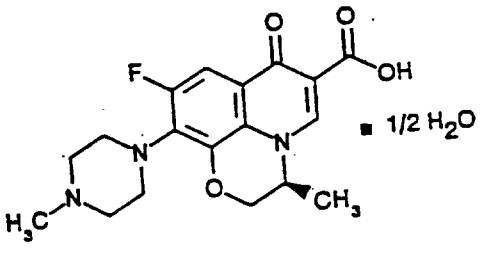
DRUG PRODUCT NAME Levaquin
Proprietary:
Nonproprietary/Levofloxacin
Code Names/#'S: RWJ-25213-097
Chemical type/
Therapeutic Class: 1S; CAS Registry No. 100986-85-4
Alternate Names: Levofloxacin hemihydrate, (l)-ofloxacin

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Antibacterial

DOSAGE FORM: Tablets
STRENGTHS: 250 mg and 500 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:



b. Molecular Formula
$C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$

c. Molecular Weight
370.38

a. Chemical Names
(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate
or
S-(-)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate
or
(-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate

*(1) United States adopted name (proposed)
levofloxacin

(2) International nonproprietary name
levofloxacin

(3) Code name
DR-3355

4) Chemical abstract [illegible] number: 100-86-85-4

SUPPORTING DOCUMENTS:
The firm has submitted following references:

IND
IND

DMF
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DMF
DMF
DMF
DMF
DMF

The DMF refers to manufacture and controls of the drug substance by method The firm has submitted a letter dated 8/29/95 from to refer to their DMF The DMF refers to synthesis of drug substance by method . The DMF refers
The firm has submitted a letter of authorization from to refer to their DMF

RELATED DOCUMENTS (if applicable):

NDA 20-635

NDA 20-634
CHEMIST REVIEW, page4

1. The trademark, LEVAQUIN, has been approved by LNC.

2. Vol.# 1.014, 1.015 and 1.016 have been submitted to HFD-005 on 12/21/95 for EA evaluation.

REMARKS/COMMENTS:

Levofloxacin (Levaquin) is the levorotatory isomer of the D, L-racemate of ofloxacin and a synthetic fluorinated carboxyquinolone. It exists in two crystalline forms: hemihydrate and monohydrate. Either form can be dehydrated with heating and converted to the anhydrous form. However, in the presence of environmental moisture, the anhydrous form converts to the original hydrate form. The hemhydrate form is the subject of this NDA filing. X-Ray diffraction patterns are qualitatively different for the two forms of Levofloxacin.

CONCLUSIONS & RECOMMENDATIONS:

approved BVS 10/16/96

The application is for manufacturing and controls under section 505 of the Act. Specific items which must be addressed are identified under the following headings: Drug Substance, Synthesis, Specifications and Methods, Drug Product stability and Environmental Assessment.

BVShetty 10/16/96
Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 20-634
HFD-520/Div File
HFD-520/PHARM/Osterberg
HFD-520/MO/Alberune
HFD-520/CHEM/Shetty
HFD-520/TeamLeader(Acting)/BDunn BBDunn 10-14-96

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 23, 1996

FROM: Frances V. LeSane
Project Manager
DAIDP/HFD-520
301-827-2125
301-827-2325/2327 FAX

SUBJECT: NDAs 20-634 & 20-635 Environmental Assessment Deficiencies.

TO: Heather L. Jordan
Associate Director
Regulatory Affairs
The R.W. Johnson PHARMACEUTICAL RESEARCH INSTITUTE
908-704-4607
908-722-5113 FAX

Please note the following deficiencies in regards to your pending NDA applications.

NDA 20-634 - 2 pages
NDA 20-635 - 2 pages

cc:
Orig. NDA 20-634
20-635
HFD-520/Div. Files
HFD-520/MO/RHopkins
HFD-520/CHEM/BShetty
HFD-520/PM/FVLeSane/9-23-96

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

LEVAQUIN

(levofloxacin)

Tablets

NDA 20-634

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-634

LEVAQUIN (levofloxacin) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **LEVAQUIN (levofloxacin) Tablets, The R.W. Johnson Pharmaceutical Research Institute** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Levofloxacin is a synthetic drug which will be administered orally in the treatment of community acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinustitis, complicated urinary tract infections, acute pylonephritis, and uncomplicated skin and soft tissue. The drug substance will be manufactured by The drug product will be manufactured at The finished drug product will be used in hospitals, clinics and by patients in their homes throughout the United States.

Levoflaxacin may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. CDER has routinely found that concentrations less than 1 ppb have no effect on relevant standard test organism, therefore the applicant has submitted a Tier 0 EA without format items 7, 8, 9, 10 and 11.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste containing levofloxacin will be sent to licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

12/3/96
DATE

Nancy B Sager

PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

12-5-96
DATE

Eric B Sheinin

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Note: In a separate communication to the agency, the applicant confirmed that the EA addendum marked confidential could be released to the public.

Attachment: Environmental Assessment

NONCONFIDENTIAL ENVIRONMENTAL ASSESSMENT

I. **DATE:** NOVEMBER 27, 1996

II. **NAME OF APPLICANT:** The R.W. Johnson Pharmaceutical Research Institute

III. **ADDRESS:** Rt. 202, P.O. Box 300
Raritan, NJ 08869-0602

IV. **PROPOSED ACTION**

New Drug Application (NDA) for Levofloxacin Tablets, 250 and 500 mg. Environmental Assessment required by 21 CFR Part 25.22 (a)(14).

The National Environmental Policy Act requires Environmental Assessments (EA) to be public documents. Part 2 (Non-Confidential Environmental Assessment) of this document contains Subsections I through XIV and accompanying Appendix A and B which are suitable for public disclosure. Proprietary information, which is contained in this part (Part 1: Confidential Environmental Assessment), including Appendices C and D, could be beneficial to competitors and, therefore, must remain confidential.

The new drug substance, levofloxacin, will be manufactured by The imported active ingredient will be formulated into a tablet dosage by The final drug product will be manufactured, packaged, labeled, and tested at this facility.

Levofloxacin is a member of the quinolone antimicrobials. It exerts antibacterial activity by antagonism of the interaction between DNA gyrase and DNA. The spectrum of activity of levofloxacin includes Gram-positive

aerobic organisms and Gram-negative bacteria, and atypical organisms (e.g., mycoplasma pneumoniae, chlamydia pneumoniae). Levofloxacin will be utilized for treatment of community acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinusitis, complicated urinary tract infections, acute pylonephritis, and complicated and uncomplicated skin and soft tissue infection. The drug product will be dispensed at hospital and home health care settings, and by pharmacies.

Disposal of prescribed product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. Production wastes contaminated with the active ingredient generated by will be disposed through high temperature incineration at approved commercial incinerators. Wastewater from the manufacturing process will be disposed through permitted discharge to the local Publicly Owned Treatment Works in Manufacturing wastes generated by during the production of the active ingredient will be managed in accord with applicable local environmental regulations.

facility is located on The facility is bordered to the West and North by public highways. To the East and Southeast are undeveloped lands. The site is not adjacent to environmentally sensitive areas. The climate is tropical.

V. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

A. DESIGNATIONS

1. Chemical Name

(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate

2. Other Name

RWJ-25213-097 - Code Designation at The R.W. Johnson Pharmaceutical Research Institute
DR-3355 - Code Designation at
USAN - Currently Unavailable
JAN - Levofloxacin

3. CAS Registry Number: 100986-85-4

4. Molecular Weight and Formula: MW = 370.38

Formula: $C_{18}H_{20}FN_3O_4 . ½H_2O$

B. PHYSICAL DESCRIPTION

Light yellowish white to yellow-white crystals or crystalline powder, odorless.

C. ADDITIVES OR IMPURITIES

The levels of impurities present in levofloxacin drug substance are extremely low (typically < 0.1%) and are:

Levofloxacin-N-oxide
Desmethyl-levofloxacin
Diamine derivative of levofloxacin
Desfluoro-levofloxacin

Additionally the D-isomer (also known as (D)-ofloxacin) is also monitored. A specification of "not to exceed 0.8%" is listed in the Chemistry, Manufacturing, and Controls Section I.D. of this NDA.

D. QUALITATIVE COMPOSITION OF FINAL PRODUCT

Product containing the drug substance: Levofloxacin tablets contain the drug substance LEVOFLOXACIN, (RWJ-25213-097) in combination with the following commonly used compendial excipients:

COMPONENTS	CAS #
Hydroxypropyl Methylcellulose 2910, USP	9004-65-3
Crospovidone, NF	9003-39-8
Microcrystalline Cellulose, NF	9004-34-6
Magnesium Stearate, NF	557-04-0
Polyethylene Glycol 8000, NF	25322-68-3

[1] This component does not appear in the final product.

Qualitative Composition

- Hydroxypropyl Methylcellulose, USP
- Titanium Dioxide, USP
- Polyethylene Glycol, NF
- Synthetic Red Iron Oxide
- Polysorbate 80, NF

Qualitative Composition

- Hydroxypropyl Methylcellulose, USP
- Titanium Dioxide, USP
- Polyethylene Glycol, NF

Synthetic Red Iron Oxide
Polysorbate 80, NF

Appendix A contains the Material Safety Data Sheets for these compounds.

The Quantitative composition is provided in the Chemistry, Manufacturing, and Controls Technical Section II (Drug Product) of this NDA. Such information is trade secret and confidential.

VI. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) will obtain the active ingredient from

Appendix B contains the statement of compliance with environmental regulations for The final drug products will be manufactured by

The potential environmental releases of the drug substance are from airborne particulates generated during the manufacturing process. This environmental assessment will address the introduction of the drug substance levofloxacin to the environment attributable to the manufacturing process. Site specific release information is provided in Sections VI.A. and VI.B., and is summarized in Table 6-1.

Table 6-1
Environmental Permits

Media	Permit No.	Govt. Agency	Expiration Date
Air	PFE-33-1291-1681-I-II-III-0	[a]EQB	11/96
Water	GDG-88-606-021	[b]PRASA	3/96

[a] EQB - Environmental Quality Board
[b] PRASA - Puerto Rico Aqueduct and Sewage Authority

1. Air

The production of levofloxacin tablets will take place within a proposed 40' × 80' addition to the manufacturing facility at The manufacturing process will consist of the following steps: granulation, milling, blending, compression, and tablet coating. Each of these steps has been evaluated for the potential to release the active as an air contaminant, with the granulation, compression, and coating steps deemed capable of generating airborne emissions.

The existing manufacturing area is equipped with a general exhaust ventilation system with a rated removal efficiency rate of 99.9%. The system is permitted by the Puerto Rico Environmental Quality Board under Permit No. PFE-33-1291-1681-I-II-III-0 (refer to Table 6-1). Air filters containing the entrapped actives will be disposed by high temperature incineration at a commercially licensed incinerator. The proposed 40' × 80' manufacturing wing will be similarly equipped with a general exhaust ventilation system at least as efficient as the present system.

Besides the aforementioned general exhaust ventilation system, the processing equipment has been designed to operate such that airborne emissions are either not generated, or if they are generated, that these emissions are controlled. For example, product transfers between processing equipment is minimized to the greatest extent practical. Where transfers are necessary, the use of connectors equipped with diaphragm seals will help eliminate airborne releases.

The initial granulation step in the manufacture of levofloxacin tablets occurs within a fluid bed granulator. This device incorporates a series of filters which capture particulates that would otherwise be released. This air filtration system relies on a HEPA Filter bank to provide for a 99.97% removal efficiency.

Following the granulation step the product undergoes a milling/blending process that serves to "de-clump" the granulation. This process is totally enclosed, meaning that there are no pathways for airborne releases. Next the product is compressed and it is this step that may generate airborne particulates. These releases will be controlled by the general exhaust system described above, providing for a 99.9% removal efficiency for

particulate matter. The final step requires that a coating be applied to the tablets. Releases from this step will be controlled by the application of filters designed to remove particulates (5 μ or greater) by a factor of 99.9% or better.

The manufacturing process is expected to limit production losses to less than 4 kg/batch. The controls exercised as described above will limit actual environmental releases of the active via the air compartment to approximately 7.4 g/batch. Filters will be cleaned with hot water, with the resultant washings discharged to the plant's wastewater treatment facility. Filter media contaminated with the active ingredient will be disposed through high temperature incineration (1600-1800 °F) at a commercial solid waste incinerator.

With the approval of this action, levofloxacin tablet production at Gurabo is expected to be ___ batches/year (5th year production schedule). This yields estimated airborne releases of approximately ___ g/year. In actuality, releases would effectively be zero.

2. Water

Waterborne releases into the facility's treatment plant are likely to occur from the cleaning of process equipment and air filters containing the entrapped active. Following product removal at the end of the batch run, the process vessels are cleaned following a standard cleaning procedure. A hot water rinse is applied to remove any residual product from the processing equipment. Although the cleaning frequency cannot be determined at this time, it is expected to occur once every 15 batches. For purposes of this assessment it will be assumed that the production

equipment will be cleaned after every batch. This will provide a very conservative estimate of waterborne releases that may be as much as 15 times higher than actual operating conditions. Therefore based on 4 full-scale test batches, this cleaning operation is expected to release approximately 4 kg/batch into the facility's wastewater stream. This wash-down residual would then undergo secondary and tertiary treatment (powdered activated carbon) on-site.

discharges treated effluent to the local Publicly Owned Treatment Works (POTW) under Permit No. GDG-88-606-021 (Table 6.1). The wastewater treatment plant provides secondary treatment for approximately 303 million-liters per day of wastewater. Effluent from the POTW is discharged 1 mile off the seacoast. Thus, the organics that remain in the effluent do not enter any body of surface water.

Effluent limitations applicable to are set by the Puerto Rico Aqueduct and Sewerage Authority (PRASA). These limits are imposed to protect the operation of the treatment plant and employees. Under the conditions of JJPP's wastewater discharge permit, the manufacture of levofloxacin tablets is not expected to result in noncompliance or to adversely affect the operation or efficiency of the POTW. Assuming that levofloxacin is not degraded by biological treatment, it is expected to be strongly adsorbed to sewerage sludge. Thus, the concentration of the active in the effluent would effectively be zero.

3. Disposal of Waste from Use

To meet patient demands, the 5th year production estimate for the drug product will require _____ kg of levofloxacin drug substance. Assuming disposal will occur through wastewater collection systems, an estimate of the Maximum Expected Emitted Concentration (MEEC) yields an environmental concentration of ___ x 10^{-} mg/L (see Appendix C for MEEC derivation). Material discarded by the consumer will be incinerated or landfilled at sanitary/municipal solid waste facilities.

Returned goods will be received and managed by Ortho-McNeil Pharmaceutical Corporation's Distribution Center in Bridgewater, New Jersey. Disposal of product will be through high temperature incineration at a commercially licensed incinerator. It is Ortho-McNeil's policy to destroy all returned products in this fashion. The high temperature of incineration (>1600 °F) is expected to destroy the active ingredient, with the resultant ash posing no environmental hazard. This practice insures that returned goods are managed in an environmentally sound manner.

VII-XI

As CDER has found that drugs at concentrations less than 1 part per billion (ppb) have no significant effect on the environment, that information for Environmental Assessment format items 7, 8, 9, 10 and 11 will normally not be needed for drugs whose maximum expected environmental concentration (EIC or EEC, whichever is greater) is less than 1 ppb.

XII. LIST OF PREPARERS

Bradford B. Gardner
Manager, Environmental Engineering
Ortho Pharmaceutical Corporation

Eleven and a half years of professional environmental experience. Eight and a half within the pharmaceutical industry, and two and a half years in hazardous waste management, and half a year with the New Jersey Department of Environmental Protection.

Bachelor of Science Degree in Environmental Science
Master of Science Degree in Environmental Health
Registered Environmental Manager, No. 5991.

Norman W. Gabel, Ph.D.
Senior Scientist
N.W Gabel and Associates

Ph.D., Organic Chemistry
M.S., Biochemistry
B.S., Chemistry

XIII. CERTIFICATION

I certify that the information presented is true and accurate and complete to the best of the knowledge of the firm responsible for the preparation of the Environmental Assessment.

Date: November 27, 1996
Signature: _____
Title: Manager, Environmental Engineering

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XV. APPENDIX A

MATERIAL SAFETY DATA SHEETS

MATERIAL SAFETY DATA SHEET
ON LEVOFLOXACIN

DATE OF ISSUE: March 18, 1993

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MATERIAL SAFETY DATA SHEET

PRODUCT:Drug

I.IDENTITY

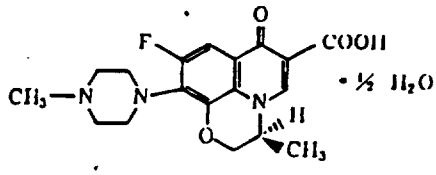
Chemical Name : (-)-S-9-fluoro-2,3,-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3-de] [1,4] benzoxazine-6-carboxylic acid hemihydrate

INN : levofloxacin (anhydrate)

JAN : levofloxacin (hemihydrate)

Code Number : DR-3355

Structure :



Formula : $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2} H_2O$

Molecular weight : 370.38

II.CHEMICAL AND PHYSICAL CHARACTERISTICS

Description : Light yellowish white to yellowish white crystals or crystalline powder without odor and with bitter taste

Solubility in Water : Sparingly soluble

Solubility in Organic Solvent : Freely soluble in glacial acetic acid and chloroform. Sparingly soluble in methanol. Slightly soluble in ethanol. Practically insoluble in ether.

Melting Point : No melting point. Degradation occurs over the range 224-229°C, and no solid can be observed at this temperature.

Inflammatory : Not inflammable

Explosion Hazard : Not explosive

Other Known Hazards : No hazards have been reported.

III. CLASSIFICATION AND LABELING

Therapeutic Category : antibacterial (for clinical use)

IV. INFORMATION ON TOXICITY

Acute toxicity (po) : LD_{50} (mg/kg)
Mouse(Male) 1881, (Female) 1803
rat(Male) 1478, (Female) 1507
monkey(Male) >250

Subacute toxicity (4-week po) : Non-toxic dose (mg/kg/day)
rat 200, monkey 30

Chronic toxicity (26-week po) : Non-toxic dose (mg/kg/day)
rat 20, monkey 62.5

Contact Hazard : No irritant upon skin contact

Carcinogenicity (two-stage study) : Indicative no carcinogenicity
rat(Male)

Mutagenicity : In vitro cytogenetic study in CHL* cells and in vitro sister chromatid exchange study were positive. But all in vivo studies have given negative results. And in vivo study of unscheduled hepatic DNA synthesis was negative.
(*CHL:Chinese hamster cell line)

Reproduction toxicity : Non-toxic dose (mg/kg/day)
Seg.I(rat, po)
360 (for reproductive toxicity on parental rats and for fetuses)
Seg.II(rat, po)
90 (for fetuses and offspring)
Seg.II(rabbit, po)
50 (for fetuses)
Seg.III(rat, po)
360 (for offspring)

Joint toxicity	: Non-toxic dose (mg/kg/day) Juvenile rat(7 days, po); 100 Juvenile dog(7 days, po); 5
Phototoxicity	: Non-toxic dose (mg/kg) mouse(single dose, po); 200
Storage precautions	: store in a light-resistance container
Handling precautions	: plastic gloves, goggles and dust mask are recommended

V. EMERGENCY AND FIRST AID PROCEDURES

Eye contact	: may irritate, if exposed flush with water
Skin irritation	: if exposed flush thoroughly with water
Ingestion	: do not induce vomiting; drink plenty of water
Inhalation	: seek medical attention, if respiratory irritation occurs.
Spillage	: small spillage can be rinsed away with water
Fire	: No irritant fumes emitted upon decomposition

XVI. APPENDIX B

COMPLIANCE STATEMENT

1. Agreement on Antipollution Measures at the

2. Written agreement on the partial revision of "Agreement on Antipollution Measures at the

3. Certifying letter from

4. Certifying letter from

Agreement on Antipollution Measures

at the

Agreement on Antipollution Measures

at the

(hereinafter referred to as "A") and (hereinafter referred to as "B") have reached an agreement on the following articles for the antipollution measures which are to be taken at the (hereinafter referred to as "Factory") built in the by B. Three original copies of this Agreement have been made to be possessed by the respective three parties.

Article 1. The principle of this Agreement

A and B shall take the best possible antipollution measures in order to protect the health of the habitants and preserve the environment of the involved regions. Particularly, B shall realize that B bears a critical responsibility to the society against environmental pollution. B, therefore, shall keep in close contact with A to implement this Agreement with sincerity, during the operation of the Factory.

Article 2. Prevention against air pollution

The emission of air-polluting substances shall be regulated according to the standards provided below on a total volume and concentrations. B shall keep the following emission standards by such means as using low sulfur oil and equipping a scrubber.

Item		Boiler	Incinerator
Sulfur oxide	Sulfur content in fuel	0.4% or less	
	Total emission volume	4.37 Nm^3/h or less	0.18 Nm^3/h or less
	Measures for an emergency	keep 80 kl or more low sulfur oil containing sulfur by 0.1% or less in stock	
Nitrogen oxide	Emission concentration	130 ppm or less	150 ppm or less
Dust	Emission concentration	0.05 g/Nm^3 or less	0.03 g/Nm^3 or less
Fluorine	Emission concentration		15 ng/Nm^3 or less
Height of chimneys		higher than 30 m	higher than 20 m

Article 3. Prevention against water pollution

B shall treat waste water yielded at each manufacturing process in the Factory by such procedures as neutralization-precipitation, biological treatment or burning and shall drain treated waste water after passing it through a fish breeding pond. B shall also minimize the drainage of waste water by means of circulatory usage. The water emission criteria for amount and quality are provided as follows:

Water amount to be drained		6,000 m^3/day or less
Water quality	Hydrogen ion concentration	6.0 ∿ 8.5
	Chemical oxygen demand	25 mg/l or less
	Suspended solid mass	25 mg/l or less
	N-hexane extract content	1 mg/l or less
	Fluorine content	10 mg/l or less
	Phenols content	0.3 mg/l or less
Temperature difference		7°C or less
Measures for an emergency		A precipitation pond of 500 m^3 or more volume is to be provided.

Article 4. Prevention against noise

B shall observe the regulation standards for the Class 4 district of subjected to the Noise Regulation Law (1968 Act No. 98).

Article 5. Prevention against offensive odors

B shall not give the surrounding communities any impact of offensive odors generated from the Factory. B shall adopt a closed system and perform a washing and incineration to cope with a source of stenchy gas and shall keep the condition in which offensive odors are not perceived on the border of the Factory lot.

Article 6. Treatment of waste matters

B shall store their waste matters such as aluminum hydroxide, spent coal and garbages inside the Factory building and shall properly treat their waste matters so as not to cause secondary pollution by such means as commission to waste matter treating professionals, incineration and burying.

Article 7. Safety measures

B shall observe relevant laws for the storage and treatment of dangerous articles and poisons and shall take the best possible measures to ensure safety and security.

Article 8. Preservation of greens

B shall limit the cutting of pine trees to a minimal extent and shall plant lawns or trees in cutovers for prevention against sand shifting and for environmental beautification. B shall also positively promote tree planting in the Factory lot.

Article 9. Voluntary monitoring

B shall provide automatic indicators on the boiler and overflow to monitor the emission status at the Factory. B shall also conduct periodical measurements of the items instructed by A for the need of environmental assessment in the nearby areas to prevent pollutions and shall report obtained data to A.

Article 10. Measures to be taken at the occurrence of pollution

1. When pollution is caused by smoke or waste water emitted from the Factory (including accidental cases, and the same hereinafter), or when a risk of pollution is indicated, B shall promptly take necessary actions including operation suspension or reduction, revision of operation systems and improvement of facilities, according to the instructions by A.

2. When air pollution and/or water pollution occur and its cause has been proven to derive from the industrial activities of the Factory through a research by A, B shall take compensative steps as well as other due steps with sincerity, regardless as to whether the causative act is intentional or accidental.

Article 11. Measures at the time of facility troubles

When troubles including damage or defects occur in pollution-related facilities, B shall promptly take due steps and shall inform A of the situation of facility troubles.

Article 12. Field inspection

A has the right to require a report from B of the matters involved in the implementation of this agreement and the right to send the staff of A to the Factory to execute a field inspection in the Factory within the scope for the implementation of this Agreement. B shall positively cooperate with such an inspection.

Article 13. Discussion for facility installation

When B is going to newly install pollution-related facilities or modify their existing pollution-related facilities, B shall have a prior discussion with A about such a plan.

Article 14. Steps at the time of violation

A has the right to order the reduction or suspension of operation of the Factory, if B violates the provisions in this Agreement. B shall obey such orders with sincerity.

Article 15. Application of this agreement

This Agreement shall be applicable on the manufacturing activities of the 7 products of B comprising a fat metabolism activator (Pantosin), a gastrointestinal function activator (Actinamin), a depressor (DJ-1461), an antipsychotic (Tolopelon), an antiulcer agent (Neuer), a cyclic nucleotide preparation (Actosin) and an antibiotic (Ofloxacin) for the purpose of environmental pollution prevention. In case that B plans to manufacture products other than the above-mentioned 7 products, B shall have a prior discussion with A to make a revised agreement if necessary.

Article 16. Particulars

Particulars related to the implementation of this Agreement shall be provided separately upon discussion between A and B.

Article 17. Others

When any questions arise about the provisions in this Agreement, when the provisions in this Agreement need to be revised, or when it is necessary for this Agreement to provide articles other than those provided in this Agreement, A and B shall have a meeting at each such time to discuss and agree about such matters.

Date:

A:

_____
(by the Prefectural Governor)

_____
(by the Mayor)

B:

_____
(by the President)