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APPLICATION NUMBER:

21-744

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDAs #: 21-744

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SUBMISSION REVIEWED: Original New Drug Application (Proquin™)

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

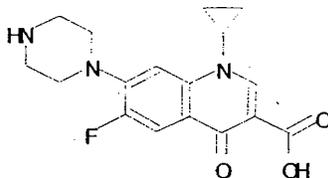
INDICATIONS: Uncomplicated Urinary Tract Infections

DOSAGE FORM: 500-mg Gastric Retentive Tablets

DRUG PRODUCT NAME

PROPRIETARY: Proquin™
NONPROPRIETARY/USAN: Ciprofloxacin hydrochloride
CHEMICAL NAME: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[1-piperazinyl]-3-quinolone-carboxylic acid

STRUCTURAL FORMULA:



Molecular Formula: C₁₇H₁₈FN₃O₃
Molecular Weight: 331.4

SUPPORTING DOCUMENTS:

None

CONCLUSIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The required microbiology revisions are listed as recommendations at the end of this review on pages 64-67.

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EXECUTIVE SUMMARY

This application is for a new formulation (500-mg gastric retentive tablet) of ciprofloxacin. This new tablet was developed to deliver 90% of the 500 mg dose to the upper gastrointestinal (GI) tract, where ciprofloxacin is best absorbed, within 6 hours of dosing. When taken after a meal the tablet swells in the stomach and releases ciprofloxacin by polymeric erosion over 6 hours to the upper GI tract. The balance between swelling and erosion maintains the size of the tablet so that it is retained in the stomach during the gastric retention/digestive phase following a meal. This drug release profile reduces the amount of drug released within the first hour after dosing into the GI tract 3- to 4-fold compared to the immediate release formulation. This drug release profile allows once a day dosing.

Following steady-state dosing under fed conditions with the gastric retentive tablet (500 mg qd for 3 days) versus the immediate-release tablets (250 mg bid for 3 days) the exposure to ciprofloxacin was determined to be similar. As expected the absorption was prolonged with the gastric retentive tablet (T_{max} of 6.06 hours) compared to the immediate-release tablet (2.45 hours). C_{max} values were approximately 30% higher for the immediate-release formulation after a single dose compared to the gastric retentive formulation. After multiple doses the immediate-release formulation had a C_{max} value about 13% higher than that of the gastric retentive formulation. AUC values were determined to be equivalent between the two formulations. Urinary recovery of unchanged ciprofloxacin following administration of the gastric retentive tablet is similar to that following the administration of 250 mg twice a day for the immediate-release tablet.

Recent surveillance studies, which evaluated uropathogens associated with uncomplicated urinary tract infections (uUTI), showed that over 90% of *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus* isolates were susceptible to ciprofloxacin. Approximately 50% of enterococci and 76% of *Proteus mirabilis* isolates were susceptible to ciprofloxacin.

At pH >6.0, little effect on the activity of ciprofloxacin was seen for all tested organisms. However, at pH \leq 5.5, the activity of ciprofloxacin against *E. coli*, *K. pneumoniae*, and *P. mirabilis* was diminished by 32-fold to 256-fold compared with the activity at pH \geq 6.0. The activity of ciprofloxacin against *S. aureus* and *E. faecalis* was decreased four-fold to 16-fold at pH \leq 5.5. This decrease in activity at lower pH values is seen with all quinolones. The effect of the type of medium did not seem to make much difference in the activity of ciprofloxacin. Calcium and magnesium cation content did not have a major effect on activity. The size of the inoculum used for susceptibility testing produced minimal effect on MICs of ciprofloxacin; modest increases of two- to fourfold were seen at an inoculum size of 10^7 CFU/mL. Minimal bactericidal concentrations (MBCs) were either the same as the MICs or only one dilution higher than the MICs for all tested organisms.

Data from Focus Technologies and Clinical Microbiology Institute (CMI) were submitted to determine the correlation between MICs obtained from broth microdilution tests and corresponding disk zone diameters. All the 800 isolates in the Focus study were collected from patients with uncomplicated UTI and most were recent clinical isolates. The 862 isolates in the CMI study comprised 68.3% recent clinical isolates and a challenge set of phenotypic resistance patterns (31.7%). Levofloxacin was used as a control in both studies.

Two similar studies were performed comparing a 500-mg tablet once daily dose of the new gastric-retentive dosage (C-GR) with two 250-mg tablets of the immediate-release dosage (C-IR) given twice daily both given for 3 days. One study (81-0005) was a small Phase II study in which only 19 patients were microbiology evaluable in each arm. The other study (81-0015) was a Phase III study with 283 patients in the microbiology evaluable population in the gastric-retentive (C-GR) arm and 257 microbiologically evaluable patients in the C-IR arm. Both studies compared the safety and efficacy of C-GR to the immediate-release (C-IR) tablet. Patients had to have at least one positive pretreatment clean-catch, mid-stream urine culture with an organism count $\geq 10^5$ CFU/mL and the pathogen had to be susceptible to ciprofloxacin. There were only 58 patients enrolled in the Phase II study and only 38 (19 on each treatment) were included in the efficacy population. A total of 1,037 patients were enrolled in the Phase III study. A total of 583 patients were included in the intent-to-treat (ITT) population and 540 in the efficacy population. The eradication rates for individual pathogens are shown in TABLE A.

The frequency distribution of MICs of ciprofloxacin obtained during the Phase III clinical trial was similar to data provided in preclinical studies to assess interpretive criteria. The preclinical data and the subsequent analyses of the Phase III clinical trial data indicated that the appropriate MIC susceptibility breakpoints should be Susceptible = ≤ 1 μ g/mL; Intermediate = 2 μ g/mL; and Resistant = ≥ 4 μ g/mL. Corresponding breakpoints for disk diffusion were Susceptible = ≥ 21 mm; Intermediate = 16-20 mm; and Resistant = ≤ 15 mm. These criteria, however, are established based on serum levels of ciprofloxacin and are not appropriate for uncomplicated UTI infections.

The sponsor is requesting an indication of uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*,

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TABLE A
 Bacteriological Eradication Rates (# isolates eradicated/# isolates at baseline)
 at Test-of-Cure Visit

Pathogen	Gastric-Retentive Tablet (500 mg QD)	Cipro Immediate Release (250 mg BID)
Study 81-0015 (Phase III)	(n = 283)	(n = 257)
<i>Escherichia coli</i>	211/222 (95.0%)	184/202 (91.1%)
<i>Klebsiella pneumoniae</i>	11/12 (91.7%)	10/13 (76.9%)
Group D <i>Streptococcus</i> <i>Enterococcus</i>	6/10 (60.0%)	7/9 (77.8%)
<i>Proteus mirabilis</i>	7/7 (100%)	8/9 (88.9%)
<i>Staphylococcus</i> species coagulase-negative	7/9 (77.8%)	5/7 (71.4%)
Beta Strep, Presumptive Group B	1/1 (100%)	6/6 (100%)
<i>Klebsiella</i> species	3/3 (100%)	1/1 (100%)
<i>Staphylococcus aureus</i>	1/1 (100%)	4/4 (100%)
<i>Enterococcus aerogenes</i>	3/3 (100%)	1/1 (100%)
<i>Enterococcus</i> species	2/2 (100%)	2/2 (100%)
<i>Citrobacter</i> species	1/1 (100%)	0 (0%)
<i>Enterobacter cloacae</i>	1/1 (100%)	1/1 (100%)
<i>Hafnia alvei</i>	1/1 (100%)	1/1 (100%)
<i>Acinetobacter baumannii</i>	1/1 (100%)	0 (0%)
Non-fermenting Gram Negative Bacilli	0 (0%)	1/1 (100%)
Study 81-0005 (Phase II)	(n = 19)	(n = 19)
<i>Escherichia coli</i>	13/16 (81.3%)	15/16 (93.8%)
<i>Proteus mirabilis</i>	1/2 (50.0%)	1/1 (100%)
<i>Klebsiella pneumoniae</i>	1/1 (100%)	1/1 (100%)
<i>Acinetobacter baumannii</i>	0 (0%)	1/1 (100%)
<i>Pseudomonas aeruginosa</i>	1/1 (100%)	0 (0%)

As usual in urinary tract infections, most of the pathogens were *Escherichia coli*. There were very few of the other pathogens detected in the clinical trial. Some organisms, such as Group D streptococci and coagulase negative staphylococci, were not speciated as they should have been. Eradication rates were good for *Escherichia coli* and *Klebsiella pneumoniae* and *Proteus mirabilis*, but were not as good for Group D streptococci or coagulase negative staphylococci.

There was one patient (# 401) in the Phase II study who received Cipro GR that had two baseline pathogens (*E. coli* and *K. pneumoniae*) both organisms were eradicated. There were three patients in the Phase III study who received Cipro IR that had two baseline pathogens (Patient 3926, *E. coli* and *Staphylococcus* species; Patient 4112, *E. coli* and group B streptococci; Patient 4822, *E. coli* and *K. pneumoniae*). All organisms were eradicated at the Test-of-Cure visit but Patient 4112 had a recurrence of the group B streptococci.

PRECLINICAL EFFICACY (IN VITRO)

MECHANISM OF ACTION

No new information has been submitted.

Ciprofloxacin is a 6-fluoroquinolone. Similar to other quinolone agents, the bactericidal action of ciprofloxacin results from inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial drugs. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials.

IN VITRO ACTIVITY AGAINST RECENT CLINICAL ISOLATES FROM UTIs

SURVEILLANCE STUDIES

An overview of the *in vitro* activity of ciprofloxacin and other uncomplicated urinary tract infection (uUTI) antimicrobial agents against organisms most frequently isolated from urinary tract infections include a 2003 surveillance study derived from the TSN® Database-USA by Focus Technologies. The study results for selected organisms are presented in TABLE 1. The systemic breakpoint of ≤ 1 $\mu\text{g/mL}$ was used to determine susceptibility.

TABLE 1
National Susceptibility Data for Ciprofloxacin for the Year 2003^a

Organism	Jan 1-Apr 30	May 1-Aug 32	Sept 1-Dec 31
<i>Escherichia coli</i>	90.2 %	90.5%	89.0%
<i>Klebsiella pneumoniae</i>	92.4%	93.6%	93.6%
<i>Proteus mirabilis</i>	76.7%	78.6%	75.7%
<i>Staphylococcus saprophyticus</i>	96.6%	98.8%	97.8%
<i>Enterococcus</i> species	Insufficient Data	53.7%	53.4%

^aTSN® Database—USA, Focus Technologies

About 90% of *Escherichia coli* and *Klebsiella pneumoniae* isolates were susceptible to ciprofloxacin. Over 95% of *Staphylococcus saprophyticus* isolates were susceptible to ciprofloxacin. Over 20% of *Proteus mirabilis* were resistant to ciprofloxacin. Over 46% of *Enterococcus faecalis* isolates were resistant to ciprofloxacin. *Enterococcus faecalis* is one of the organism listed under UTI in the present ciprofloxacin tablet labels. It is listed in the microbiology subsection of the present ciprofloxacin tablet labels with the qualifier that many strains are only moderately susceptible.

The percentages in the above table are based on breakpoints established for systemic infections. The amount of ciprofloxacin in urine is much higher than in plasma, so ciprofloxacin should be effective in urinary tract infections against organisms that would appear to be resistant using these breakpoints.

An evaluation of the susceptibility of *Escherichia coli* in the nine U.S. Census regions showed that the susceptibility was similar in six of the nine regions; the susceptibility rate was 90.1% to 97.8% in these six regions (TABLE 2). In the Mid Atlantic, South Atlantic, and West South Central regions, the ciprofloxacin susceptibility of *E. coli* was somewhat lower at 86.1% to 88.6%.

TABLE 2
Ciprofloxacin Surveillance Data for *E. coli* UTI Isolates /2003/By Region*

Organism	Total Number	% Susceptible	% Intermediate	% Resistant
East North Central	35,249	92.3	0.1	7.6
East South Central	11,968	92.4	0.1	7.5
Mid Atlantic	36,761	88.6	0.2	11.2
Mountain	25,754	94.1	0.4	5.5
New England	3,278	97.8	0.0	2.2
Pacific	56,953	90.1	0.2	9.7
South Atlantic	53,456	86.1	0.2	13.7
West North Central	13,637	92.5	0.1	7.4
West South Central	24,543	88.2	0.2	11.6

*TSN™ Database—USA. 2003 Focus Technologies, INC.

In another *in vitro* evaluation, trends in antimicrobial resistance among uUTI isolates of *E. coli* from female outpatients in the United States were studied by Karlowky et al. (1) for the years 1995 to 2001. TABLE 3 shows that the overall susceptibilities of *E. coli* to ciprofloxacin ranged from 99.2% (1995) to 97.4% (2001). These data demonstrate that ciprofloxacin resistance is increasing but it has gone up less than 2% in six years.

TABLE 3
Susceptibility of *Escherichia coli* to Ciprofloxacin by Year

Year	Number of Isolates	% Susceptible
1995	1,653	99.2
1996	10,937	99.3
1997	22,748	99.1
1998	45,509	98.8
1999	64,815	98.3
2000	82,460	97.8
2001	58,065	97.4

DATA FROM THE CLINICAL STUDIES

This application has two similar studies (a Phase II study and a Phase III study). These were randomized, double-blind, parallel group studies to compare the safety and efficacy of once daily gastric retentive (C-GR) tablets and twice daily immediate-release (C-IR) tablets in the treatment of uncomplicated female urinary tract infections. The primary endpoint for these studies was the microbiological response at the test-of-cure visit (4 to 11 days after the completion of therapy) and clinical and microbiological responses at the Late Post-Treatment visit (5 weeks \pm 7 days post-treatment).

Urine specimens were cultured, pathogens were identified, and susceptibility tests were performed by a central laboratory. Susceptibility tests were performed on uropathogens that produced colony counts $\geq 10^5$ cfu/mL at the pre-therapy visit. Testing was performed according to the NCCLS guidelines using broth microdilution methodology. Interpretive criteria for the MIC susceptibility tests were Susceptible, ≤ 1 $\mu\text{g/mL}$; Intermediate, 2 $\mu\text{g/mL}$; and Resistant, ≥ 4 $\mu\text{g/mL}$.

The ciprofloxacin susceptibility test results for the primary uropathogens that were isolated pre-therapy from all randomized patients in both the C-CR and C-IR study groups are presented in TABLE 4. The range of MICs for 486 isolates of *E. coli* and 30 isolates of *K. pneumoniae* was ≤ 0.06 to >2 $\mu\text{g/mL}$. The MIC₉₀s were 0.25 $\mu\text{g/mL}$ and 0.5 $\mu\text{g/mL}$ for *E. coli* and *K. pneumoniae*, respectively. The MICs for isolates of *P. mirabilis* ranged from ≤ 0.06 to 1 $\mu\text{g/mL}$; the MIC₉₀ was 0.5 $\mu\text{g/mL}$. The range of MICs for *Enterococcus* Group D was 0.5 to 1 $\mu\text{g/mL}$ and the MIC₉₀ was 1 $\mu\text{g/mL}$. The range and MIC₉₀ were 0.5 $\mu\text{g/mL}$ for the isolates of *Staphylococcus coagulase-negative*.

TABLE 4
 MICs of Pre-therapy Isolates in C-GR and C-IR Arms

Organism	Total Number	Range ($\mu\text{g/mL}$)	MIC ₅₀ ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)
<i>Escherichia coli</i>	486	≤ 0.06 - >2	≤ 0.06	0.25
<i>Klebsiella pneumoniae</i>	30	≤ 0.06 - >2	≤ 0.06	0.5
<i>Proteus mirabilis</i>	18	≤ 0.06 -1	≤ 0.06	0.5
<i>Enterococcus</i> Group D	20	0.5-1	1	1
<i>Staphylococcus coagulase-negative</i>	18	0.5	0.5	0.5

PHARMACOKINETICS/BIOAVAILABILITY

The proposed dose is a single 500-mg tablet taken once a day for 3 days.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

Data analyses are based on the rationale that fluoroquinolones show concentration-dependent killing of bacteria *in vitro*. Animal models have shown that the 24-hour AUC/MIC ratio is the best predictor of bacterial killing *in vivo*, and the peak plasma concentration C_{max} /MIC ratio is important for the prevention of the emergence of resistance during treatment. A 24-hour AUC/MIC ratio of approximately 100 and a C_{max} /MIC ratio of 10 are usually the targets given for maximal clinical and bacteriological effects.

MIC data for ciprofloxacin were obtained from a report from the Clinical Microbiology Institute, Wilsonville, Oregon (2). Eight strains with various ciprofloxacin MICs were chosen for a PK/PD analysis. The strains and their MICs are shown in TABLE 5.

TABLE 5
MIC values (pH 7.3) of the pathogens commonly found in uUTIs

Organism	Strain	MIC ($\mu\text{g/mL}$)
<i>E. coli</i> ATCC 25922	Strain 1	0.016
<i>E. faecalis</i> ATCC 29212	Strain 2	1
<i>S. aureus</i> ATCC 29213	Strain 3	0.5
<i>E. coli</i> N9688	Strain 4	0.04*
<i>K. pneumoniae</i> N9189	Strain 5	0.016
<i>E. faecalis</i> ST12,296	Strain 6	>32
<i>S. saprophyticus</i> SP8822	Strain 7	0.5
<i>P. mirabilis</i> N9287	Strain 8	0.045*

* mean value of two tests

Figure 1 shows the mean plasma concentration curves from the absorption study for C-GR 500 mg (once daily) compared to C-IR 250 mg (twice daily) as seen in the absorption study on day 3.

Figure 1
 Mean Plasma Concentrations of C-GR and C-IR

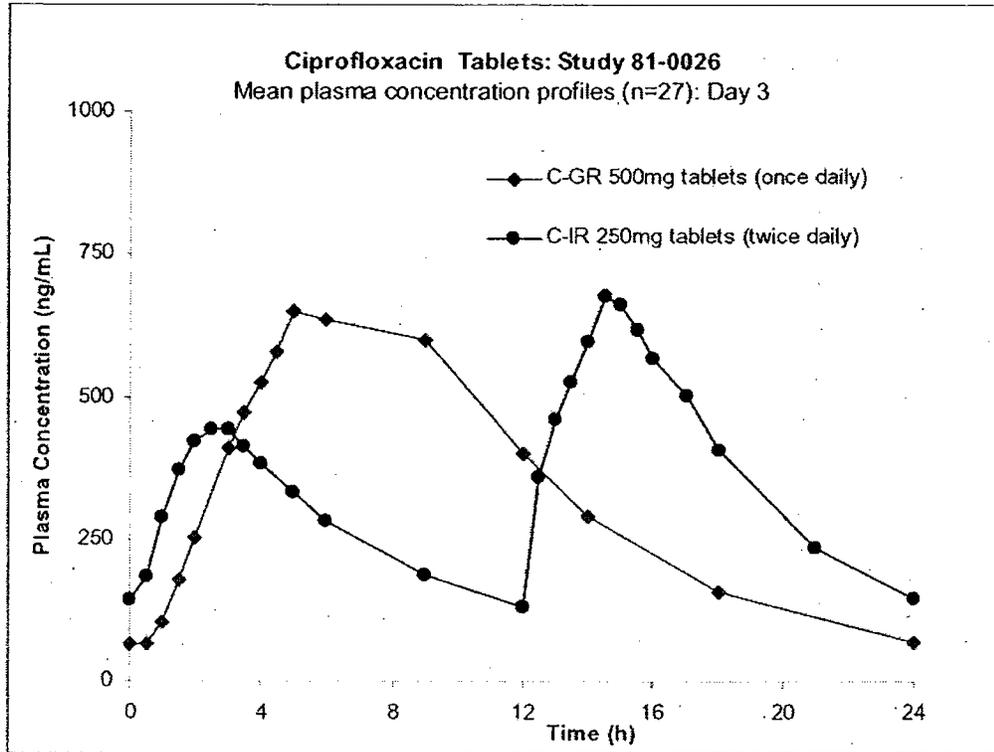


TABLE 6 shows the pharmacokinetic parameters of the two tablet formulations on day 3. The mean C_{max} values were calculated as the average from the individual C_{max} values and are not taken from the mean plasma concentration profiles shown in Figure 1. As seen in TABLE 6 the AUC values for the C-GR and C-IR treatments are almost identical on day 3.

TABLE 6
 Pharmacokinetic Parameters of C-GR and C-IR on Day 3

Treatment	AUC (0-24 hours) (ng.h/mL)	C_{max} (ng/mL)
C-GR 500 mg QD	7667.6	824.1
C-IR 250 mg BID	7834.6	934.1

The AUC/MIC ratios for C-GR and C-IR are presented in TABLE 7. Since the AUC values for both treatments are almost identical, the AUC/MIC values are also similar for each treatment. Therefore, the therapeutic effect of C-GR, when expressed as the AUC/MIC value, is basically equivalent to that seen with C-IR.

TABLE 7
 AUC/MIC Ratios for Selected uUTI Isolates at Day 3

Strain	MIC ($\mu\text{g/mL}$)	C-GR 500 mg QD	C-IR 250 mg BID
<i>E. coli</i> ATCC 25922	0.016	493.30	493.64
<i>E. faecalis</i> ATCC 29212	1	7.89	7.90
<i>S. aureus</i> ATCC 29213	0.5	15.79	15.80
<i>E. coli</i> N9688	0.04	175.39	175.52
<i>K. pneumoniae</i> N9189	0.016	493.30	493.64
<i>E. faecalis</i> ST12,296	>32	0.25	0.25
<i>S. saprophyticus</i> SP8822	0.5	15.79	15.80
<i>P. mirabilis</i> N9287	0.045	175.39	175.52

As seen in the above table the AUC/MIC ratio is below the targeted value of 100 as expected for the resistant strain of *E. faecalis* ST12,296 which has a MIC value of >32 $\mu\text{g/mL}$. The AUC/MIC ratio is also below the targeted value for three other strains with MICs of 0.5 -1.0 $\mu\text{g/mL}$. Since these values are based on plasma concentrations and not on the amount of drug available in the urine, the drug should still be effective for most of these strains.

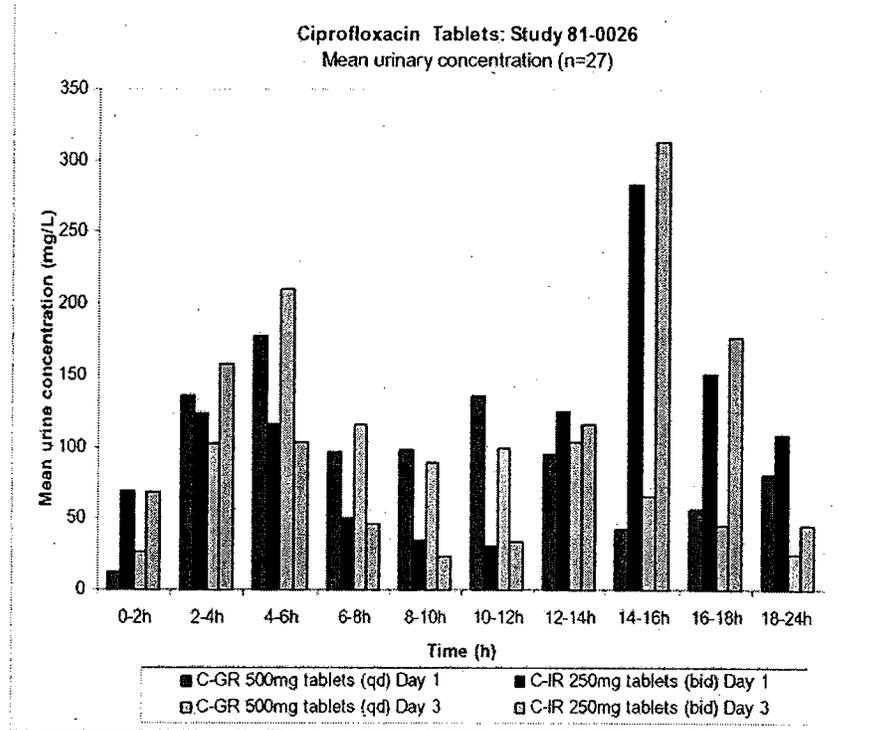
The C_{max} /MIC ratios for C-GR and C-IR are shown in TABLE 8. The C_{max} /MIC ratio for C-GR was similar to the C_{max} /MIC ratio for C-IR on day 3. Many of the ratios are below the targeted value of 10, but once again these values are based on plasma levels and not the amount of drug in the urine.

TABLE 8
 C_{max} /MIC Ratios for Selected uUTI Isolates at Day 3

Strain	MIC ($\mu\text{g/mL}$)	C-GR 500 mg QD	C-IR 250 mg BID
<i>E. coli</i> ATCC 25922	0.016	53.57	60.50
<i>E. faecalis</i> ATCC 29212	1	0.86	0.97
<i>S. aureus</i> ATCC 29213	0.5	1.71	1.94
<i>E. coli</i> N9688	0.04	19.05	21.51
<i>K. pneumoniae</i> N9189	0.016	53.57	60.50
<i>E. faecalis</i> ST12,296	>32	0.03	0.03
<i>S. saprophyticus</i> SP8822	0.5	1.71	1.94
<i>P. mirabilis</i> N9287	0.045	19.05	21.51

The observed mean urinary concentrations of ciprofloxacin in the 24-hour periods consisting of Day 1 and Day 3 from the two treatment groups are compared in Figure 2. The differences between the profile of the two treatments are clearly seen in this data presentation. Because of the formulation design of C-GR, the ciprofloxacin urinary concentrations are more homogeneous throughout the 24 hour periods.

Figure 2
 Mean Urinary Concentrations of C-GR and C-IR



The cumulative amounts of ciprofloxacin excreted in urine (Ae) after administration of C-GR and C-IR are summarized in TABLE 9. These data demonstrate the comparability of the two regimens in terms of total drug excreted within 24 hours.

TABLE 9
 Pharmacokinetic Parameters of C-GR and C-IR in Urine

Treatment	Day	Ae (geometric mean, mg)	Volume of urine excreted in 24 h (mean, mL)	Mean pH
C-GR 500 mg QD	1	134.4	2127	6.5
	3	131.8	2121	6.5
C-IR 250 mg BID	1	149.3	2069	6.5
	3	164.1	2311	6.5

The mean Ae/MIC ratios for the period of 24 hours for the C-GR and C-IR treatments are shown in TABLE 10. The observed Ae/MIC ratios for C-GR and C-IR are similar. The high Ae/MIC ratios on Days 1 and 3 of treatment indicate substantially higher urinary concentrations of ciprofloxacin than the MICs of the primary strains that cause UTI and predict good antibacterial activity at the site of infections for both C-GR and C-IR treatments.

TABLE 10
 The Mean Ae/MIC Ratios for C-GR and C-IR

Strain	MIC (µg/mL)	C-GR 500 mg QD		C-IR 250 mg BID	
		Day 1	Day 3	Day 1	Day 3
<i>E. coli</i> ATCC 25922	0.016	3455.7	5018.5	3914.9	4345.0
<i>E. faecalis</i> ATCC 29212	1	85.4	109.1	96.4	105.9
<i>S. aureus</i> ATCC 29213	0.5	180.8	222.8	203.3	222.8
<i>E. coli</i> N9688	0.04	1153.2	1771.4	1298.6	1449.8
<i>K. pneumoniae</i> N9189	0.016	1487.1	2344.8	1668.2	1867.9
<i>E. faecalis</i> ST12,296	>32	4.4	4.4	4.8	5.2
<i>S. saprophyticus</i> SP8822	0.5	233.5	233.5	231.4	252.3
<i>P. mirabilis</i> N9287	0.045	1083.0	1558.9	1226.4	1360.1

FACTORS AFFECTING *IN VITRO* SUSCEPTIBILITY TEST METHODS

Brown and Traczewski (2,3) evaluated the effects of environmental variables on the activity of ciprofloxacin against selected uUTI pathogens. These variables included the effects of pH, cations, type of test medium, inoculum size, and the relationship between the MIC (minimal inhibitory concentration) and MBC (minimal bactericidal concentration). The quality control strains of *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 (excluding pH effects), *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213, as well as one clinical strain each of *E. coli* N9688, *K. pneumoniae* N9189, *E. faecalis* ST12,296, *S. saprophyticus* SP8822, and *P. mirabilis* N9287 were tested for all environmental variables.

Effect of pH on *in vitro* Activity

The effects of media pH on the MICs of ciprofloxacin were performed by broth microdilution susceptibility tests according to NCCLS guidelines with the exception of pH, which ranged from pH 4.5 to pH 8.5 in 0.5 increments, including the standard pH of 7.8 (2). Results can be seen in TABLE 11.

TABLE 11
 Variations in Ciprofloxacin MICs ($\mu\text{g/mL}$) as a Function of Media pH

Organism	pH 4.5	pH 5.0	pH 5.5	pH 6.0	pH 6.5	pH 7.0	pH 7.3	pH 7.5	pH 8.0	pH 8.5
<i>E. coli</i> ATCC 25922	1	0.25	0.25	0.06	0.03	0.016	0.016	0.008	0.008	0.008
<i>E. faecalis</i> ATCC 29212	8	8	4	2	1	1	1	0.5	0.5	0.5
<i>S. aureus</i> ATCC 29213	8	4	2	0.5	0.25	0.25	0.5	0.25	0.5	0.5
<i>E. coli</i> N9688	4	1	2	0.12	0.06	0.03	0.03	0.03	0.016	0.016
<i>K. pneumoniae</i> N9189	4	1	2	0.12	0.03	0.03	0.016	0.016	0.016	0.016
<i>E. faecalis</i> ST12296	>32	>32	>32	>32	>32	>32	>32	>32	32	32
<i>S. saprophyticus</i> SP8822	NG	NG	2	0.5	0.5	0.5	0.5	0.5	0.5	0.5
<i>P. mirabilis</i> N9287	1	1	2	0.12	0.12	0.03	0.03	0.03	0.03	0.03

NG = no growth

Compared with the standard pH of 7.3, the MICs of ciprofloxacin for *E. coli*, *K. pneumoniae*, and *P. mirabilis* were within 1 to 2 doubling dilutions at pH 6.0 to 8.5. At lower pH values of 5.5, 5.0, and 4.5, the MIC increased up to 6 log₂ for *E. coli*, 8 log₂ for *K. pneumoniae*, and 5 log₂ for *P. mirabilis* at pH 4.5. For *E. faecalis* ATCC 29212, the MICs increased four- to eightfold at pH 5.5 and 4.5. The MICs for the clinical isolate of *E. faecalis*, which was resistant to ciprofloxacin, did not change over the pH range. The MICs of ciprofloxacin for *S. aureus* ATCC 29213 were within 1 doubling dilution at pH 6.0 to 8.5; however, MICs increased four- to 16-fold at pH 5.5 and 4.5. The increase in MICs at low pH was also seen for *S. saprophyticus* as the MICs increased fourfold at pH 5.5, although the organism did not grow at pH 5.0 and 4.5. At pH 6.0 to 8.5, the MICs were within one doubling dilution compared with the standard pH 7.3 result. This increase in MICs at pH \leq 5.5 is seen with most if not all of the fluoroquinolones.

Effect of Cations on *In vitro* Activity

Variations in cation concentrations on the MICs of ciprofloxacin were performed by broth microdilution susceptibility tests according to NCCLS guidelines with the exception of the magnesium and calcium concentrations, which ranged from 5 to 50 $\mu\text{g/mL}$ magnesium and 10 to 50 $\mu\text{g/mL}$ calcium (3). The standard cation content of 12.5 $\mu\text{g/mL}$ magnesium and 25 $\mu\text{g/mL}$ calcium was included as the control (shaded in TABLE). Results are shown in TABLE 12.

Compared with the standard cation content, the MICs of ciprofloxacin for *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa* were within one doubling dilution at all concentrations of calcium and magnesium. Slight increases in MICs occurred at a magnesium concentration of 50 µg/mL compared with MICs obtained at a magnesium concentration of 5 µg/mL for both *E. coli* isolates, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa*. The MICs for *E. faecalis* ATCC 29212 were twofold higher at a magnesium concentration of 50 µg/mL compared with lower concentrations and control. The clinical isolate of *E. faecalis* ST12296, which was resistant to ciprofloxacin, did not change over the range of cation concentrations. The MICs of ciprofloxacin for *S. aureus* ATCC 29213 were twofold higher at magnesium concentrations of 50 µg/mL compared with the control concentration. For *S. saprophyticus*, the MICs were unchanged at higher concentrations of magnesium and twofold lower than the control MICs at a magnesium concentration of 5 µg/mL.

High magnesium concentrations have been shown to affect all fluoroquinolones. The effect is usually seen around 9-10 mM (218.8 µg/mL – 243.1 µg/mL) of magnesium and may be due to competition between magnesium and the drugs for binding sites on the broken single-stranded DNA. The concentrations used in this experiment were not high enough to show much of a change in MICs due to higher magnesium concentrations. Unsupplemented Mueller-Hinton medium is 0.3 mM (7.3 µg/mL) in magnesium concentration and normal human serum is about 1.1 mM (26.7 µg/mL). Changes in activity due to magnesium only occur at much greater concentrations than those that would be seen clinically. Calcium has also been shown to effect quinolone activity but usually only at concentrations of 50 mM (2004 µg/mL) or more.

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Effect of Type of Test Medium on *In vitro* Activity

Tests to determine the influence of the type of media used to determine the MICs of ciprofloxacin were performed by broth microdilution susceptibility tests according to NCCLS guidelines (3). MICs obtained using brain heart infusion broth (BHIB) and IsoSensitest broth (ISB) were compared with MICs produced by the NCCLS standard cation-adjusted Mueller-Hinton broth (CAMHB). Results are shown in TABLE 13.

TABLE 13
 Effects of Media Type on Ciprofloxacin MICs

Organism	Ciprofloxacin MICs (µg/mL)		
	CAMHB	BHIB	ISB
<i>E. coli</i> ATCC 25922	0.016	0.008	0.016
<i>P. aeruginosa</i> ATCC 27853	0.25	0.12	0.25
<i>E. faecalis</i> ATCC 29212	0.5	0.5	1
<i>S. aureus</i> ATCC 29213	0.5	0.5	0.5
<i>K. pneumoniae</i> N9189	0.03	0.016	0.03
<i>P. mirabilis</i> N9287	0.03	0.03	0.03
<i>E. coli</i> N9688	0.03	0.016	0.03
<i>E. faecalis</i> ST12296	>32	>32	>32

CAMHB = cation-adjusted Mueller-Hinton broth

BHIB = Brain heart infusion broth

ISB = IsoSensitest broth

For *Pseudomonas aeruginosa*, MICs on brain heart infusion broth (BHIB) were fourfold lower than those obtained with cation-adjusted Mueller-Hinton broth (CAMHB) and twofold lower with IsoSensitest broth (ISB). Similarly, MICs obtained with ISB for *Enterococcus faecalis* ATCC 29212 were twofold higher than those obtained with either CAMHB or BHIB. The remaining tests on BHIB and ISB yielded MICs equal to or within one doubling dilution of those obtained using CAMHB. For most fluoroquinolones the type of media used makes little difference in the MICs obtained.

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Effect of Inoculum Size

The effects of inoculum size on the MICs of ciprofloxacin were evaluated by broth microdilution susceptibility testing according to NCCLS guidelines with the exception of the inoculum size, which ranged from 10^3 to 10^7 CFU/mL (3). The NCCLS guideline requires an inoculum of 10^5 CFU/mL. Results are shown in TABLE 14.

TABLE 14
 Effects of Variations in Inoculum Size on Ciprofloxacin MICs

Organism	Ciprofloxacin MICs ($\mu\text{g/mL}$)				
	10^3 CFU/mL	10^4 CFU/mL	10^5 CFU/mL	10^6 CFU/mL	10^7 CFU/mL
<i>E. coli</i> ATCC 25922	0.016	0.016	0.016	0.016	0.03
<i>P. aeruginosa</i> ATCC 27843	0.25	0.25	0.25	0.5	0.5
<i>E. faecalis</i> ATCC 29212	0.5	0.5	0.5	1	1
<i>S. aureus</i> ATCC 29213	0.25	0.25	0.5	1	1
<i>K. pneumoniae</i> N9189	0.016	0.016	0.03	0.03	0.03
<i>P. mirabilis</i> N9287	0.016	0.03	0.03	0.06	0.12
<i>E. coli</i> N9688	0.03	0.03	0.03	0.03	0.03
<i>S. saprophyticus</i> SP8822	0.25	0.25	0.5	0.5	1
<i>E. faecalis</i> ST12296	32	>32	>32	>32	>32

The size of the inoculum had little effect on MICs for both isolates of *E. coli* and for *K. pneumoniae*. For *P. mirabilis*, a two- to fourfold increase in MICs occurred at an inoculum of 10^6 and 10^7 CFU/mL compared with an inoculum of 10^5 CFU/mL. The MICs for *P. aeruginosa* increased twofold at inocula of 10^6 and 10^7 CFU/mL. The MICs for *S. aureus* ATCC 29213 and *E. faecalis* 29212 also increased twofold at these higher inocula. The MICs of ciprofloxacin for *S. saprophyticus* increased twofold at an inoculum of 10^7 CFU/mL and decreased twofold at inocula of 10^4 and 10^3 CFU/mL. As seen with most fluoroquinolones most MICs were within one doubling dilution of the MIC seen at 10^5 CFU/mL for all inocula, high inocula of around 10^7 CFU/mL can cause an increase in MICs for some fluoroquinolones.

RELATIONSHIP BETWEEN THE MIC AND MBC

The relationship between the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of ciprofloxacin for each organism was determined by broth microdilution performed according to NCCLS guidelines (3). MBCs were determined by culturing all wells with no discernible growth. All of the MBC were either the same as the MICs or only one dilution higher than the MICs for all organisms tested. Ciprofloxacin appears to be bactericidal for all the tested organisms. Most other fluoroquinolones are bactericidal for these organisms. Results are shown in TABLE 15.

TABLE 15
Minimum Inhibitory Concentration/Minimum Bactericidal Concentration

Organism	Ciprofloxacin MIC ($\mu\text{g/mL}$)	Ciprofloxacin MBC ($\mu\text{g/mL}$)
<i>E. coli</i> ATCC 25922	0.016	0.016
<i>P. aeruginosa</i> ATCC 27853	0.25	0.5
<i>E. faecalis</i> ATCC 29212	0.5	1
<i>S. aureus</i> ATCC 29213	0.5	1
<i>K. pneumoniae</i> N9189	0.03	0.03
<i>P. mirabilis</i> N9287	0.03	0.03
<i>E. coli</i> N9688	0.03	0.03
<i>S. saprophyticus</i> SP8822	0.5	0.5
<i>E. faecalis</i> ST12296	>32	>32

SUSCEPTIBILITY TEST METHODS ANALYSIS

Quality Control Parameters

Standardized susceptibility testing requires the use of laboratory control microorganisms to control technical aspects of a laboratory's methodology. The parameters for testing ciprofloxacin against the Enterobacteriaceae, staphylococci, and enterococci by a dilution method (agar or broth) have been established and published in NCCLS Document M7-A6. Standard ciprofloxacin powder should provide the following established MIC ($\mu\text{g/mL}$) ranges: *E. faecalis* ATCC 29212, 0.25-2.0; *E. coli* ATCC 25922, 0.004-0.015; *S. aureus* ATCC 29213, 0.12-0.5.

For Enterobacteriaceae and staphylococci, quality control ranges for susceptibility testing by the standardized disk diffusion method with the 5- μg ciprofloxacin disk have been established and published in NCCLS Document M2-A8. The 5- μg ciprofloxacin disk, when used on the appropriate standardized medium, should provide zone diameters (mm) for the following laboratory test quality control strains: *E. coli* ATCC 25922, 30-40; *S. aureus* ATCC 25923, 22-30.

In Vitro Test Methods

Focus Technologies (Focus) and Clinical Microbiology Institute (CMI) conducted studies to determine the correlation between MICs obtained from broth microdilution tests and corresponding disk zone diameters obtained from disk diffusion tests using a 5- μ g ciprofloxacin disk (4,5). In both studies tests were performed according to NCCLS guidelines. Both studies evaluated recent isolates in the organism groups Enterobacteriaceae, staphylococci, and enterococci that encompassed the common uropathogens associated with uUTI. All of the 800 isolates in the Focus study were collected from patients with uUTI and most were recent isolates (2003). The 862 isolates in the CMI study comprised 68.3% recent clinical isolates and a challenge set of phenotypic resistance patterns (31.7%). Levofloxacin was the control antimicrobial agent and the ATCC quality control strains were included on each day of testing.

The susceptibilities of the major uUTI pathogens to ciprofloxacin from each of the two studies are presented in TABLES 16 and 17. The ranges of MICs for the organism groups, as well as the individual species, were similar in both studies. The MIC₉₀s also were similar for the Enterobacteriaceae and all enterococci; however, the MIC₉₀ for all staphylococci in the study conducted by CMI was 4 μ g/mL, while the MIC₉₀ for all staphylococci in the Focus study was 64 μ g/mL. In the CMI study, analysis of MICs of ciprofloxacin for methicillin-susceptible and -resistant isolates showed that the MIC₉₀ for resistant isolates was >16 μ g/mL, while the MIC₉₀ for susceptible isolates was 0.5 μ g/mL. The MIC₉₀ for all enterococci was >16 μ g/mL in both studies. Subsets of isolates of *E. faecalis* in the CMI study showed that the MIC₅₀ (2.0 μ g/mL) and MIC₉₀ (>16 μ g/mL) for vancomycin-susceptible isolates and vancomycin intermediate/resistant isolates were identical; thus, vancomycin resistance did not affect ciprofloxacin MICs in this species. The MIC₉₀s for the other major uUTI pathogens were \leq 1 μ g/mL in both studies except for *Klebsiella pneumoniae* in the CMI study, for which the MIC₉₀ was 2.0 μ g/mL; 88.5% of these isolates were susceptible at an MIC of \leq 0.5 μ g/mL. Other isolates of Enterobacteriaceae that were tested included *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Providencia rettgeri*, *Providencia stuartii*, *Proteus vulgaris*, and *Serratia marcescens*. All MIC₉₀s were \leq 1 μ g/mL, except for *K. oxytoca* (>16 μ g/mL), *P. rettgeri* (2 μ g/mL), and *P. stuartii* (>16 μ g/mL). The results from these two studies were in good agreement with one another and with recent surveillance data (TSN®-Database).

TABLE 16
 Ciprofloxacin Susceptibility of Selected uUTI Pathogens (CMI Study)

Organism	Number Tested	Range ($\mu\text{g/mL}$)	MIC ₅₀ ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)
Enterobacteriaceae	609	0.008->16	0.03	0.5
<i>E. coli</i>	201	0.008->16	0.016	0.03
<i>K. pneumoniae</i>	61	0.008-16	0.03	2
<i>P. mirabilis</i>	62	0.015->16	0.03	0.12
All Enterococci	124	0.5->16	16	>16
<i>E. faecalis</i>	102	0.5->16	1-2	>16
All Staphylococci	129	0.12->16	0.25	4
<i>S. saprophyticus</i>	16	0.5	0.5	0.5

TABLE 17
 Ciprofloxacin Susceptibility of Selected uUTI Pathogens (Focus Study)

Organism	Number Tested	Range ($\mu\text{g/mL}$)	MIC ₅₀ ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)
Enterobacteriaceae	600	0.004->128	0.015	0.25
<i>E. coli</i>	351	0.004->128	0.015	0.03
<i>K. pneumoniae</i>	95	0.004-128	0.03	1
<i>P. mirabilis</i>	93	0.015->128	0.03	1
All Enterococci	100	0.12->128	1	64
<i>E. faecalis</i>	90	0.12-128	1	64
All Staphylococci	100	0.06->128	0.25	64
<i>S. saprophyticus</i>	18	0.25-0.5	0.5	0.5

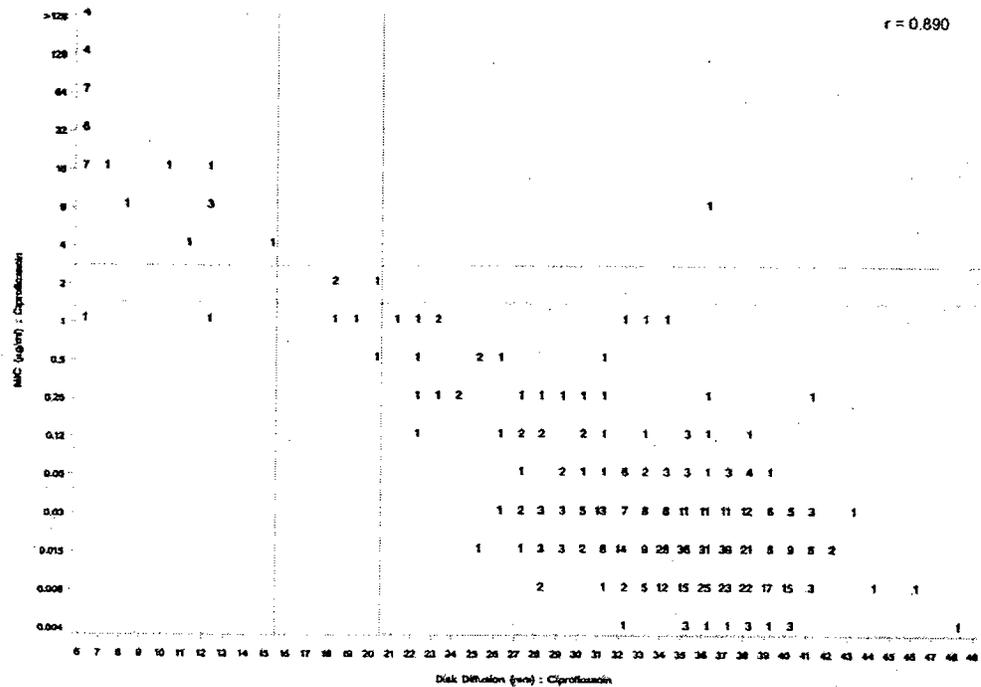
Enterobacteriaceae

Regression analyses for the Enterobacteriaceae are shown in Figures 3 and 4. Based on the population distribution and pharmacokinetic/pharmacodynamic parameters, an MIC of $\leq 1 \mu\text{g/mL}$ and a corresponding zone diameter of $\geq 21 \text{ mm}$ appear to be appropriate for a breakpoint of susceptible. If we allow one dilution for an Intermediate category ($2 \mu\text{g/mL}$) then Resistance would be defined by an MIC of $\geq 4 \mu\text{g/mL}$. The corresponding zone diameter is $\leq 15 \text{ mm}$.

In Figure 3, the correlation coefficient for 600 isolates of Enterobacteriaceae is 0.89. MICs of $\leq 1 \mu\text{g/mL}$ (S) and $\geq 4 \mu\text{g/mL}$ (R) and zone diameters of $\geq 21 \text{ mm}$ (S) and $\leq 15 \text{ mm}$ (R) produced one (0.2%) very major errors, two (0.3%) major errors, and three (0.5%) minor errors. The very major error was due to an isolate of *Enterobacter cloacae* that had an MIC of $8 \mu\text{g/mL}$ and a zone diameter of 36 mm . The major errors were due to one isolate each of *Escherichia coli* (MIC, $1 \mu\text{g/mL}$; zone diameter, 6 mm) and *Klebsiella pneumoniae* (MIC, $1 \mu\text{g/mL}$; zone diameter 12 mm).

The correlation coefficient for 609 isolates of Enterobacteriaceae in Figure 4 was 0.962. MICs of $\leq 1 \mu\text{g/mL}$ (S) and $\geq 4 \mu\text{g/mL}$ (R) and corresponding zone diameters of 21 mm (S) and ≤ 15 mm (R) produced no (0%) very major errors of major errors and six (1%) minor errors.

Figure 3
 MIC vs. Zone Diameters for Enterobacteriaceae/Focus
 All Enterobacteriaceae (n = 600)



	n (%)	
Very major errors	Major errors	Minor errors
1 (0.2%)	2 (0.3%)	3 (0.5%)

Figure 4
 MIC vs. Zone Diameter for Enterobacteriaceae/CMI
 All Gram-Negative Strains Combined (n = 609)

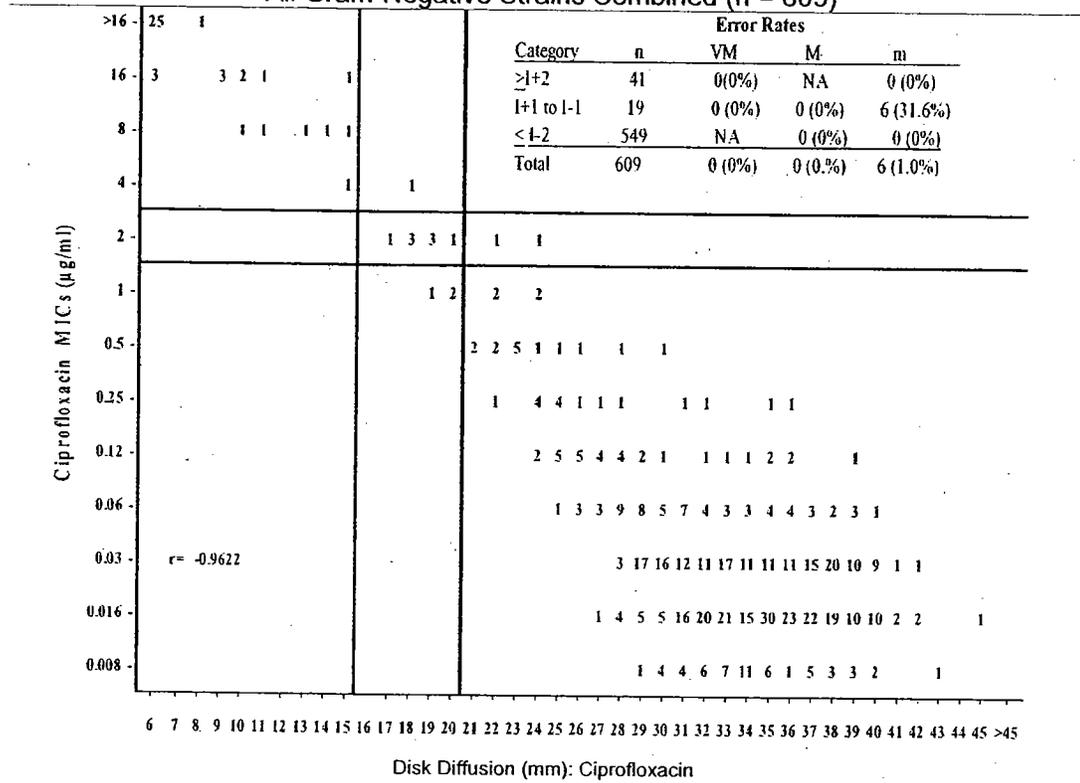


TABLE 18 shows the MIC range, MIC₅₀, and MIC₉₀, and % susceptible, intermediate, or resistant to ciprofloxacin and levofloxacin for the Enterobacteriaceae in the Focus study. TABLE 19 shows the same information for the CMI study.

TABLE 18
 MIC Data for Enterobacteriaceae (Focus Study)

Organism	Total tested	MIC (µg/mL)			n (%) S	n (%) I	n (%) R
		Range	MIC ₅₀	MIC ₉₀			
<i>Enterobacteriaceae</i>							
Ciprofloxacin	600	0.004->128	0.015	0.25	559 (93.2)	3 (0.5)	38 (6.3)
Levofloxacin	600	0.008-128	0.03	0.5	563 (93.8)	2 (0.3)	35 (5.8)
<i>Escherichia coli</i>							
Ciprofloxacin	351	0.004->128	0.015	0.03	334 (95.2)	0 (0)	17 (4.6)
Levofloxacin	351	0.008-128	0.03	0.06	334 (95.2)	0 (0)	17 (4.8)
<i>Klebsiella pneumoniae</i>							
Ciprofloxacin	95	0.004-128	0.03	1	88 (92.6)	1 (1.1)	6 (6.3)
Levofloxacin	95	0.015-64	0.06	2	90 (94.7)	0 (0)	5 (5.3)
<i>Proteus mirabilis</i>							
Ciprofloxacin	93	0.015->128	0.03	1	85 (91.4)	1 (1.1)	7 (7.5)
Levofloxacin	93	0.015-128	0.06	1	86 (92.5)	1 (1.1)	6 (6.5)

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TABLE 19
 MIC Data for Enterobacteriaceae (CMI Study)

Organism	Total tested	MIC ($\mu\text{g/mL}$)			(% S)	(% I)	(% R)
		Range	MIC ₅₀	MIC ₉₀			
All Gram-negatives							
Ciprofloxacin	609	0.008->16	0.03	0.5	91.3	1.6	7.1
Levofloxacin	609	0.015->16	0.06	1	91.8	0.8	5.7
<i>Citrobacter freundii</i>							
Ciprofloxacin	20	0.008-2	0.03	0.12	95.0	5.0	0.0
Levofloxacin	20	0.03-4	0.12	0.25	95.0	5.0	0.0
<i>Citrobacter koseri</i>							
Ciprofloxacin	41	0.008->16	0.008	0.016	97.6	0.0	2.4
Levofloxacin	41	0.015-8	0.03	0.06	97.6	0.0	2.4
<i>Enterobacter aerogenes</i>							
Ciprofloxacin	21	0.008-1	0.06	0.5	100.0	0.0	0.0
Levofloxacin	21	0.06-0.03	0.12	0.5	100.0	0.0	0.0
<i>Enterobacter cloacae</i>							
Ciprofloxacin	20	0.008-0.03	0.03	0.03	100.0	0.0	0.0
Levofloxacin	20	0.03-0.12	0.06	0.06	100.0	0.0	0.0
<i>Escherichia coli</i>							
Ciprofloxacin	201	0.008->16	0.016	0.03	96.5	0.0	3.5
Levofloxacin	201	0.03-16	0.06	0.06	96.5	0.0	3.5
<i>E. coli</i> ESBL+							
Ciprofloxacin	20	0.015->16	0.5	>16	50.0	0.0	50.0
Levofloxacin	20	0.03->16	1	>16	50.0	0.0	50.0
<i>Klebsiella oxytoca</i>							
Ciprofloxacin	19	0.008->16	0.03	>16	78.9	0.0	21.1
Levofloxacin	19	0.06->16	0.06	>16	78.9	0.0	21.1
<i>Klebsiella pneumoniae</i>							
Ciprofloxacin	61	0.008-16	0.03	2	88.5	3.3	8.2
Levofloxacin	61	0.03->16	0.06	4	88.5	3.3	8.2
<i>K. pneumoniae</i> ESBL+							
Ciprofloxacin	21	0.03-32	0.5	8	81.0	4.8	14.3
Levofloxacin	21	0.06-32	1	16	85.7	0.0	14.3
<i>Morganella morganii</i>							
Ciprofloxacin	20	0.008-8	0.016	1	90.0	0.0	10.0
Levofloxacin	20	0.03-8	0.06	2	90.0	0.0	10.0
<i>Proteus mirabilis</i>							
Ciprofloxacin	62	0.015->16	0.03	0.12	96.8	1.6	1.6
Levofloxacin	62	0.04->16	0.06	0.12	98.4	0.0	1.6
<i>Providencia rettgeri</i>							
Ciprofloxacin	21	0.015-4	0.06	2	85.7	0.0	14.3
Levofloxacin	21	0.12-8	0.25	8	85.7	0.0	14.3
<i>Providencia stuartii</i>							
Ciprofloxacin	21	0.008->16	2	>16	47.6	14.3	38.1
Levofloxacin	21	0.06->16	2	>16	52.4	9.5	38.1

TABLE 19 (Continued)
 MIC Data for Enterobacteriaceae (CMI Study)

Organism	Total tested	MIC ($\mu\text{g/mL}$)			(% S)	(% I)	(% R)
		Range	MIC ₅₀	MIC ₉₀			
<i>Proteus vulgaris</i>							
Ciprofloxacin	21	0.015-0.12	0.03	0.03	100.0	0.0	0.0
Levofloxacin	21	0.06-0.25	0.06	0.06	100.0	0.0	0.0
<i>Shigella</i> species							
Ciprofloxacin	10	0.015->16	0.016	0.5	90.0	0.0	10.0
Levofloxacin	10	0.03->16	0.06	0.5	90.0	0.0	10.0
<i>Salmonella</i> species							
Ciprofloxacin	10	0.008-0.25	0.03	0.03	100.0	0.0	0.0
Levofloxacin	10	0.015-0.5	0.06	0.12	100.0	0.0	0.0
<i>Serratia marcescens</i>							
Ciprofloxacin	20	0.06-0.5	0.12	0.25	100.0	0.0	0.0
Levofloxacin	20	0.12-1	0.25	0.5	100.0	0.0	0.0

A histogram depicting the frequency of distribution by MICs for the Enterobacteriaceae in the Focus study is presented in Figure 5. An MIC of $\leq 1 \mu\text{g/mL}$ inhibited 93.2% of the isolates. The MIC₅₀ was 0.015 $\mu\text{g/mL}$ and the MIC₉₀ was 0.25 $\mu\text{g/mL}$. The histogram in Figure 6 shows the distribution of Enterobacteriaceae in the CMI study. Although the MICs in this study tended to be one doubling dilution higher than those in the Focus study, $\leq 1 \mu\text{g/mL}$ inhibited 91.3% of the isolates. The MIC₅₀ was 0.03 $\mu\text{g/mL}$ and the MIC₉₀ was 0.5 $\mu\text{g/mL}$. This breakpoint is, however, based on plasma levels of the drug and is not really appropriate for a drug that will be used only for uncomplicated urinary tract infections.

Figure 5
 Distribution of MICs of Ciprofloxacin and Levofloxacin/Focus Study
 All Enterobacteriaceae (n = 600)

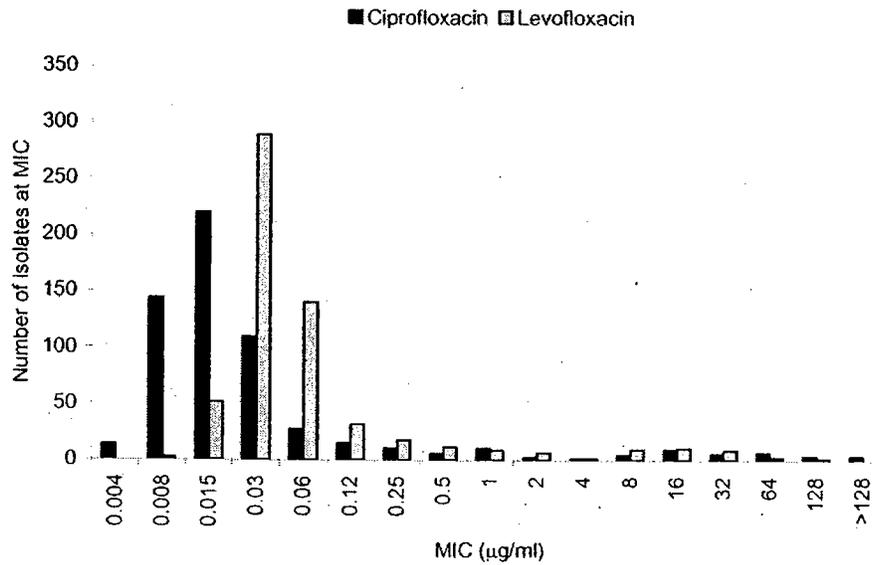
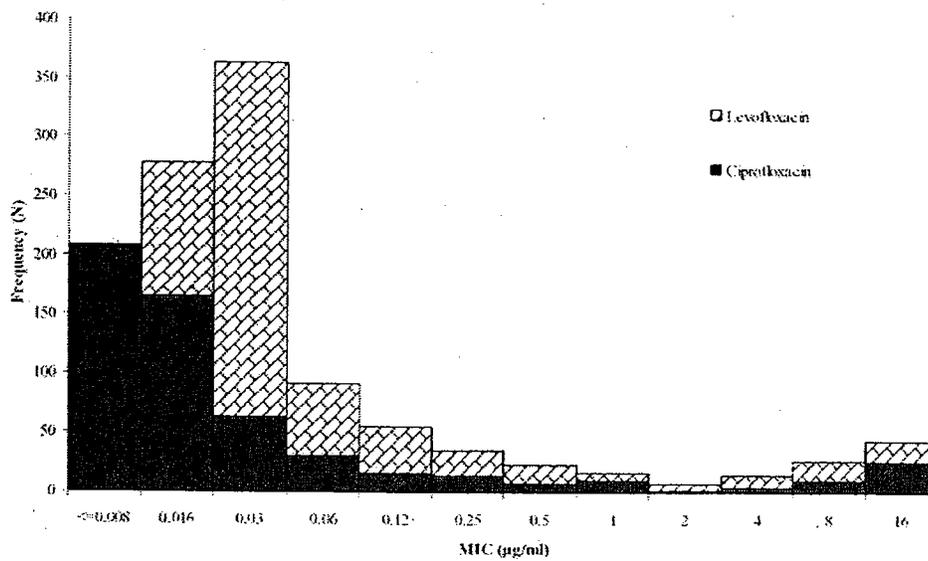


Figure 6
 Distribution of MICs of Ciprofloxacin and Levofloxacin/CMI Study
 All Enterobacteriaceae (n = 609)



Staphylococci

Regression analyses for the staphylococci are presented in Figures 7 and 8. Based on the population distribution and pharmacokinetic/pharmacodynamic parameters, an MIC of $\leq 1 \mu\text{g/mL}$ and a corresponding zone diameter of $\geq 21 \text{ mm}$ appear to be appropriate for a breakpoint of susceptible. If we allow one dilution for an Intermediate category ($2 \mu\text{g/mL}$) then Resistance would be defined by an MIC of $\geq 4 \mu\text{g/mL}$. The corresponding zone diameter is $\leq 15 \text{ mm}$.

In Figure 7, the correlation coefficient for 100 isolates of staphylococci in the Focus study was 0.949. The scattergram showed that most isolates had a MIC $\leq 1 \mu\text{g/mL}$ and a zone diameter of $\geq 21 \text{ mm}$. MICs of $\leq 1 \mu\text{g/mL}$ (Susceptible) and $\geq 4 \mu\text{g/mL}$ (Resistant) and corresponding zone diameters of $\geq 21 \text{ mm}$ (S) and $\leq 15 \text{ mm}$ (R) produced no very major errors, no major errors, and 2 (2%) minor errors.

In Figure 8, the correlation coefficient for 129 isolates of staphylococci in the CMI study was 0.775. MICs of $\leq 1 \mu\text{g/mL}$ (Susceptible) and $\geq 4 \mu\text{g/mL}$ (Resistant) and corresponding zone diameters of $\geq 21 \text{ mm}$ (S) and $\leq 15 \text{ mm}$ (R) produced no very major or major errors and 6 (4.7%) minor errors.

Figure 7
 MIC vs. Zone Diameter for Staphylococci/Focus Study
 All Staphylococci (n = 100)

Very major errors	Major errors	Minor errors
0	0	2 (2%)

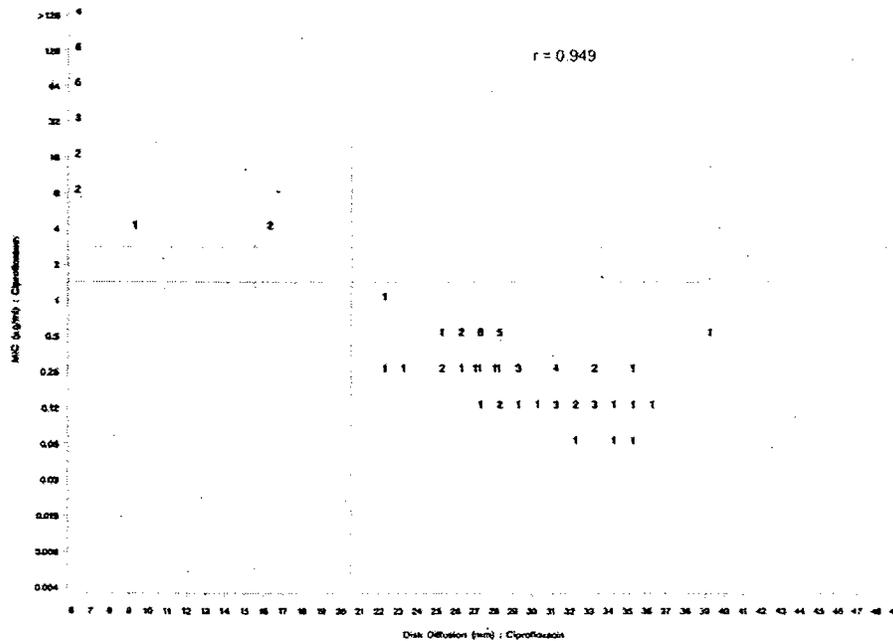


Figure 8
 MIC vs. Zone Diameter for Staphylococci/CMI Study
 All Staphylococci (n = 129)

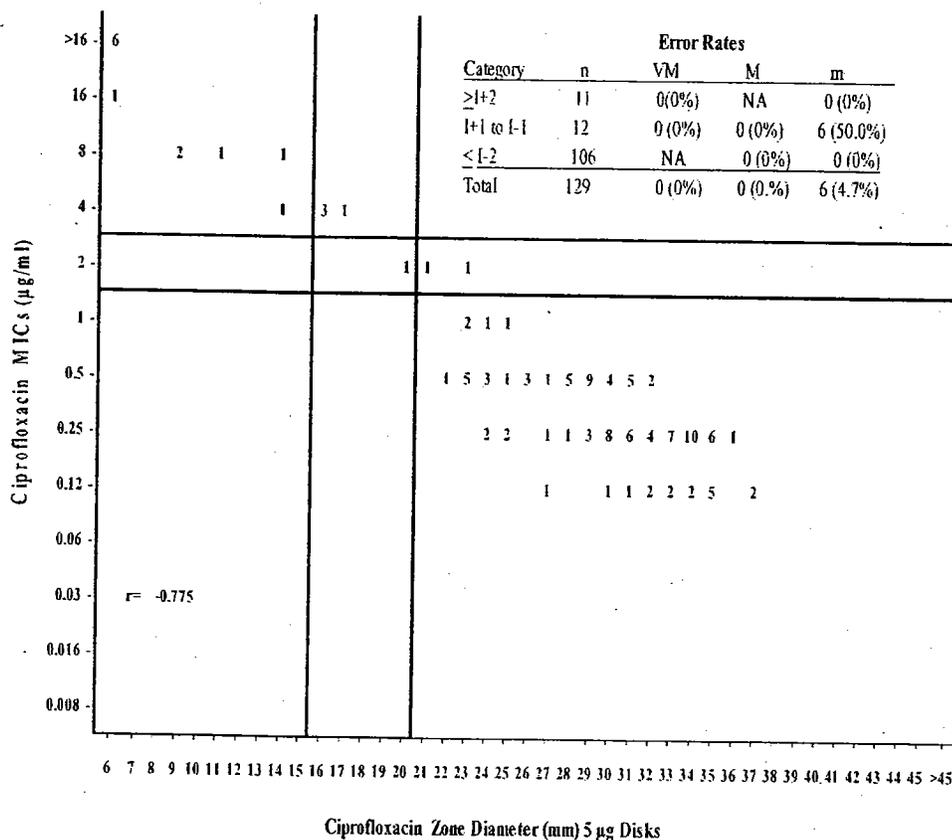


TABLE 20 shows the MIC range, MIC₅₀, and MIC₉₀, and % susceptible, intermediate, or resistant to ciprofloxacin and levofloxacin for the staphylococci in the Focus study. TABLE 21 shows the same information for the CMI study.

TABLE 20
 MIC Data for Staphylococci (Focus Study)

Organism	Total tested	MIC (µg/mL)			n (%) S	n (%) I	n (%) R
		Range	MIC ₅₀	MIC ₉₀			
<i>Staphylococci</i>							
Ciprofloxacin	100	0.06->128	0.25	64	74 (74.0)	0 (0)	26 (26.0)
Levofloxacin	100	0.06->128	0.5	32	75 (75.0)	5 (5.0)	20 (20.0)
<i>S. saprophyticus</i>							
Ciprofloxacin	18	0.25-0.5	0.5	0.5	18 (100)	0 (0)	0 (0)
Levofloxacin	18	0.25-0.5	0.5	0.5	18 (100)	0 (0)	0 (0)

TABLE 21
 MIC Data for Staphylococci (CMI Study)

Organism	Total tested	MIC (µg/mL)			(% S)	(% I)	(% R)
		Range	MIC ₅₀	MIC ₉₀			
All Staphylococci							
Ciprofloxacin	129	0.12->16	0.25	4	85.3	2.3	12.4
Levofloxacin	129	0.12->16	0.25	4	87.6	4.7	7.8
All Methicillin-Resistant							
Ciprofloxacin	57	0.12->16	0.5	>16	71.9	3.5	24.6
Levofloxacin	57	0.12->16	0.5	16	75.4	7.1	17.5
All Methicillin-Susceptible							
Ciprofloxacin	72	0.12-8	0.25	0.5	95.8	1.4	2.8
Levofloxacin	72	0.12-4	0.25	0.5	97.2	2.8	0.0
<i>S. aureus</i> Methicillin-R							
Ciprofloxacin	12	0.12-2	0.5	0.5	91.7	8.3	0.0
Levofloxacin	12	0.12-0.5	0.25	0.5	100.0	0.0	0.0
<i>S. aureus</i> Methicillin-S							
Ciprofloxacin	29	0.12-2	0.5	1	96.6	3.4	0.0
Levofloxacin	29	0.12-1	0.25	0.5	100.0	0.0	0.0
<i>S. aureus</i> Methicillin-R Vancomycin-Intermediate							
Ciprofloxacin	3	>16	NA	NA	0.0	0.0	100.0
Levofloxacin	3	>16	NA	NA	0.0	0.0	100.0
All Coagulase-Negative							
Ciprofloxacin	85	0.12->16	0.25	4	83.5	1.2	15.3
Levofloxacin	85	0.12-16	0.25	4	84.7	7.1	8.2
<i>S. epidermidis</i> Methicillin-R							
Ciprofloxacin	21	0.12->16	0.25	8	66.7	0.0	33.3
Levofloxacin	21	0.12-16	0.25	8	66.7	19.0	14.3
<i>S. epidermidis</i> Methicillin-S							
Ciprofloxacin	37	0.12-8	0.25	0.5	94.6	0.0	5.4
Levofloxacin	37	0.12-4	0.25	0.5	94.6	5.4	0.0
All <i>S. haemolyticus</i>							
Ciprofloxacin	11	0.25->16	0.5	>16	54.6	9.1	36.4
Levofloxacin	11	0.12->16	0.5	16	63.6	0.0	36.4
<i>S. haemolyticus</i> Methicillin-R							
Ciprofloxacin	6	0.25->16	NA	NA	16.7	16.7	66.7
Levofloxacin	6	0.25-16	NA	NA	33.3	0.0	66.7
<i>S. haemolyticus</i> Methicillin-S							
Ciprofloxacin	5	0.25-0.5	NA	NA	100.0	0.0	0.0
Levofloxacin	5	0.12-0.5	NA	NA	100.0	0.0	0.0
All <i>S. saprophyticus</i>							
Ciprofloxacin	16	0.5	0.5	0.5	100.0	0.0	0.0
Levofloxacin	16	0.5-1	0.5	1	100.0	0.0	0.0
<i>S. saprophyticus</i> Methicillin-R							
Ciprofloxacin	15	0.25-0.5	0.5	0.5	100.0	0.0	0.0
Levofloxacin	15	0.12-0.5	0.5	1	100.0	0.0	0.0

A histogram presenting the frequency of distribution by MIC for the staphylococci in the Focus study is presented in Figure 9. The bimodal population in the histogram is apparent and a MIC of 1 $\mu\text{g}/\text{mL}$ separated the susceptible and resistant isolates. A MIC of ≤ 1 $\mu\text{g}/\text{mL}$ inhibited 74% of the isolates; the MIC_{50} was 0.25 $\mu\text{g}/\text{mL}$ and the MIC_{90} was 64 $\mu\text{g}/\text{mL}$. Figure 10 shows the distribution of staphylococci in the CMI study. Similar to the Focus study, a bimodal population was seen. A MIC of ≤ 1 $\mu\text{g}/\text{mL}$ inhibited 85.3% of the isolates. The MIC_{50} was 0.25 $\mu\text{g}/\text{mL}$ and the MIC_{90} was 4 $\mu\text{g}/\text{mL}$. Once again these breakpoints are based on plasma levels of the drug and are probably not appropriate for a drug that will be used only for uncomplicated urinary tract infections.



Figure 9
 Distribution of MICs of Ciprofloxacin and Levofloxacin/Focus Study
 All Staphylococci (n = 100)

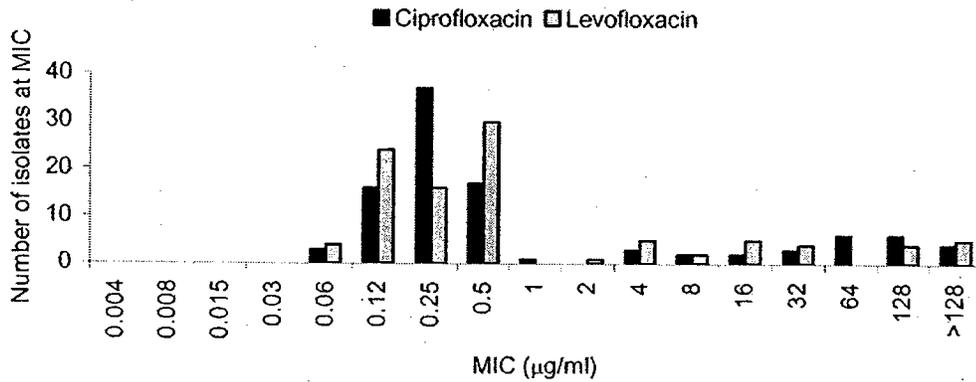
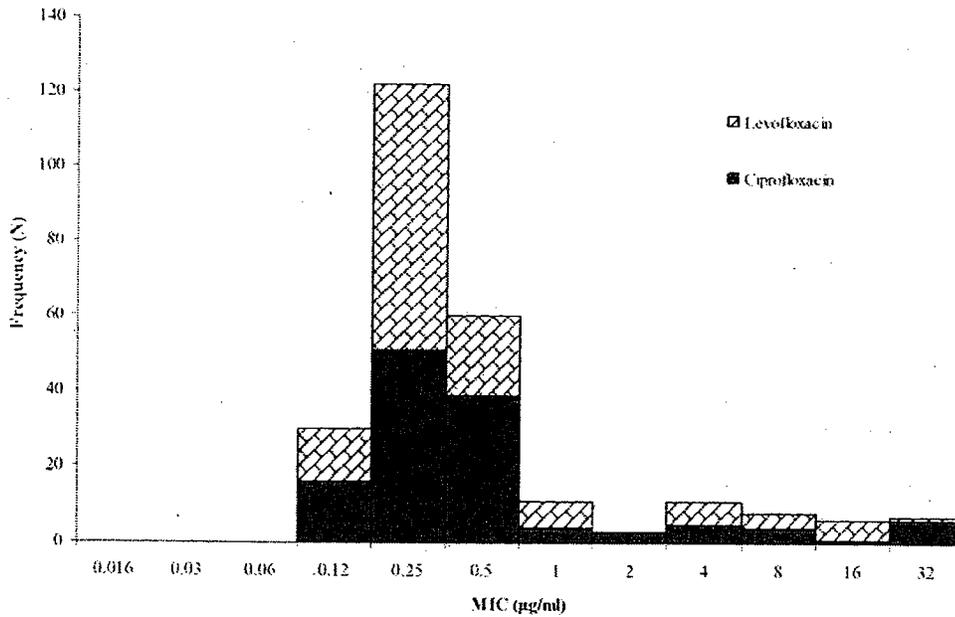


Figure 10
 Distribution of MICs of Ciprofloxacin and Levofloxacin/CMI Study
 All Staphylococci (n = 129)



Enterococci

Regression analyses for the enterococci are presented in Figure 11 and Figure 12. A MIC of ≤ 1 $\mu\text{g/mL}$ and a corresponding zone diameter of ≥ 21 mm were selected for a breakpoint of susceptible in both regression analyses based on pharmacokinetic/pharmacodynamic parameters and by population distribution. If we allow one dilution for an Intermediate category (2 $\mu\text{g/mL}$) then Resistance would be defined by an MIC of ≥ 4 $\mu\text{g/mL}$. The corresponding zone diameter is ≤ 15 mm.

In Figure 11, the correlation coefficient for 100 isolates of enterococci in the Focus study was 0.909. Although a zone diameter of 21 mm did identify susceptible isolates at MIC ≤ 1 $\mu\text{g/mL}$, this breakpoint also split the MIC susceptible isolates and shifted them into the Intermediate category. MICs of ≤ 1 $\mu\text{g/mL}$ (Susceptible) and ≥ 4 $\mu\text{g/mL}$ (Resistant) and corresponding zone diameters of ≥ 21 mm (S) and ≤ 15 mm (R) produced no very major errors, one (1%) major errors, and 25 (25%) minor errors.

In Figure 12, the correlation coefficient for 124 isolates of enterococci in the CMI study was 0.992. Again, an MIC of 1 $\mu\text{g/mL}$ and a zone diameter of 21 mm separated susceptible and resistant populations, although the zone diameter of 21 mm shifted otherwise susceptible isolates into the Intermediate category. MICs of ≤ 1 $\mu\text{g/mL}$ (Susceptible) and ≥ 4 $\mu\text{g/mL}$ (Resistant) and corresponding zone diameters of ≥ 21 mm (S) and ≤ 15 mm (R) produced no very major or major errors and 18 (14.5%) minor errors.

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Figure 11
 MIC vs. Zone Diameter for Ciprofloxacin/Focus Study
 All Enterococci (n = 100)

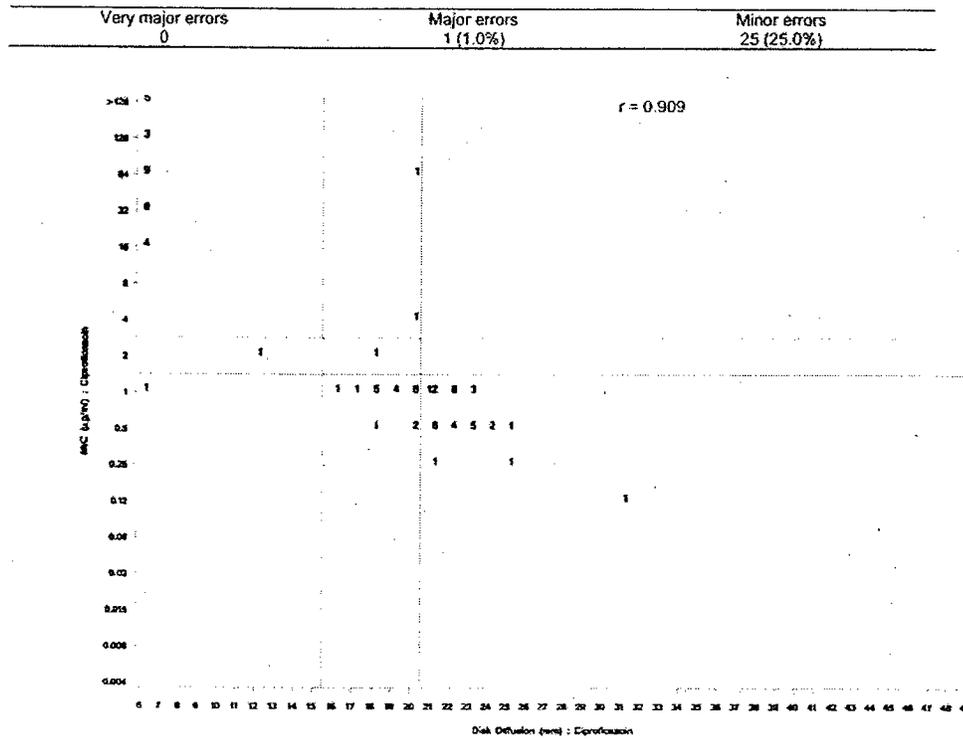


Figure 12
 MIC vs. Zone Diameter for Enterococci/CMI Study
 All Enterococci (n = 124)

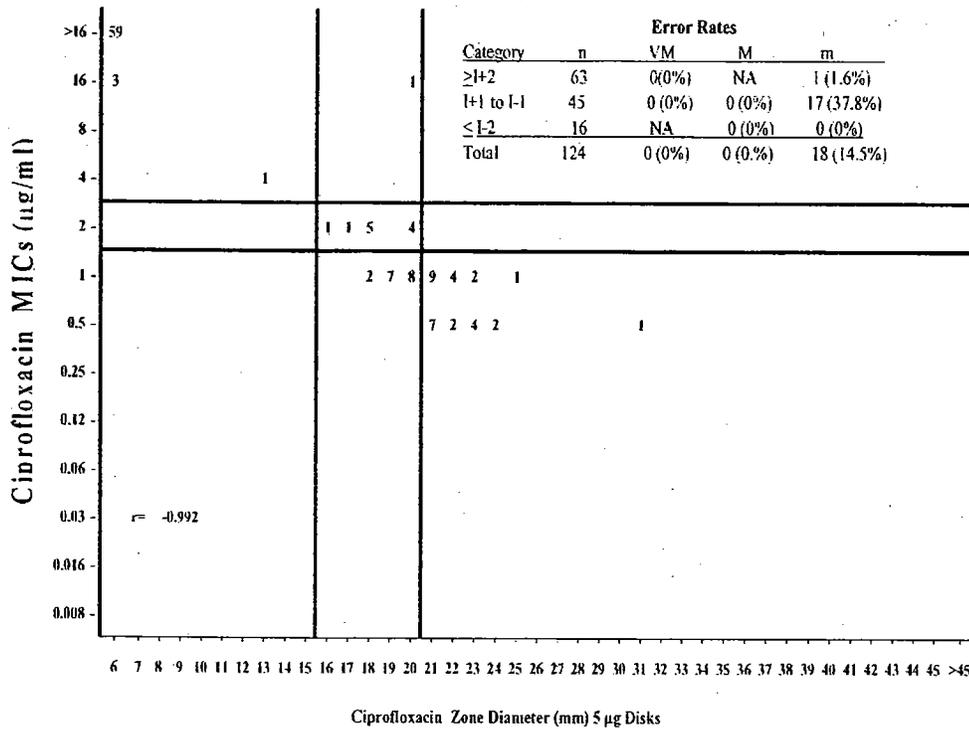


TABLE 22 shows the MIC range, MIC₅₀, and MIC₉₀, and % susceptible, intermediate, or resistant to ciprofloxacin and levofloxacin for the enterococci in the Focus study. TABLE 23 shows the same information for the CMI study.

TABLE 22
 MIC Data for Enterococci (Focus Study)

Organism	Total tested	MIC (µg/mL)			n (%) S	n (%) I	n (%) R
		Range	MIC ₅₀	MIC ₉₀			
Enterococci							
Ciprofloxacin	100	0.12->128	1	64	67 (67.0)	2 (2.0)	31 (31.0)
Levofloxacin	100	0.12->128	1	64	69 (69.0)	0 (0)	31 (31.0)
<i>E. faecalis</i>							
Ciprofloxacin	90	0.12-128	1	64	65 (72.2)	2 (2.2)	23 (25.6)
Levofloxacin	90	0.12-64	1	32	67 (74.4)	0 (0)	23 (25.5)

TABLE 23
 MIC Data for Enterococci (CMI Study)

Organism	Total tested	MIC ($\mu\text{g/mL}$)			(% S)	(% I)	(% R)
		Range	MIC ₅₀	MIC ₉₀			
All Enterococci							
Ciprofloxacin	124	0.5->16	16	>16	39.5	8.9	51.6
Levofloxacin	124	0.5->16	16	>16	48.4	0.8	50.8
<i>E. faecalis</i> Vancomycin-I/R							
Ciprofloxacin	31	0.5->16	1	>16	51.6	0.0	48.4
Levofloxacin	31	0.5->16	2	>16	51.6	0.0	48.4
<i>E. faecalis</i> Vancomycin-S							
Ciprofloxacin	71	0.5->16	2	>16	46.5	12.7	40.8
Levofloxacin	71	1->16	2	>16	59.2	0.0	40.8
<i>E. faecium</i> Vancomycin-R							
Ciprofloxacin	11	>16	>16	>16	0.0	0.0	100.0
Levofloxacin	11	>16	>16	>16	0.0	0.0	100.0
<i>E. faecium</i> Vancomycin-S							
Ciprofloxacin	11	2->16	>16	>16	0.0	18.2	81.8
Levofloxacin	11	1->16	>16	>16	18.2	9.1	72.7

A histogram presenting the frequency of distribution by MIC for the enterococci in the Focus study is presented in Figure 13. The bimodal population in the histogram is apparent and an MIC of 1 $\mu\text{g/mL}$ separated the susceptible and resistant isolates. A MIC of $\leq 1 \mu\text{g/mL}$ inhibited 67% of the isolates; the MIC₅₀ was 1.0 $\mu\text{g/mL}$ and the MIC₉₀ was 64 $\mu\text{g/mL}$. The histogram in Figure 14 shows the distribution of enterococci in the CMI study. A MIC of $\leq 1 \mu\text{g/mL}$ inhibited 39.5% of the enterococci. The MIC₅₀ was 16.0 $\mu\text{g/mL}$ and the MIC₉₀ was >16 $\mu\text{g/mL}$.

Figure 13
 Distribution of MICs of Ciprofloxacin and Levofloxacin/Focus Study
 All Enterococci (n = 100)

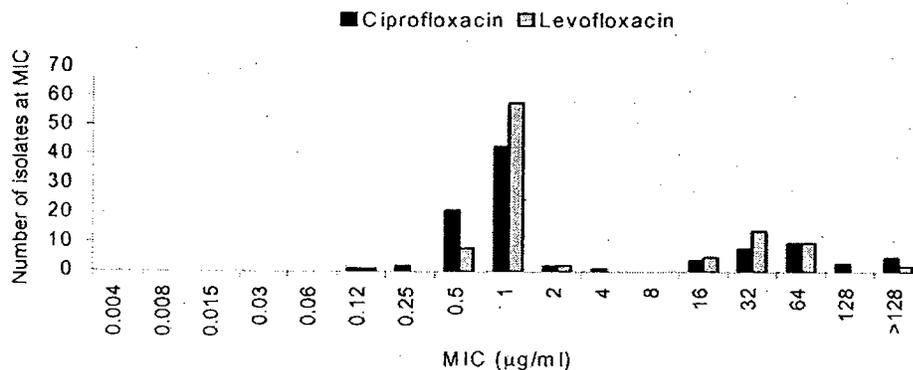
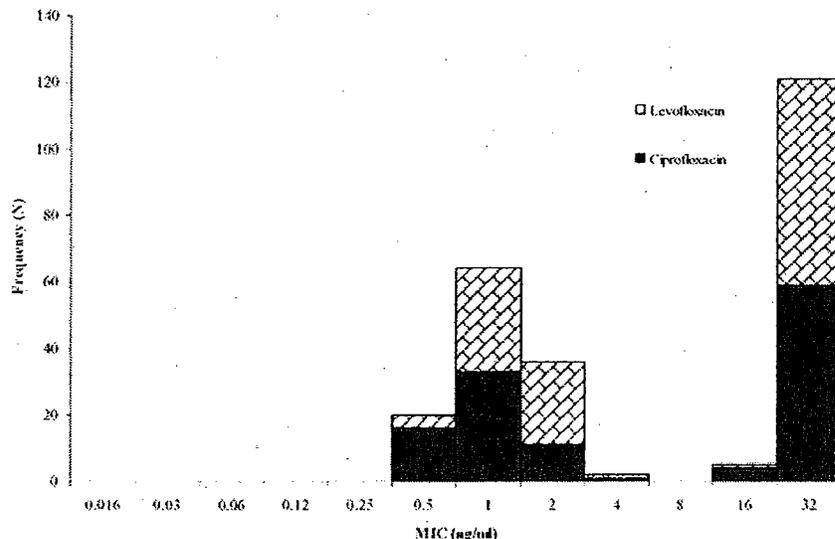


Figure 14

Distribution of MICs of Ciprofloxacin and Levofloxacin/CMI Study
 All Enterococci (n = 124)



RESULTS FROM CLINICAL TRIALS

The efficacy of ciprofloxacin gastric retentive tablets (C-GR) for the treatment of acute, uncomplicated urinary tract infections (UTIs) in adult female patients was determined in two similar clinical studies (Phase II study, 81-0005 and Phase III study, 81-0015). Both studies were multicenter, randomized, double-blind, active-controlled, out-patient studies designed to compare the efficacy and safety of C-GR (ciprofloxacin-gastric retentive), 500-mg tablet once daily for 3 days with ciprofloxacin immediate-release (C-IR), 250-mg tablets twice a day for 3 days in the treatment of uncomplicated UTI in female patients. Patients were evaluated at baseline, at a Test-of-Cure Visit (4-11 days after completion of therapy), and at a Late Post-Treatment Visit (5 weeks \pm 7 days after completion of therapy). Patients had to have at least one positive pretreatment clean-catch, mid-stream urine culture (defined as $\geq 10^5$ CFU/mL) collected on the day of study enrollment and a demonstrated *in vitro* susceptibility of the uropathogen to ciprofloxacin.

A total of 1,095 patients were enrolled in the two clinical studies (1,037 in Phase III and 58 in Phase II). A summary of patient enrolled is presented in TABLE 24.

TABLE 24
Enrollment Summary: All Patients in Clinical Studies 81-0015 and 81-0005

Study	Control	Treatment Group		Total
		C-GR	C-IR	
81-0015	Active controlled	524	513	1037
81-0005	Active controlled	29	29	58
Total	Active	553	542	1095

In the Phase III study, 1037 patients were enrolled and randomized; 583 were included in the ITT population and 540 patients were included in the efficacy population. In the Phase II study, 58 patients were enrolled and randomized; 41 patients were included in the ITT population and 38 patients were included in the efficacy population. The reason for exclusion from the ITT population was not meeting the criteria of having a baseline uropathogen count of $\geq 10^5$ CFU/mL and/or the pathogen not being susceptible to ciprofloxacin. ITT patients missing microbiological data at the Test-of-Cure Visit were excluded from the efficacy population. A summary of patient disposition is provided in TABLE 25.

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TABLE 25
 Patient Disposition Summary: All randomized Patients

Study	Analysis Population	Treatment Group		Total
		C-GR	C-IR	
81-0015 (Phase III)	All randomized patients	524	513	1037
	ITT population	307	276	583
	Efficacy population	283	257	540
	Safety population	518	509	1027
81-005 (Phase II)	All randomized patients	29	29	58
	ITT population	20	21	41
	Efficacy population	19	19	38
	Safety population	29	29	58

ITT = intent-to-treat; the ITT population included all randomized patients who met the enrollment criteria for positive urine microbiology ($\geq 10^5$ CFU/mL) and uropathogen susceptibility (susceptible to ciprofloxacin).

Efficacy population included all randomized patients who met the enrollment criteria for positive urine microbiology and uropathogen susceptibility with available microbiological data at the Test-of-Cure Visit.

Safety population included all randomized patients who received study medication.

In the Phase III study, 982 patients completed three days of study medication and 45 patients prematurely discontinued study medication. The most common reasons for discontinuation of study medication were lost to follow-up (28 patients) and adverse events (10 patients). All 58 patients in the Phase II study completed three days of study medication. Reasons for discontinuation of study medication in the Phase III study are presented in TABLE 26.

TABLE 26
 Reasons for Discontinuation of Study Medication: All Randomized Patients

	Treatment Group		Total (n = 1037)
	C-GR (n = 524)	C-IR (n = 513)	
Randomized	524	513	1037
Received assigned treatment	517	509	1026
Completed the study medication	490 (94.6%)	492 (96.7%)	982 (95.6%)
Prematurely discontinued the study medication	28 (5.4%)	17 (3.3%)	45 (4.4%)
Reason for discontinuation:			
Adverse event	7 (1.4%)	3 (0.6%)	10 (1.0%)
Withdrawal of consent	2 (0.4%)	2 (0.4%)	4 (0.4%)
Lost to follow-up	16 (3.1%)	12 (2.4%)	28 (2.7%)
Other reason	3 (0.6%)	0 (0.0%)	3 (0.3%)

A total of 985 patients (929 Phase III, 56 Phase II) completed the studies and 100 patients (98 Phase III, 2 Phase II) prematurely terminated from the studies. The most common reasons for premature termination were lost to follow-up (62 patients) and withdrawal of consent (27 patients). A summary of the reasons for study termination is presented in TABLE 27.

TABLE 27
Reasons for Study Termination: All Randomized Patients

Study	Treatment Group		Total
	C-GR (n = 524)	C-IR (n = 513)	
81-0015 (Phase III)			(n = 1037)
Randomized	524	513	1037
Received assigned treatment	517	509	1026
Completed study	471 (90.9%)	458 (90.0%)	929 (90.5%)
Prematurely terminated study	47 (9.1%)	51 (10.0%)	98 (9.5%)
Reason for termination:			
Adverse event	6 (1.2%)	3 (0.6%)	9 (0.9%)
Investigator decision	1 (0.2%)	0 (0.0%)	1 (0.1%)
Withdrawal of consent	9 (1.7%)	16 (3.1%)	25 (2.4%)
Lost to follow-up	31 (6.0%)	31 (6.1%)	62 (6.0%)
Other reason	0 (0.0%)	1 (0.2%)	1 (0.1%)
81-0005 (Phase II)	(n = 29)	(n = 29)	(n = 58)
Randomized	29	29	58
Received assigned treatment)	29	29	58
Completed study	29 (100.0%)	27 (93.1%)	56 (96.6%)
Prematurely terminated study	0 (0.0%)	2 (6.9%)	2 (3.4%)
Reason for termination:			
Withdrawal of consent	0 (0.0%)	2 (6.9%)	2 (3.4%)

The ITT population included patients with a positive baseline urine culture ($\geq 10^5$ CFU/mL) which was susceptible to ciprofloxacin. The efficacy population included ITT patients who had microbiological data available at the Test-of-Cure Visit. Patients who received other antibiotics to treat diseases including UTI were excluded from the microbiological data analyses for the ITT and efficacy population after the start of the other antibiotics. Patients who used other antibiotics for non-UTI diseases during the course of the study were excluded from the analyses of clinical outcomes in both the efficacy and ITT populations after the start of the other medications. A summary of patients included in the microbiological and clinical data analyses is presented in TABLE 28.

TABLE 28
 Patient Populations for Data Analysis: Clinical Studies 81-0015 and 81-0005

Study	Treatment Group		Total
	C-GR	C-IR	
81-0015 (Phase III)			
Intent-to-Treat Population	307	276	583
Population for microbiological Data analysis at Test-of-Cure Visit	307	276	583
Population for clinical data analysis at Test-of-Cure Visit	307	276	583
Efficacy Population	283	257	540
Population for microbiological data analysis:			
Test-of-Cure Visit	283	257	540
Late Post-Treatment Visit	221	202	423
Population for clinical data analysis:			
Test-of-Cure Visit	283	257	540
Late Post-Treatment Visit	259	222	481
81-0005 (Phase II)			
Efficacy Population	19	19	38
Population for microbiological data analysis:			
Test-of-Cure Visit	19	19	38
Late Post-Treatment Visit	15	13	28
Population for clinical data analysis:			
Test-of-Cure Visit	19	19	38
Late Post-Treatment Visit	19	14	33

ITT = intent-to-treat; the ITT population included all randomized patients who met the enrollment criteria for positive urine microbiology ($\geq 10^5$ CFU/mL) and uropathogen susceptibility (susceptible to ciprofloxacin).

Efficacy population included all randomized patients who met the enrollment criteria for positive urine microbiology and uropathogen susceptibility with available microbiological data at the Test-of-Cure Visit.

Microbiological Eradication at Test-of-Cure Visit

In the Phase III study, the microbiological eradication rates for the efficacy population at the Test-of-Cure Visit were similar for the C-GR group (254/272; 93.4%) and the C-IR group (225/251; 89.6%). The difference in eradication rates between the two groups was 3.8%.

The eradication rates in the Phase II study were 15/19 (78.9%) in the C-GR group and 18/19 (94.7%) in the C-IR group. The difference between the two groups was 15.8%. The large percentage difference is due to the small number of patients in this study.

A summary of microbiological eradication rates at the Test-of-Cure Visit for the efficacy population is shown in TABLE 29.

TABLE 29
 Microbiological Eradication at Test-of-Cure: Efficacy Population

Study	Treatment Group		Difference (C-GR-C-IR)
	C-GR	C-IR	
81-0015 (Phase III)	(n = 283)	(n = 257)	
Number of Patients with Data	272	251	
Number of Patients with Uropathogen <10 ⁴ CFU/mL	254	225	
Microbiological Eradication Rate	93.4%	89.6%	3.80%
Number of Failures (%)	18 (6.6%)	26 (10.4%)	
81-005 (Phase II)	(n = 19)	(n = 19)	
Number of Patients with Data	19	19	
Number of Patients with Uropathogen <10 ⁴ CFU/mL	15	18	
Microbiological Eradication Rate	79.9%	94.7%	-15.80%
Number of Failures (%)	4 (21.1%)	1 (5.3%)	

For the ITT population in the Phase III study, the microbiological eradication rates at the Test-of-Cure Visit were 254/293 (86.7%) in the C-GR group and 225/268 (84.0%) in the C-IR group. The difference in eradication rates between the two treatment groups was 2.7%. A summary of microbiological eradication rates at the Test-of-Cure Visit for the ITT population is shown in TABLE 30.

TABLE 30
 Microbiological Eradication at Test-of-Cure: ITT Population Study 81-015

Study	Treatment Group		Difference (C-GR-C-IR)
	C-GR (n = 307)	C-IR (n = 276)	
Number of Patients with Data	293	268	
Number of Patients with Uropathogen 10^4 CFU/mL	254	225	
Microbiological Eradication Rate	86.7%	84.0%	2.70%
Number of Failures (%)	39 (13.3%)	43 (16.0%)	

Clinical Cure at Test-of-Cure Visit

In the efficacy population in the Phase III study, the clinical cure rates were similar in the C-GR (233/281; 82.9%) and the C-IR group (216/255; 84.7%). The difference in the clinical cure rates between the two treatment groups was 1.8%.

In the Phase II study, the clinical cure rates were 12/19 (63.2%) in the C-GR group and 16/19 (84.2%) in the C-IR group. The difference in clinical cure rates between the two treatment groups was 21.0%. The large percentage difference is due to the small number of patients in this study.

A summary of clinical cure rates at the Test-of-Cure Visit for the efficacy population is shown in TABLE 31.

TABLE 31
 Clinical Cure Rates at Test-of-Cure: Efficacy Population

Study	Treatment Group		Difference (C-GR-C-IR)
	C-GR	C-IR	
81-0015 (Phase III)	(n = 283)	(n = 257)	
Number of Patients with Data	281	255	
Number of Patients with Uropathogen 10^4 CFU/mL	233	216	
Microbiological Eradication Rate	82.9%	84.7%	-1.80%
Number of Failures (%)	48 (17.1%)	39 (15.3%)	
81-005 (Phase II)	(n = 19)	(n = 19)	
Number of Patients with Data	19	19	
Number of Patients with Uropathogen 10^4 CFU/mL	12	16	
Microbiological Eradication Rate	63.2%	84.2%	-21.00%
Number of Failures (%)	7 (36.8%)	3 (15.8%)	

For the ITT population in the Phase III study, the clinical cure rates at the Test-of-Cure Visit were 233/305 (76.4%) in the C-GR group and 216/274 (78.8%) in the C-IR group. The difference in clinical cure rates between the two treatment groups was 2.4%. A summary of clinical cure rates at the Test-of-Cure Visit for the ITT population is shown in TABLE 32.

TABLE 32
 Clinical Cure Rates at Test-of-Cure: ITT Population Study 81-015

Study	Treatment Group		Difference (C-GR-C-IR)
	C-GR (n = 307)	C-IR (n = 276)	
Number of Patients with Data	305	274	
Number of Patients with Uropathogen <10 ⁴ CFU/mL	233	216	
Microbiological Eradication Rate	76.4%	78.8%	-2.40%
Number of Failures (%)	72 (23.6%)	58 (21.2%)	

Correlation between Clinical Cure and Microbiological Eradication

In the Phase III study, there was a significant correlation between clinical cure rate and microbiological eradication rate at the Test-of-Cure Visit for both treatment groups. In the C-GR group, 81.6% of patients had both clinical cure and microbiological eradication, compared with 77.7% of patients in the C-IR group.

In the Phase II study, no correlation was seen between clinical cure and microbiological eradication at the Test-of-Cure Visit. The proportion of patients with clinical cure and microbiological eradication was 52.6% in the C-GR group and 84.2% in the C-IR group.

A summary of the correlation between clinical cure and microbiological eradication rates in the two studies is presented in TABLE 33.

TABLE 33
 Correlation between Clinical Cure and Microbiological Eradication Rates
 At Test-of-Cure Visit: Efficacy Population

Clinical Cure	Microbiological Eradication	Treatment Group		Total
		C-GR	C-IR	
81-0015 (Phase III)		(n = 283)	(n = 257)	(n = 540)
Patients with Data		272	251	523
Yes	Yes	222 (81.6%)	195 (77.7%)	417 (79.7%)
Yes	No	11 (4.0%)	21 (8.4%)	32 (6.1%)
No	Yes	32 (11.8%)	30 (12.0%)	62 (11.9%)
No	No	7 (2.6%)	5 (2.0%)	12 (2.3%)
81-0005 (Phase II)		(n = 19)	(n = 19)	(n = 38)
Patients with Data		19	19	38
Yes	Yes	10 (52.6%)	16 (84.2%)	26 (68.4%)
Yes	No	2 (10.5%)	0 (0.0%)	2 (5.3%)
No	Yes	5 (26.3%)	2 (10.5%)	7 (18.4%)
No	No	2 (10.5%)	1 (5.3%)	3 (7.9%)

Microbiological Response at Test-of-Cure Visit by Baseline Organism

Escherichia coli was the most common infecting organism identified in both studies. In the Phase III study, 81.1% of patients had *E. coli* infections. Eradication rates for *E. coli* at the Test-of-Cure Visit were similar in the C-GR group (211/222; 95.0%) and the C-IR group (184/202; 91.1%). The *E. coli* eradication rates in the Phase II study were 13/16 (81.3%) for the C-GR group and 15/16 (93.8%) for the C-IR group.

The microbiological eradication rates for other common infecting organisms in the Phase III study for the C-GR group were *K. pneumoniae* 11/12 (91.7%); *P. mirabilis* 7/7 (100%), *Enterococcus* Group D 6/10 (60.0%), and *Staphylococcus* species coagulase-negative 7/9 (77.8%). For the C-IR group eradication rates were *K. pneumoniae* 10/13 (76.9%), *P. mirabilis* 8/9 (88.9%), *Enterococcus* Group D 7/9 (77.8%), and *Staphylococcus* species coagulase-negative 5/7 (71.4%).

Microbiological eradication by baseline pathogen is presented in TABLE 34.

TABLE 34
 Microbiological Eradication by Baseline Pathogen at Test-of-Cure Visit: Efficacy Population

Study	Treatment Group	
	C-GR	C-IR
81-0015 (Phase III)	(n = 283)	(n = 257)
Organism	Eradication: n (%)	
<i>Escherichia coli</i>	211/222 (95.0%)	184/202 (91.1%)
<i>Klebsiella pneumoniae</i>	11/12 (91.7%)	10/13 (76.9%)
Group D <i>Streptococcus</i> <i>Enterococcus</i>	6/10 (60.0%)	7/9 (77.8%)
<i>Proteus mirabilis</i>	7/7 (100.0%)	8/9 (88.9%)
<i>Staphylococcus</i> species, coagulase-negative	7/9 (77.8%)	5/7 (71.4%)
Beta Strep. Presumptive Group B	1/1 (100.0%)	6/6 (100.0%)
<i>Klebsiella</i> species	3/3 (100.0%)	1/1 (100.0%)
<i>Staphylococcus aureus</i>	1/1 (100.0%)	4/4 (100.0%)
<i>Enterobacter aerogenes</i>	3/3 (100.0%)	1/1 (100.0%)
<i>Enterobacter</i> species	2/2 (100.0%)	2/2 (100.0%)
<i>Citrobacter</i> species	1/1 (100.0%)	0 (0.0%)
<i>Enterobacter cloacae</i>	1/1 (100.0%)	1/1 (100.0%)
<i>Hafnia alvei</i>	1/1 (100.0%)	1/1 (100.0%)
<i>Acinetobacter baumannii</i>	1/1 (100.0%)	0 (0.0%)
Non-fermenting Gram-Negative Bacilli	0 (0.0%)	1/1 (100%)
81-0005 (Phase II)	(n = 19)	(n = 19)
<i>Escherichia coli</i>	13/16 (81.3%)	15/16 (93.8%)
<i>Proteus mirabilis</i>	½ (50.0%)	1/1 (100.0%)
<i>Klebsiella pneumoniae</i>	1/1 (100.0%)	1/1 (100.0%)
<i>Acinetobacter baumannii</i>	0 (0.0%)	1/1 (100.0%)
<i>Pseudomonas aeruginosa</i>	1/1 (100.0%)	0 (0.0%)

There was one patient (# 401) in the Phase II study who received Cipro GR that had two baseline pathogens (*E. coli* and *K. pneumoniae*) both organisms were eradicated. There were three patients in the Phase III study who received Cipro IR that had two baseline pathogens (Patient 3926, *E. coli* and *Staphylococcus* species; Patient 4112, *E. coli* and group B streptococci; Patient 4822, *E. coli* and *K. pneumoniae*). All organisms were eradicated at the Test-of-Cure visit but Patient 4112 had a recurrence of the group B streptococci.

The data in the above table show that most of the pathogens were *E. coli*. There were also more than 10 isolates of *Klebsiella pneumoniae*. Group D enterococci and coagulase-negative staphylococci were not identified to the species level as they should have been. The eradication rate for Group D enterococci was only 60.0%.

In the pivotal Phase III clinical trial, there were 7 patients infected with *Proteus mirabilis* in the C-GR treatment group with $\geq 10^5$ CFU/mL, compared to 9 patients in the C-IR treatment group. Success rates of 100% (7/7) and 85.7% (6/7) were obtained for the C-GR group for microbiological eradication and clinical cure, respectively, with corresponding rates of 88.9% (8/9) and 60% (6/10) for the C-IR group.

TABLE 35 presents a summary of microbiological eradication and clinical cure rates of *P. mirabilis*.

TABLE 35
 Eradication and Clinical Cure Rates of *Proteus mirabilis* at Test-of-Cure Visit

Bacterial Count Trial	Microbiological Eradication Rate		Clinical Cure Rate	
	C-GR	C-IR	C-GR	C-IR
$\geq 10^5$ CFU/mL				
Phase III Trial	7/7 (100%)	8/9 (88.9%)	6/7 (85.7%)	6/10 (60.0%)*
Phase II Trial	1/2 (50%)	1/1 (100%)	0/2 (0%)	0/1 (0%)
Combined	8/9 (88.9%)	9/10 (90.0%)	6/9 (66.7%)	6/11 (54.5%)
$\geq 10^4$ CFU/mL				
Phase III Trial	7/8 (87.5%)	8/9 (88.9%)	7/8 (87.5%)	6/10 (60.0%)
Phase II Trial	1/2 (50%)	1/1 (100%)	0/2 (0%)	0/1 (0%)
Combined	8/10 (80.0%)	9/10 (90.0%)	7/10 (70.0%)	6/11 (54.5%)

* Patient 5703 was a clinical failure but no Test-of-Cure Culture was performed.

Based on the criteria of $\geq 10^4$ CFU/mL at the baseline culture, 3 additional patients (all clinical cures) infected with *P. mirabilis*, 2 in the C-GR group and 1 in the C-IR group will qualify for inclusion. However, one patient from the C-GR group and another one from the C-IR group, do not have a culture result at the Test-of-Cure Visit, and therefore, do not qualify for inclusion into the efficacy population. Therefore, only one additional patient who was treated with C-GR (Patient 1809), a clinical cure without eradication, qualifies for the efficacy population if patients with $\geq 10^4$ CFU/mL cultures are included.

The patients with $\geq 10^4$ CFU/mL are as follows:

1	Patient 1809 C-GR treatment	80,000 CFU/mL	Persistence	Clinical Cure Sustained Cure
2	Patient 2805 C-IR treatment	10, 000 CFU/mL	No TOC culture	Clinical Cure Sustained Cure
3	Patient 2918 C-GR treatment	20, 000 CFU/mL	No TOC culture	Clinical Cure Sustained Cure

Clinical Response at Test-of-Cure by Baseline Organism

For patients with *E. coli* infections, the clinical cure rate in the Phase III study was 197/227 (86.8%) in the C-GR group and 176/204 (86.3%) in the C-IR group. Clinical cure rates for patients with other common baseline pathogens in the C-GR group were *K. pneumoniae* 8/14 (57.1%), *P. mirabilis* 6/7 (85.7%), *Enterococcus* Group D 9/10 (90.0%), and *Staphylococcus* species coagulase-negative 6/10 (60.0%).

Clinical cure by baseline organism at the Test-of-Cure Visit is presented in TABLE 36.

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TABLE 36
 Clinical Cure by Baseline Pathogen at Test-of-Cure Visit
 Efficacy Population

Study	Treatment Group	
	C-GR	C-IR
81-0015 (Phase III)	(n = 283)	(n = 257)
Organism	Eradication: n (%)	
<i>Escherichia coli</i>	197/227 (86.8%)	176/204 (86.3%)
<i>Klebsiella pneumoniae</i>	8/14 (57.1%)	12/14 (85.7%)
Group D <i>Streptococcus</i> <i>Enterococcus</i>	9/10 (90.0%)	8/9 (88.9%)
<i>Proteus mirabilis</i>	6/7 (85.7%)	6/10 (60.0%)
<i>Staphylococcus</i> species, coagulase-negative	6/10 (60.0%)	6/7 (85.7%)
Beta Strep. Presumptive Group B	0/1 (0.0%)	4/6 (66.7%)
<i>Klebsiella</i> species	2/3 (66.7%)	1/1 (100.0%)
<i>Staphylococcus aureus</i>	1/1 (100.0%)	2/4 (50.0%)
<i>Enterobacter aerogenes</i>	3/3 (100.0%)	1/1 (100.0%)
<i>Enterobacter</i> species	2/2 (100.0%)	2/2 (100.0%)
<i>Citrobacter</i> species	0/2 (0.0%)	0 (0.0%)
<i>Enterobacter cloacae</i>	0/1 (0.0%)	1/1 (100.0%)
<i>Hafnia alvei</i>	0/1 (0.0%)	1/1 (100.0%)
<i>Acinetobacter baumannii</i>	1/1 (100.0%)	0 (0.0%)
Non-fermenting Gram-Negative Bacilli	0 (0.0%)	1/1 (100%)
81-0005 (Phase II)	(n = 19)	(n = 19)
<i>Escherichia coli</i>	12/16 (75.0%)	14/16 (87.5%)
<i>Proteus mirabilis</i>	0/2 (0.0%)	0/1 (0.0%)
<i>Klebsiella pneumoniae</i>	0/1 (0.0%)	1/1 (100.0%)
<i>Acinetobacter baumannii</i>	0 (0.0%)	1/1 (100.0%)
<i>Pseudomonas aeruginosa</i>	0/1 (0.0%)	0 (0.0%)

New Infections by Organism at Test-of-Cure Visit

In the Phase III study, the majority of new organisms isolated at the Test-of-Cure Visit were *Enterococcus* species (group D *Streptococcus*); 24 of 42 patients with new infections in the C-GR group and 23 of 36 patients with new infections in the C-IR group had *Enterococcus* species infections.

In the Phase II study, new organisms isolated at the Test-of-Cure Visit were *Enterococcus* species and *Hafnia alvei*.

A summary of new infections by organism at the Test-of-Cure Visit is presented in TABLE 37.

TABLE 37
 New Infections by Organism at Test-of-Cure Visit
 Efficacy Population

Study Organism Present	Treatment Group		Total
	C-GR	C-IR	
81-0015 (Phase III)	(n = 283)	(n = 257)	(n = 540)
Number of Patients with Data	272	251	523
<i>Acinetobacter baumannii</i>	1 (0.4%)	0 (0%)	1 (0.2%)
<i>Acinetobacter</i> species	2 (0.7%)	1 (0.4%)	3 (0.6%)
Beta <i>Strep.</i> Presumptive Group B	3 (1.1%)	1 (0.4%)	4 (0.7%)
<i>Citrobacter</i> species	1 (0.4%)	0 (0%)	1 (0.2%)
<i>Escherichia coli</i>	4 (1.5%)	0 (0%)	4 (0.7%)
Gamma <i>Streptococcus</i>	1 (0.4%)	1 (0.4%)	2 (0.4%)
Group D <i>Streptococcus Enterococcus</i>	24 (8.8%)	23 (9.2%)	47 (9.0%)
Group D <i>Streptococcus</i> not <i>Enterococcus</i>	0 (0%)	1 (0.4%)	1 (0.2%)
<i>Klebsiella oxytoca</i>	0 (0%)	1 (0.4%)	1 (0.2%)
<i>Klebsiella pneumoniae</i>	2 (0.7%)	3 (1.2%)	5 (0.9%)
<i>Klebsiella</i> species	0 (0%)	1 (0.4%)	1 (0.2%)
Nonfermenting Gram-Negative Bacilli	2 (0.7%)	0 (0%)	2 (0.4%)
<i>Proteus mirabilis</i>	0 (0%)	1 (0.4%)	1 (0.2%)
<i>Pseudomonas</i> species	0 (0%)	1 (0.4%)	1 (0.2%)
<i>Serratia marcescens</i>	1 (0.4%)	1 (0.4%)	2 (0.4%)
<i>Staphylococcus aureus</i>	1 (0.4%)	1 (0.4%)	2 (0.4%)
<i>Staphylococcus</i> species, coagulase negative	2 (0.7%)	1 (0.4%)	3 (0.6%)
81-005 (Phase II)	(n = 19)	(n = 19)	(n = 38)
Number of Patients with Data	19	19	38
<i>Enterococcus</i> species	4 (21.1%)	5 (26.3%)	9 (23.7%)
<i>Hafnia alvei</i>	1 (5.3%)	0 (0.0%)	1 (2.6%)

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Microbiological Outcomes at Late Post-Treatment Visit

In the Phase III study, there was no significant difference between treatment groups for sustained eradication at the Late Post-Treatment Visit (5 weeks \pm 7 days post-treatment). The sustained eradication rates were 182/221 (82.4%) in the C-GR group and 168/202 (83.2%) in the C-IR group. The five-week sustained eradication rates for the Phase III study are presented in TABLE 38.

TABLE 38
 Sustained Microbiological Eradication at Late Post-Treatment Visit
 Efficacy Population (Study 81-0015)

	Treatment Group		Difference (C-GR-C-IR)
	C-GR (n = 283)	C-IR (n = 257)	
Number of Patients with Data	221	202	
Number with Sustained Eradication	182	168	
Sustained Eradication Rate	82.4%	83.2%	-0.80%
Number of Failures (%)	39 (17.6%)	34 (16.8%)	

The rates of recurrence, persistence, and new infection at the Late Post-Treatment Visit were similar between the two treatment groups in both studies. Microbiological outcomes at the Late Post-Treatment Visit are presented in TABLE 39.

TABLE 39
 Microbiological Outcomes at Late Post-Treatment Visit
 Efficacy Population

Study	Treatment Group		Difference (C-GR-C-IR)
	C-GR	C-IR	
81-0015 (Phase III)	(n = 283)	(n = 257)	
Microbiological Response			
Sustained eradication: n (%)	182/221 (82.4%)	168/202 (83.2%)	-0.82%
Recurrence	29/221 (13.1%)	19/202 (9.4%)	3.72%
Persistence	10/221 (4.5%)	15/202 (7.4%)	-2.90%
New Infection	46/220 (20.9%)	40/201 (19.9%)	1.00%
81-0005 (Phase II)	(n = 19)	(n = 19)	
Microbiological Response			
Sustained eradication: n (%)	9/15 (60.0%)	8/13 (61.5%)	-1.54%
Recurrence	3/15 (20.0%)	4/13 (30.8%)	-10.77%
Persistence	3/15 (20.0%)	1/13 (7.7%)	12.31%
New Infection	5/15 (33.3%)	5/13 (38.5%)	-5.20%

Clinical Outcome at Late Post-Treatment Visit

In the Phase III study, the sustained clinical cure rates were 75.7% in the C-GR group and 78.8% in the C-IR group. The difference in sustained clinical cure rates was 3.1%. Sustained clinical cure rates at the Late Post-Treatment Visit for the Phase III study are presented in TABLE 40.

TABLE 40
 Sustained Clinical Cure at Late Post-Treatment Visit
 Efficacy Population (Study 81-0015)

81-0015 (Phase III)	Treatment Group		Difference (C-GR-C-IR)
	C-GR (n = 283)	C-IR (n = 257)	
Number of Patients with Data	259	222	
Number with Sustained Eradication	196	175	
Sustained Eradication Rate	75.7%	78.8%	-3.10%
Number of Failures (%)	63 (24.3%)	47 (21.2%)	

In the Phase II study the sustained clinical cure rates were slightly lower than in the Phase III study (8/19, 42.1%, in the C-GR group and 7/14, 50.0% in the C-IR group). The clinical relapse and failure rates at the Late Post-Treatment Visit were similar between the two treatment groups in both studies.

Clinical outcomes at the Late Post-Treatment Visit are presented in TABLE 41.

TABLE 41
 Clinical Outcomes at Late Post-Treatment Visit
 Efficacy Population

Study	Treatment Group		Difference (C-GR-C-IR)
	C-GR	C-IR	
81-0015 (Phase III)	(n = 283)	(n = 257)	
Clinical Response			
Sustained cure: n (%)	196/259 (75.7%)	175/222 (78.8%)	-3.15%
Relapse	18/259 (6.9%)	16/22 (7.2%)	-0.26%
Failure	45/259 (17.4%)	31/222 (14.0%)	3.41%
81-0005 (Phase II)	(n = 19)	(n = 19)	
Clinical Response			
Sustained cure: n (%)	8/19 (42.1%)	7/14 (50.0%)	-7.89%
Relapse	4/19 (21.1%)	4/14 (28.6%)	-7.52%
Failure	7/19 (36.8%)	3/14 (21.4%)	15.41%

Microbiological Response at Late Post-Treatment Visit by Baseline Organism

In the Phase III study, there were no significant differences between treatment groups for microbiological eradication by baseline organism. For *E. coli*, the most frequently isolated organism at baseline, the eradication rates were 153/187 (81.8%) in the C-GR group and 138/167 (82.6%) in the C-IR group. A summary of microbiological response at the Late Post-Treatment Visit by baseline organism is presented in TABLE 42.

TABLE 42
 Microbiological Eradication by Baseline Pathogen at Late Post-Treatment Visit
 Efficacy Population

Study	Treatment Group	
	C-GR	C-IR
81-0015 (Phase III)	(n = 283)	(n = 257)
Organism	Sustained Eradication: n (%)	
<i>Escherichia coli</i>	153/187 (81.8%)	138/167 (82.6%)
<i>Klebsiella pneumoniae</i>	6/6 (100%)	7/9 (77.8%)
Group D <i>Streptococcus</i> <i>Enterococcus</i>	5/7 (71.4%)	4/4 (100.0%)
<i>Proteus mirabilis</i>	4/4 (100.0%)	5/5 (100.0%)
<i>Staphylococcus</i> species, coagulase- negative	6/7 (85.7%)	5/6 (83.3%)
Beta Strep. Presumptive Group B	0 (0.0%)	4/5 (80.0%)
<i>Klebsiella</i> species	1/3 (33.3%)	1/1 (100.0%)
<i>Staphylococcus aureus</i>	1/1 (100.0%)	3/3 (100.0%)
<i>Enterobacter aerogenes</i>	3/3 (100.0%)	1/1 (100.0%)
<i>Enterobacter</i> species	2/2 (100.0%)	1/2 (50.0%)
<i>Citrobacter</i> species	1/1 (100.0%)	0 (0.0%)
<i>Enterobacter cloacae</i>	0 (0.0%)	1/1 (100.0%)
<i>Hafnia alvei</i>	1/1 (100.0%)	1/1 (100.0%)
<i>Acinetobacter baumannii</i>	1/1 (100.0%)	0 (0.0%)
Non-fermenting Gram-Negative Bacilli	0 (0.0%)	1/1 (100%)
81-0005 (Phase II)	(n = 19)	(n = 19)
<i>Escherichia coli</i>	7/12 (58.3%)	7/12 (58.3%)
<i>Proteus mirabilis</i>	½ (50.0%)	1/1 (100.0%)
<i>Klebsiella pneumoniae</i>	1/1 (100.0%)	0 (0.0%)
<i>Acinetobacter baumannii</i>	0 (0.0%)	1/1 (100.0%)
<i>Pseudomonas aeruginosa</i>	1/1 (100.0%)	0 (0.0%)

New Infections at Late Post-Treatment Visit

In the Phase III study, the majority of new organism isolates at the Late Post-Treatment Visit were *Enterococcus* species (group D *Streptococcus*): 14 patients in the C-GR group and 10 patients in the C-IR group had *Enterococcus* species infections at the Late Post-Treatment Visit.

For the Phase II study, new organism isolates at the Late Post-Treatment Visit were *Enterococcus* species, *Enterobacter cloacae*, and *Streptococcus agalactiae*.

A summary of new infections by organism at the Late Post-Treatment Visit is presented in TABLE 43.

TABLE 43
 New Infections by Organism at Late Post-Treatment Visit
 Efficacy Population

Study Organism Present	Treatment Group		Total
	C-GR	C-IR	
81-0015 (Phase III)	(n = 283)	(n = 257)	(n = 540)
Number of Patients with Data	220	201	421
Beta <i>Strep.</i> Presumptive Group B	2 (0.9%)	0 (0.0%)	2 (0.3%)
<i>Citrobacter</i> species	0 (0.0%)	1 (0.5%)	1 (0.2%)
<i>Enterobacter cloacae</i>	0 (0.0%)	1 (0.5%)	1 (0.2%)
<i>Escherichia coli</i>	1 (0.4%)	5 (2.3%)	6 (1.3%)
Group D <i>Streptococcus</i> (<i>Enterococcus</i>)	14 (6.4%)	10 (5.0%)	24 (5.7%)
<i>Klebsiella pneumoniae</i>	4 (1.8%)	2 (1.0%)	6 (1.4%)
<i>Klebsiella</i> species	0 (0.0%)	1 (0.5%)	1 (0.2%)
Nonfermenting Gram-Negative Bacilli	1 (0.5%)	0 (0.0%)	1 (0.2%)
<i>Staphylococcus</i> species, coagulase negative	0 (0.0%)	1 (0.5%)	1 (0.2%)
81-005 (Phase II)	(n = 19)	(n = 19)	(n = 38)
Number of Patients with Data	15	13	28
<i>Enterobacter cloacae</i>	0 (0.0%)	1 (7.7%)	1 (3.6%)
<i>Enterococcus</i> species	2 (13.3%)	4 (30.8%)	6 (21.4%)
<i>Streptococcus agalactiae</i>	1 (6.7%)	0 (0.0%)	1 (3.6%)

Susceptibility Test Results of Ciprofloxacin for Primary Pathogens

The ciprofloxacin susceptibility test results for the primary uropathogens that were isolated pre-therapy from all randomized patients in both the C-GR and C-IR treatment groups are presented in TABLE 44. The range of MICs for 486 isolates of *Escherichia coli* and 30 isolates of *Klebsiella pneumoniae* was ≤ 0.06 to >2 $\mu\text{g/mL}$. The MIC₉₀s were 0.25 $\mu\text{g/mL}$ and 0.5 $\mu\text{g/mL}$ for *E. coli* and *K. pneumoniae*, respectively. MICs for isolates of *Proteus mirabilis* ranged from ≤ 0.06 to 1 $\mu\text{g/mL}$; the MIC₉₀ was 0.5 $\mu\text{g/mL}$. The range of MICs for *Enterococcus* Group D was 0.5 to 1 $\mu\text{g/mL}$ and the MIC₉₀ was 1 $\mu\text{g/mL}$. The range and MIC₉₀ were 0.5 $\mu\text{g/mL}$ for the isolates of *Staphylococcus coagulase-negative*.

TABLE 44
 Susceptibility of Primary Pre-therapy Uropathogens

	Number	Range ($\mu\text{g/mL}$)	MIC ₅₀ ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)
<i>E. coli</i>	486	≤ 0.06 - >2	≤ 0.06	0.25
<i>K. pneumoniae</i>	30	≤ 0.06 - >2	≤ 0.06	0.5
<i>P. mirabilis</i>	18	≤ 0.06 -1	≤ 0.06	0.5
<i>Enterococcus</i> Group D	20	0.5-1	1	1
<i>Staphylococcus coagulase-negative</i>	18	0.5	0.5	0.5

Microbiological Response by MICs for Primary Pathogens

The microbiological responses of eradication and persistence by the MICs for each of the primary urinary pathogens at the Test-of-Cure Visit (TOC) for the C-GR treated patients are shown in TABLE 45. The range of MICs was ≤ 0.06 to 1 $\mu\text{g/mL}$. This range is slightly different than the range for isolates from all randomized patients shown in TABLE 44. The majority of isolates of *E. coli* (201/222) had ciprofloxacin MICs of ≤ 0.06 $\mu\text{g/mL}$; eradication occurred for 190 (94.5%) isolates and 11 isolates were persisters. The remaining 21 *E. coli* isolates with MICs ≥ 0.12 $\mu\text{g/mL}$ were eradicated including an isolate with a MIC of 1 $\mu\text{g/mL}$. All 12 isolates of *K. pneumoniae* had a MIC of ≤ 0.06 $\mu\text{g/mL}$; 11/12 (91.7%) were eradicated and one isolate persisted. All six isolates of *P. mirabilis* at a MIC of ≤ 0.06 $\mu\text{g/mL}$ were eradicated as was the one isolate with a MIC of 1 $\mu\text{g/mL}$. For *Enterococcus* Group D, the range of MICs was 0.5 to 1 $\mu\text{g/mL}$. Of the six isolates with a MIC of 0.5 $\mu\text{g/mL}$, 4/6 were eradicated and 2/4 isolates with a MIC of 1 $\mu\text{g/mL}$ were eradicated. All nine isolates of *Staphylococcus coagulase-negative* had MICs of 0.5 $\mu\text{g/mL}$; 7/9 were eradicated.

TABLE 45
 Microbiological Response at Test-of-Cure Visit for Primary
 Pre-therapy Organisms by MIC: Efficacy Population

MIC (µg/mL) by Baseline Pathogen	Microbiological Response	Treatment Group	
		C-GR (n = 283)	C-IR (n = 257)
<i>E. coli</i> – n (%)			
0.06	All	201 (100%)	166 (100%)
	Eradication	190 (94.5%)	149 (89.8%)
	Persistence	11 (5.5%)	17 (10.2%)
0.12	All	4 (100%)	12 (100%)
	Eradication	4 (100%)	12 (100%)
	Persistence	0 (0%)	0 (0%)
0.25	All	8 (100%)	13 (100%)
	Eradication	8 (100%)	13 (100%)
	Persistence	0 (0%)	0 (0%)
0.5	All	8 (100%)	7 (100%)
	Eradication	8 (100%)	7 (100%)
	Persistence	0 (0%)	0 (0%)
1.0	All	1 (100%)	4 (100%)
	Eradication	1 (100%)	3 (75.0%)
	Persistence	0 (0%)	1 (25.0%)
All	All	222 (100%)	202 (100%)
	Eradication	211 (95.0%)	184 (91.1%)
	Persistence	11 (5.0%)	18 (8.9%)
<i>K. pneumoniae</i> – n (%)			
0.06	All	12 (100%)	9 (100%)
	Eradication	11 (91.7%)	8 (88.9%)
	Persistence	1 (8.3%)	1 (11.1%)
0.12	All	0 (0%)	1 (100%)
	Eradication	0 (0%)	0 (0%)
	Persistence	0 (0%)	0 (0%)
0.25	All	0 (0%)	1 (100%)
	Eradication	0 (0%)	0 (0%)
	Persistence	0 (0%)	1 (100%)
0.5	All	0 (0%)	1 (100%)
	Eradication	0 (0%)	1 (100%)
	Persistence	0 (0%)	0 (0%)
1	All	0 (0%)	1 (100%)
	Eradication	0 (0%)	1 (100%)
	Persistence	0 (0%)	0 (0%)
All	All	12 (100%)	13 (100%)
	Eradication	11 (91.7%)	10 (76.9%)
	Persistence	1 (8.3%)	3 (23.1%)

TABLE 45 (continued)
 Microbiological Response at Test-of-Cure Visit for Primary
 Pre-therapy Organisms by MIC: Efficacy Population

MIC (µg/mL) by Baseline Pathogen	Microbiological Response	Treatment Group	
		C-GR (n = 283)	C-IR (n = 257)
<i>P. mirabilis</i> -n (%)			
0.06	All	6 (100%)	9 (100%)
	Eradication	6 (100%)	8 (88.9%)
	Persistence	0 (0%)	1 (11.1%)
1.0	All	1 (100%)	0 (0%)
	Eradication	1 (100%)	0 (0%)
	Persistence	0 (0%)	0 (0%)
All	All	7 (100%)	9 (100%)
	Eradication	7 (100%)	8 (88.9%)
	Persistence	0 (0%)	1 (11.1%)
<i>Group D Enterococcus</i> -n (%)			
0.5	All	6 (100%)	3 (100%)
	Eradication	4 (66.7%)	3 (100%)
	Persistence	2 (33.3%)	0 (0%)
1	All	4 (100%)	6 (100%)
	Eradication	2 (50.0%)	4 (66.7%)
	Persistence	2 (50.0%)	2 (33.3%)
All	All	10 (100%)	9 (100%)
	Eradication	6 (60.0%)	7 (77.8%)
	Persistence	4 (40.0%)	2 (22.2%)
<i>Staphylococcus</i> Species, Coagulase Negative-n (%)			
0.5	All	9 (100%)	7 (100%)
	Eradication	7 (77.8%)	5 (71.4%)
	Persistence	2 (22.2%)	2 (28.6%)

The pre-therapy and post-therapy MICs for persistent causative organisms in the C-GR group that increased by more than one doubling dilution are presented in TABLE 46. It appears that 5/11 *E. coli* persisters had an increase in MIC value post-treatment. The one *K. pneumoniae* persister also had a MIC increase. Most of these patients were clinical failures or had a relapse. No testing, however, was performed to make sure that the organism pre-treatment and post-treatment was the same. It is possible that the original organism was eradicated and the post-treatment pathogen was a new infecting organism that just happen to be the same species as the pre-treatment organism.

TABLE 46
 MICs for Persisting Organisms from the C-GR Treated Patients^a

Patient No.	Organism	Pre-therapy MIC (µg/mL)	Post-therapy (TOC) MIC (µg/mL)	Clinical Response Late Post Therapy
1902	<i>K. pneumoniae</i>	0.12	0.5	Failure
3914	<i>E. coli</i>	≤0.06	0.5	Relapse
4405	<i>E. coli</i>	≤0.06	>2	Failure
4409	<i>E. coli</i>	≤0.06	0.5	Relapse
4902	<i>E. coli</i>	≤0.06	>2	Cure
4913	<i>E. coli</i>	≤0.06	>2	Failure

^a Isolates that had > twofold increase in ciprofloxacin MIC post-therapy compared with MIC of pre-therapy isolate

Frequency Distribution of MICs Obtained during the Clinical Trial

The frequency distribution by MICs for the organisms that were isolated during the Phase III clinical trial was determined for the organism groups Enterobacteriaceae, staphylococci, and enterococci in order to compare these data with those generated in the Focus and CMI studies. Since isolates having MIC ≥ 2 µg/mL excluded patients from the efficacy population, the histograms for Enterobacteriaceae and staphylococci incorporated all isolates from randomized patients in order to capture organisms with high MICs. No isolates of enterococci had MICs > 1 µg/mL; therefore the efficacy population was used for the frequency distribution.

Figure 15 shows the frequency distribution of the MICs for the Enterobacteriaceae. The majority of the isolates had ciprofloxacin MICs of ≤0.06 µg/mL. The distribution of MICs for the Enterobacteriaceae in this histogram is similar to the distribution seen in Figure 5 and Figure 6 from the Focus and CMI studies, respectively.

The frequency distribution of MICs for staphylococci is presented in Figure 16. Although the number of isolates was small, the histogram shows a divided population with a few isolates with MICs ≥2 µg/mL. These data are similar to the histograms presented in Figure 9 and Figure 10, using data from the Focus and CMI studies.

Figure 17 shows the histogram for enterococci. All of the MICs were either 0.5 or 1 µg/mL. Figures 13 and Figure 14 were the histograms from the Focus and CMI studies and contained more isolates.

In summary, the distribution of MIC data generated during the Phase III study with C-GR was similar to the data provided in the spectrum of activity studies performed by Focus and CMI.

Figure 15
Distribution of Enterobacteriaceae (n = 555)
All Randomized Patients

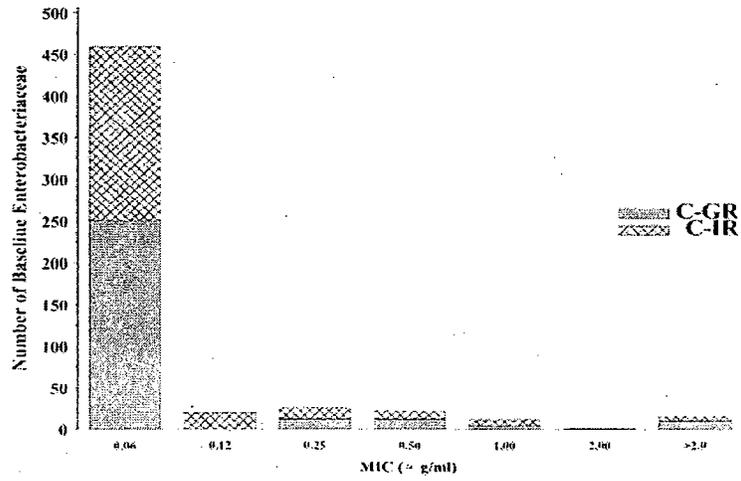


Figure 16
Distribution of Staphylococci (n = 26)
All Randomized Patients

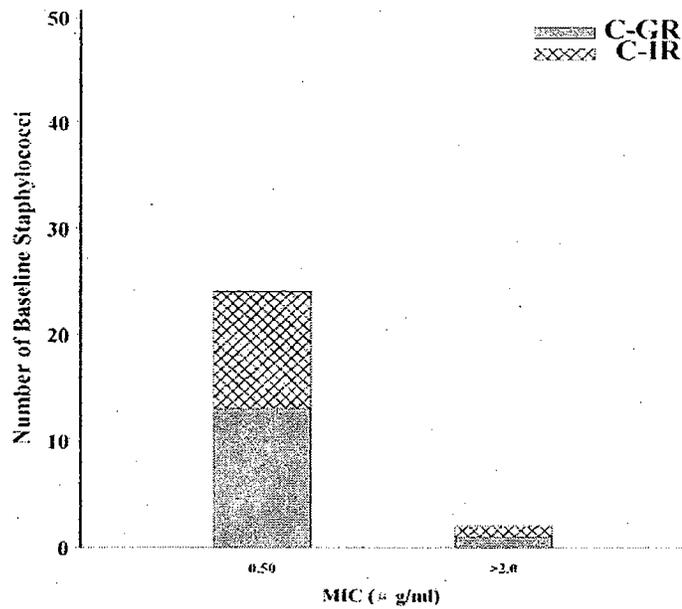
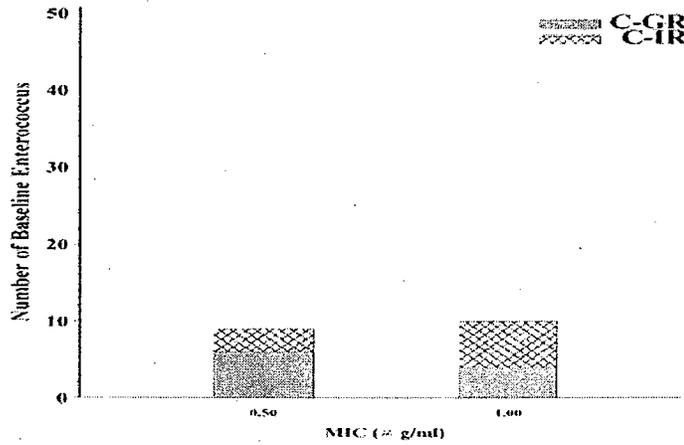


Figure 17
Distribution of Enterococci (n = 19)
Efficacy Population



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NDA REFERENCES

1. Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, and Sahm DS. Trends in Antimicrobial Resistance among Urinary Tract Infection Isolates of *Escherichia coli* from Female Outpatients in the United States. *Antimicrobial Agents and Chemotherapy*, 2002; **48**:2540-2545.
2. Report 83-0001, Brown SD and Traczewski MM "Variation in Ciprofloxacin MICs as a Function of Media pH". The Clinical Microbiology Institute (CMI), Wilsonville, Oregon. Effective JAN 2004.
3. Report 83-0002, Brown SD and Traczewski MM "Variables Effecting Ciprofloxacin MICs". The Clinical Microbiology Institute (CMI), Wilsonville, Oregon. Effective APR 2004.
4. Report 83-0003, Sahm DF, Karlowsky JA, Flamm RK, and Blosser RS. "Antimicrobial Susceptibility Testing of Ciprofloxacin against a Collection of Gram-Negative and Gram-Positive Bacteria Isolates from Putative Uncomplicated Urinary Tract Infections". Focus Technologies, Inc. Effective 24 JUN 2004.
5. Report 83-0004, Brown SD and Traczewski MM "Ciprofloxacin: *In vitro* Potency Compared to Levofloxacin and Establishment of Disk Diffusion Breakpoints". The Clinical Microbiology Institute (CMI), Wilsonville, Oregon. Effective JUN 2004.

RECOMMENDATIONS

(To Be Communicated to Sponsor after Internal Labeling Discussion)

The sponsor should be notified of the following:

- 1 ~~_____~~ must be deleted from the label.
2. There were very few isolates of *Proteus mirabilis* in the clinical trials. ~~_____~~
This organism may be allowed into the label in list #2.
- 3 ~~_____~~ this organism will not be allowed into list #2.
4. Since Susceptibility Testing criteria are based on serum drug levels and not levels of the drug in urine they are not appropriate for drugs indicated for uncomplicated urinary tract infections only. These criteria may be more appropriate if complicated urinary tract infections are also indicated. The Susceptibility Testing Section of the label should state that interpretive criteria for urinary tract infections have not been established and that criteria established for systemic infections may not be appropriate for uncomplicated urinary tract infections.

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Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir _____ Signature _____ Date _____
HFD-590/TLMicro _____ Signature _____ Date _____

CC:
HFD-590/Original NDA # 21-774
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/JMeyer
HFD-520/Pharm/SHundley
HFD-590/Chem/MSeggal
HFD-590/CSO/YYu

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Peter Dionne
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shukal signed on 11/26/04

Shukal Bala
12/9/04 10:28:08 AM
MICROBIOLOGIST