

Efficacy and Safety of a Novel Once-Daily Extended-Release Ciprofloxacin Tablet Formulation for Treatment of Uncomplicated Urinary Tract Infection in Women

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The efficacy and safety of a novel once-daily extended-release ciprofloxacin (ciprofloxacin ER) 500-mg dose were compared with those of an immediate-release ciprofloxacin (ciprofloxacin IR) 250-mg twice-daily dose, each administered orally for 3 days in the treatment of acute uncomplicated urinary tract infection (uUTI) in women. Adult female outpatients (mean age, 39 years) with clinical signs and symptoms of acute uUTI and a positive pretreatment urine culture ($\geq 10^5$ CFU/ml) were enrolled in a multicenter, randomized, double-blind, noninferiority trial. Patients were assessed at a test-of-cure visit (4 to 11 days posttreatment) and a late-posttreatment visit (4 to 6 weeks posttreatment) for microbiological and clinical outcomes and safety. The primary efficacy endpoint and microbiological eradication rate at the test-of-cure visit in the ciprofloxacin ER group (254/272; 93.4%) were noninferior to those in the ciprofloxacin IR group (225/251; 89.6%) (95% confidence interval [CI] of difference, -0.99% , 8.59%). Clinical-cure rates at the test-of-cure visit were 85.7% (233/272) for ciprofloxacin ER and 86.1% (216/251) for ciprofloxacin IR (95% CI of difference, -6.37% , 5.57%). At the late-posttreatment visit, microbiological and clinical outcomes were similar for the two treatments and consistent with test-of-cure results. Both treatments were well tolerated, but the frequencies of nausea and diarrhea were lower in the ciprofloxacin ER group than in the ciprofloxacin IR group (nausea, ER, 0.6%; IR, 2.2%; $P = 0.033$; diarrhea, ER, 0.2%; IR, 1.4%; $P = 0.037$). Once-daily ciprofloxacin ER was safe, effective, and noninferior to twice-daily ciprofloxacin IR in the treatment of acute uUTI. Additionally, ciprofloxacin ER was associated with significantly reduced frequencies of nausea and diarrhea.

Urinary tract infections (UTIs) account for over 7 million physician office visits (mostly for cystitis) and 1 million emergency department visits per year in the United States (3, 8, 15, 24, 25, 29). Trimethoprim-sulfamethoxazole (TMP-SMX) is currently the first-line treatment for acute uncomplicated UTI (uUTI) or acute uncomplicated bacterial cystitis, but bacterial resistance to TMP-SMX is increasing (9, 11, 14, 19, 22), and therefore, fluoroquinolones are recommended as the first-line therapy in areas where resistance to TMP-SMX is high ($>10\%$ to 20%) (29). Ciprofloxacin, a fluoroquinolone antimicrobial agent with a broad spectrum of activity against both gram-negative and gram-positive bacteria, is an effective treatment for a wide variety of bacterial infections, including uUTI (5, 7, 27). However, gastrointestinal (GI) adverse events, such as nausea and diarrhea, remain the most common cause of discontinuation of ciprofloxacin therapy (5, 7).

Ciprofloxacin ER is a new extended-release tablet formulation intended for once-daily administration. When administered after a meal, the ciprofloxacin ER tablet enlarges by absorbing water from the gastric fluid and gradually releases drug through dissolution of the polymeric matrix (17). The tablet releases approximately 90% of the 500-mg dose over a 6-hour period (16) to the upper GI tract, where ciprofloxacin is best absorbed (12). The extended-release profile of ciprofloxacin ER provides peak plasma ciprofloxacin levels that maintain the high area under the plasma concentration-time curve/MIC and maximum plasma concentration/MIC ratios (>100 and >10 , respectively) (16) that are required to optimize bacterial killing and clinical efficacy and avoid bacterial resistance (26) while providing reduced concentrations of ciprofloxacin in the lower GI tract (17). This mechanism of drug delivery markedly contrasts with that of the currently marketed once-daily extended-release ciprofloxacin tablet (CIPRO XR), where drug release is complete within 1.5 to 2 h (2).

By reducing the rate of release of ciprofloxacin and targeting its delivery predominantly to the upper GI tract, the convenience of once-daily ciprofloxacin ER treatment may be associated with a low frequency of GI side effects, such as nausea and diarrhea, and possibly improved patient compliance and reduced treatment costs. Therefore, the objective of this phase III randomized, controlled trial was to compare the efficacy and safety of once-daily ciprofloxacin ER, 500 mg, with those of immediate-release ciprofloxacin (ciprofloxacin IR), 250 mg twice daily, each given for 3 days, for the treatment of acute uUTI in women.

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MATERIALS AND METHODS

The study protocol and amendments were approved by an institutional review board at each site, and the study was conducted in accordance with the Inter-

national Conference on Harmonization Guidelines for Good Clinical Practice. Each patient provided written informed consent prior to undergoing any study procedures.

Study population. Female patients who presented to their physicians with a suspected UTI were considered for enrollment in the clinical study. Eligible patients were nonpregnant, at least 18 years of age, with clinical signs and symptoms of acute uUTI (dysuria, frequency, urgency, pyuria, and/or suprapubic pain) with onset of symptoms not more than 72 h prior to study entry. In addition, patients were required to have a positive pretreatment clean-catch, midstream urine culture, defined as $\geq 10^5$ CFU/ml of an identified single uropathogen and a demonstrated in vitro susceptibility of the uropathogen to ciprofloxacin.

Exclusion criteria included patients with three or more UTIs in the previous 12 months; signs or symptoms of a vaginal infection; known hypersensitivity to ciprofloxacin or other quinolone antibiotics; renal insufficiency (creatinine clearance of < 30 ml/min or serum creatinine of > 3.0 mg/dl); or a history of gastric or duodenal ulcers, upper GI or bowel surgery, active GI disease, gastric reduction surgery, chronic gastroparesis, or severe GI symptoms. Patients who received any cation-containing products (e.g., antacids, sucralfate, didanosine, or calcium, iron, or zinc supplements) or other antimicrobials within 48 h prior to study entry or who received theophylline or warfarin or its derivatives were also excluded.

Study design. This was a prospective, multicenter, randomized, double-blind (double-dummy), parallel-group, noninferiority study, conducted at 70 centers in the United States between June 2003 and January 2004. Patients were randomized in a 1:1 ratio according to a computer-generated randomization code to receive either ciprofloxacin ER (Proquin XR; Depomed, Inc., Menlo Park, CA), 500 mg once daily (QD) for 3 days, or ciprofloxacin IR (CIPRO; Bayer Pharmaceutical Corp., West Haven, CT), 250 mg twice daily (BID) for 3 days. The ciprofloxacin ER dose was chosen to be equivalent to the recommended CIPRO dose of 250 mg BID for 3 days (1), a current standard therapy for acute uUTI (29). Patients were evaluated at baseline and reevaluated at a test-of-cure visit (4 to 11 days after completion of treatment) and at a late-posttreatment visit (4 to 6 weeks after completion of treatment). Adherence to therapy was assessed by pill count.

Microbiological and clinical efficacy outcomes. The primary efficacy endpoint was microbiological eradication in the efficacy population at the test-of-cure visit. Secondary efficacy endpoints included additional microbiological outcomes (persistence and new infection) at the test-of-cure visit, clinical cure and clinical failure at the test-of-cure visit, microbiological outcomes (sustained eradication, persistence, recurrence, and new infection) at the late-posttreatment visit, and clinical outcomes (sustained cure, relapse, and failure) at the late-posttreatment visit. In addition, patients' global evaluations of whether their uUTI had been successfully treated ("yes" or "no") were performed at the test-of-cure visit.

Microbiological eradication was defined as a clean-catch, midstream urine culture at the test-of-cure visit that demonstrated that all uropathogens present at $\geq 10^5$ CFU/ml at baseline had been reduced to $< 10^4$ CFU/ml. Microbiological persistence was defined as the presence of $\geq 10^4$ CFU/ml of the original uropathogen after the completion of therapy. Recurrence was defined as the presence of $\geq 10^4$ CFU/ml of any original uropathogen at the late-posttreatment visit after eradication at the test-of-cure visit. New infection was defined as the presence of $\geq 10^5$ CFU/ml of a uropathogen not present at baseline. Clinical cure was defined as the resolution of all clinical signs (pyuria and hematuria) and symptoms (dysuria, frequency, urgency, and suprapubic pain) of uUTI and no other antibiotic use. Clinical failure was persistence or recurrence of any clinical signs or symptoms after completion of therapy. Relapse was the recurrence of any clinical signs or symptoms following resolution at the test-of-cure visit.

Adverse events were recorded throughout the study by direct questioning and observation of patients and from the results of physical examinations and clinical laboratory tests. All adverse events were assessed for severity and possible relationship to the study drug.

Microbiologic methods. Clean-catch, midstream urine samples collected at the baseline pretreatment visit were sent to a central laboratory (Pathway Diagnostics, Garden Grove, CA), where the urine was cultured by standard techniques for the identification and quantitative determination of uropathogens. Uropathogens were identified to the species level. Uropathogens present at $\geq 10^5$ CFU/ml were tested for susceptibility to ciprofloxacin according to the CLSI (formerly NCCLS) criteria (21).

Statistical methods. Assuming a microbiological eradication rate of 80% for both treatment groups, as obtained from the ciprofloxacin ER groups in a previous pilot study (4), a sample size of 576 patients (288 patients per treatment group) was calculated. This calculation was based on a one-sided test with an α of 0.025, a maximum acceptable treatment difference of 10%, and 85% power.

To allow for up to a 40% nonevaluable rate, an enrollment of approximately 960 patients (480 per group) was required for this study.

The modified intent-to-treat (mITT) population included all randomized patients who met the enrollment criteria for positive urine culture (i.e., $\geq 10^5$ CFU/ml) and uropathogen susceptibility. The efficacy population included mITT patients who had microbiological data at the test-of-cure visit. Patients who used additional antimicrobial agents prior to the test-of-cure visit were excluded from the mITT and efficacy populations for the analysis of microbiological data. Patients who used additional antimicrobial agents were classified as clinical failures if the additional agents were used to treat the uUTI. Data from all study centers were pooled for analysis.

The primary efficacy parameter was the microbiological eradication rate at the test-of-cure visit for the efficacy population. The ciprofloxacin ER treatment was considered noninferior to the ciprofloxacin IR treatment if the lower boundary of the 95% confidence interval (CI) of the difference in microbiological eradication rates between the two treatment groups (ciprofloxacin ER minus ciprofloxacin IR) was not less than -10% . The same analysis of the microbiological eradication rate was also performed for the mITT population.

A two-sided Fisher's exact test was used for the analysis of secondary categorical efficacy parameters, i.e., event rates for the microbiological and clinical outcomes at the test-of-cure visit and the late-posttreatment visit. A 95% CI of the event rates of each treatment group was constructed. In addition, a 95% CI of the difference in event rates between the two treatment groups was constructed. The Cochran-Mantel-Haenszel test for general association with treatment as a stratification factor was used to test the correlation between microbiological eradication status (yes/no) and clinical-cure status (yes/no) at the test-of-cure visit.

Adverse-event summaries and analyses were performed for the safety population, which included all randomized patients who received at least one dose of study drug. The Fisher exact test was used to compare the frequency of adverse events between the treatment groups.

RESULTS

Characteristics of study population. A total of 1,037 female patients were enrolled and randomized; 1,027 patients received a study drug and were included in the safety population, and 540 patients were included in the efficacy population. The most common reason for exclusion from the efficacy population was the absence of a baseline uropathogen at $\geq 10^5$ CFU/ml (434 patients; 41.9%); 20 patients (1.9%) had a baseline organism that was not susceptible to ciprofloxacin (Fig. 1).

Demographic and baseline characteristics (Table 1) were not significantly different between the two treatment groups for the efficacy population and for all randomized patients. The mean age of all randomized patients was 39 years (range, 18 to 89 years), and a majority (93.4%) were younger than 65 years of age. The most common clinical symptoms at baseline were urinary frequency, urgency, and dysuria, each of which was experienced by at least 90% of patients in the efficacy population.

The most common uropathogen at baseline was *Escherichia coli* (81.1% of all patients), and the ciprofloxacin MICs for isolated *E. coli* strains were 0.06 to 1.0 $\mu\text{g/ml}$. Other isolated pathogens (and ciprofloxacin MICs) included *Klebsiella pneumoniae* (0.06 to 1.0 $\mu\text{g/ml}$), *Proteus mirabilis* (0.06 or 1.0 $\mu\text{g/ml}$), group D *Streptococcus*, *Enterococcus* (0.5 or 1.0 $\mu\text{g/ml}$), and *Staphylococcus* species, coagulase negative (0.5 $\mu\text{g/ml}$).

Microbiological outcomes. The microbiological eradication rates at the test-of-cure visit in the efficacy population were similar in the ciprofloxacin ER group (254/272; 93.4%) and the ciprofloxacin IR group (225/251; 89.6%), with a between-group difference of 3.8% (95% CI, -0.99% , 8.59%), demonstrating the noninferiority of ciprofloxacin ER treatment to ciprofloxacin IR treatment. The results of the mITT analysis for micro-

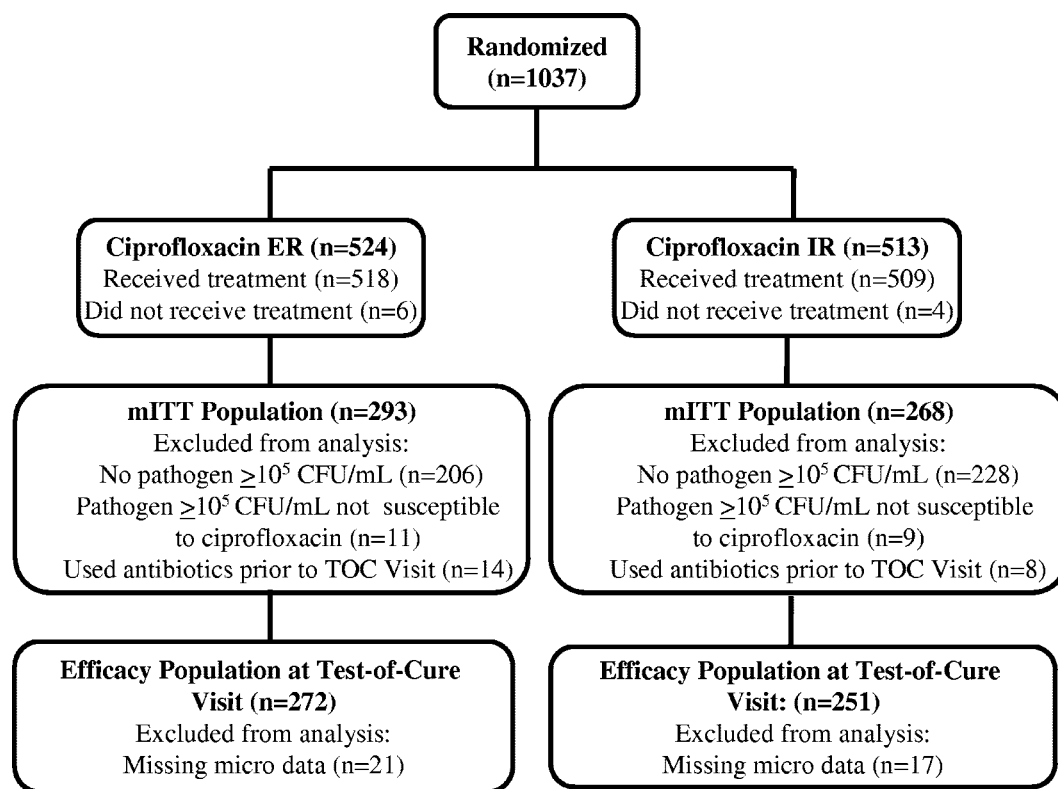


FIG. 1. Disposition of patients. TOC, test of cure.

biological eradication rates at the test-of-cure visit (ciprofloxacin ER, 254/293, 86.7%; ciprofloxacin IR, 225/268, 84.0%; difference, 2.70%; 95% CI, -3.16%, 8.56%) were similar and consistent with the efficacy population results.

The microbiological eradication rates, by the most common baseline uropathogens, for the efficacy population are shown in Table 2. Eradication rates for all common uropathogens, in-

cluding *E. coli*, the most common uropathogen, were comparable in the two treatment groups at the test-of-cure visit.

At the test-of-cure visit, microbiological persistence and new-infection rates observed in the ciprofloxacin ER group were similar to those obtained for the ciprofloxacin IR group (Table 3). Persistent uropathogens were *E. coli* (11 ciprofloxacin ER- and 18 ciprofloxacin IR-treated patients), *K. pneu-*

TABLE 1. Patient demographics and baseline characteristics^a

Parameter	Efficacy population		All randomized patients	
	Ciprofloxacin ER, 500 mg QD for 3 days (n = 283)	Ciprofloxacin IR, 250 mg BID for 3 days (n = 257)	Ciprofloxacin ER, 500 mg QD for 3 days (n = 524)	Ciprofloxacin IR, 250 mg BID for 3 days (n = 513)
Age (yr)				
Mean (SD)	39 (14.7)	40 (15.0)	39 (15.1)	39 (14.8)
Range	18-83	18-86	18-89	18-86
Race [n (%)]				
Caucasian	226 (79.9)	215 (83.7)	401 (76.5)	415 (80.9)
Black	18 (6.4)	15 (5.8)	39 (7.4)	30 (5.8)
Asian	6 (2.1)	2 (0.8)	9 (1.7)	4 (0.8)
Hispanic	33 (11.7)	21 (8.2)	72 (13.7)	58 (11.3)
Native American	0 (0)	1 (0.4)	1 (0.2)	2 (0.4)
Other	0 (0)	3 (1.2)	2 (0.4)	4 (0.8)
Clinical signs and symptoms [n (%)]				
Frequency	265 (93.6)	247 (96.1)	489 (93.3)	481 (93.8)
Urgency	260 (91.9)	239 (93.0)	473 (90.3)	461 (89.9)
Dysuria	252 (89.0)	234 (91.1)	450 (85.9)	455 (88.7)
Suprapubic pain	185 (65.4)	170 (66.1)	336 (64.1)	330 (64.3)
Pyuria	282 (99.6)	255 (99.2)	520 (99.2)	504 (98.2)
Hematuria	5 (1.8)	4 (1.6)	10 (1.9)	6 (1.2)

^a P values for statistical comparisons of all parameters between the two treatment groups were >0.05 in both patient populations.

TABLE 2. Microbiological eradication rates by baseline uropathogen at test-of-cure and late-posttreatment visits: efficacy population

Baseline uropathogen ^a	Eradication rate ^b			
	Test-of-cure visit		Late-posttreatment visit	
	Ciprofloxacin ER, 500 mg QD for 3 days	Ciprofloxacin IR, 250 mg BID for 3 days	Ciprofloxacin ER, 500 mg QD for 3 days	Ciprofloxacin IR, 250 mg BID for 3 days
<i>E. coli</i>	211/222 (95.0)	184/202 (91.1)	153/187 (81.8)	138/167 (82.6)
<i>K. pneumoniae</i>	11/12 (91.7)	10/13 (76.9)	6/6 (100.0)	7/9 (77.8)
Group D <i>Streptococcus</i> , <i>Enterococcus</i>	6/10 (60.0)	7/9 (77.8)	5/7 (71.4)	4/4 (100.0)
<i>P. mirabilis</i>	7/7 (100.0)	8/9 (88.9)	4/4 (100.0)	5/5 (100.0)
<i>Staphylococcus</i> species, coagulase negative	7/9 (77.8)	5/7 (71.4)	6/7 (85.7)	5/6 (83.3)
Beta <i>Streptococcus</i> , presumptive group B	1/1 (100.0)	6/6 (100.0)	0/0	4/5 (80.0)

^a Includes uropathogens isolated in at least five patients in either treatment group.

^b Values indicate the number of patients with eradication of baseline uropathogen/total number of patients (%). The test-of-cure visit was at 4 to 11 days, and the late-posttreatment visit was at 4 to 6 weeks after completion of double-blind treatment.

moniae (1 ciprofloxacin ER and 3 ciprofloxacin IR), group D *Streptococcus*, *Enterococcus* (4 ciprofloxacin ER and 2 ciprofloxacin IR), *P. mirabilis* (1 ciprofloxacin IR), and *Staphylococcus* species, coagulase negative (2 ciprofloxacin ER and 2 ciprofloxacin IR). The most common new infection was group D *Streptococcus*, *Enterococcus* (Table 4); gram-negative rods were reported as new infections in only 10 patients treated with ciprofloxacin ER and 7 patients treated with ciprofloxacin IR.

At the late-posttreatment visit, the sustained eradication rate in the ciprofloxacin ER group (82.4%) was noninferior to that in the ciprofloxacin IR group (83.2%) (difference, $-0.8%$; 95% CI, $-8.00%$, $6.40%$) (Table 3). Similarly, high eradication rates for *E. coli* were maintained and were similar in the two treatment groups at the late-posttreatment visit (Table 2). In addition, rates of recurrence, persistence, and new infection in the ciprofloxacin ER and ciprofloxacin IR groups were comparable (Table 3). Persistent organisms were *E. coli* (7 cipro-

floxacin ER- and 13 ciprofloxacin IR-treated patients), *K. pneumoniae* (1 ciprofloxacin IR), group D *Streptococcus*, *Enterococcus* (2 ciprofloxacin ER), and *Staphylococcus* species, coagulase negative (1 ciprofloxacin ER and 1 ciprofloxacin IR). The most common new infection was group D *Streptococcus*, *Enterococcus* (Table 4).

Clinical outcomes. The clinical cure rates at the test-of-cure visit for the efficacy population were also similar in the ciprofloxacin ER group (233/272; 85.7%) and the ciprofloxacin IR group (216/251; 86.1%). The between-group difference in clinical-cure rates was $-0.4%$ (95% CI, $-6.37%$, $5.57%$), again demonstrating the noninferiority of ciprofloxacin ER to ciprofloxacin IR. For patients with *E. coli* infection at baseline, clinical-cure rates were 197/227 (86.6%) in the ciprofloxacin ER group and 176/204 (86.3%) in the ciprofloxacin IR group at the test-of-cure visit.

Sustained clinical-cure rates at the late-posttreatment visit were 75.7% in the ciprofloxacin ER group and 78.8% in the ciprofloxacin IR group (difference, $-3.1%$; 95% CI, $-10.60%$, $4.40%$) (Table 3). Clinical-cure rates by baseline uropathogen were also similar between the two treatment groups at the late-posttreatment visit. In addition, the clinical-relapse rate at the late posttreatment visit in the ciprofloxacin ER group (6.9%) was similar to that observed in the ciprofloxacin IR group (7.2%) (Table 3).

There was a statistically significant positive correlation between clinical-cure status and microbiological-eradication status at the test-of-cure visit for all patients ($P = 0.009$), with 81.6% (222/272) of patients in the ciprofloxacin ER group and 77.7% (195/251) of patients in the ciprofloxacin IR group having both clinical cure and microbiological eradication. Similar numbers of patients in each group rated their treatment as successful in the patient global evaluation of treatment success (ciprofloxacin ER, 92.9%; IR, 95.7%; difference, 2.80%; 95% CI of difference, $-6.69%$, $1.09%$; $P = 0.196$).

Safety results. Ciprofloxacin ER and ciprofloxacin IR were both well tolerated during the study, with a low overall frequency of adverse events. Sixty-six (12.7%) patients in the ciprofloxacin ER group and 75 (14.7%) patients in ciprofloxacin IR group experienced at least one adverse event during study treatment (the dosing period plus the 3-day period after dosing) (Table 5). The types of adverse events were qualitatively similar in the two treatment groups, and most were of

TABLE 3. Microbiological and clinical response rates at test-of-cure and late-posttreatment visits: efficacy population

Response	Response rate ^a	
	Ciprofloxacin ER, 500 mg QD for 3 days	Ciprofloxacin IR, 250 mg BID for 3 days
Microbiological		
Test-of-cure visit		
Eradication	254/272 (93.4)	225/251 (89.6)
Persistence	18/272 (6.6)	26/251 (10.4)
New infection	42/272 (15.4)	36/251 (14.3)
Late-posttreatment visit		
Sustained eradication	182/221 (82.4)	168/202 (83.2)
Recurrence	29/221 (13.1)	19/202 (9.4)
Persistence	10/221 (4.5)	15/202 (7.4)
New infection	46/220 (20.9)	40/201 (19.9)
Clinical		
Test-of-cure visit		
Cure	233/272 (85.7)	216/251 (86.1)
Failure	39/272 (14.3)	35/251 (13.9)
Late-posttreatment visit		
Sustained cure	196/259 (75.7)	175/222 (78.8)
Relapse	18/259 (6.9)	16/222 (7.2)
Failure	453/259 (17.4)	31/222 (14.0)

^a Values indicate the number of patients with response/number of patients in the efficacy population (%). The test-of-cure visit was at 4 to 11 days, and the late-posttreatment visit was at 4 to 6 weeks after completion of double-blind treatment.

TABLE 4. New infections at test-of-cure and late-posttreatment visits: efficacy population

New-infection uropathogen ^a	No. (%) of new infections			
	Test-of-cure visit		Late post-treatment visit ^b	
	Ciprofloxacin ER, 500 mg QD for 3 days	Ciprofloxacin IR, 250 mg BID for 3 days	Ciprofloxacin ER, 500 mg QD for 3 days	Ciprofloxacin IR, 250 mg BID for 3 days
No. of patients with data	272	251	220	201
Any	42 (15.4)	36 (14.3)	46 (20.9)	40 (19.9)
<i>Acinetobacter</i> species	2 (0.7)	1 (0.4)	0 (0)	0 (0)
Beta <i>Streptococcus</i> , presumptive group B	3 (1.1)	1 (0.4)	2 (0.9)	0 (0)
<i>Escherichia coli</i>	4 (1.5)	0 (0)	1 (0.4)	5 (2.3)
Group D <i>Streptococcus</i> , <i>Enterococcus</i>	24 (8.8)	23 (9.2)	14 (6.4)	10 (5.0)
<i>Klebsiella pneumoniae</i>	2 (0.7)	3 (1.2)	4 (1.8)	2 (1.0)
<i>Staphylococcus</i> species, coagulase negative	2 (0.7)	1 (0.4)	0 (0)	1 (0.5)

^a Includes newly isolated uropathogens in more than two patients at either visit.
^b The test-of-cure visit was at 4 to 11 days, and the late-posttreatment visit was at 4 to 6 weeks after completion of double-blind treatment.

mild to moderate severity. The most common adverse events occurred in the gastrointestinal (4.0% of all patients) and nervous (2.5% of all patients) systems. Overall, the most common events were headache (1.7% of all patients) and nausea (1.4% of all patients). Gastrointestinal adverse events were less frequently reported in the ciprofloxacin ER group (2.9%) than in the ciprofloxacin IR group (5.1%). The frequencies of nausea and diarrhea were significantly lower in the ciprofloxacin ER group than in the ciprofloxacin IR group (nausea, ER, 0.6%; IR, 2.2%; $P = 0.033$; diarrhea, ER, 0.2%; IR, 1.4%; $P = 0.037$) (Table 5).

Three patients (0.6%) in the ciprofloxacin ER group and six patients (1.2%) in the ciprofloxacin IR group experienced serious adverse events, none of which were considered to be related to the study drug. Seven patients (1.4%) in the ciprofloxacin ER group and three patients (0.6%) in the ciprofloxacin IR group had adverse events leading to discontinuation of the study drug.

DISCUSSION

Acute uUTIs are among the most commonly encountered bacterial infections in clinical practice. Almost half of all women will experience at least one urinary tract infection in their lifetime (6, 8, 20). The increasing trend in the United States in rates of resistance to TMP-SMX (11, 14, 19, 22), the

current standard therapy for uUTI, indicates an increasing need for alternative safe and effective fluoroquinolone therapy in areas where resistance rates exceed 10 to 20% (29). The in vitro activities of TMP-SMX, ciprofloxacin, and nitrofurantoin found in a recent study led the authors to suggest that ciprofloxacin or nitrofurantoin could provide adequate alternative therapy to TMP-SMX, which validates an earlier recommendation for the use of fluoroquinolones where TMP-SMX therapy is no longer prudent because of high resistance rates (>10 to 20%) (19). This underscores the need to develop effective fluoroquinolone treatments that have reduced side effects and hence the potential to improve patient compliance, convenience, and cost effectiveness. This treatment strategy should warrant considerable interest from patients, providers, and health care organizations (10).

The results of this large, multicenter study demonstrate that ciprofloxacin ER, 500 mg QD, is effective and noninferior to ciprofloxacin IR, 250 mg BID, when administered for 3 days for the treatment of acute uUTI in women. The consistent results obtained for the efficacy and mITT populations demonstrate the robustness of the study results. The high eradication rate of 93.4% observed for ciprofloxacin ER in this study is comparable to the rates of 94.5% observed for a currently marketed extended-release formulation of ciprofloxacin, 500 mg, given once daily for 3 days (13, 30) and 93.7% for ciprofloxacin IR, 250 mg, given twice daily for 3 to 7 days (13, 18, 28).

As expected, *E. coli* was the isolated uropathogen in the majority (81%) of patients in both treatment groups. The ciprofloxacin ER treatment showed high microbiological eradication rates for the most common uropathogens of uUTI, including *E. coli*, *K. pneumoniae*, and *P. mirabilis*, which were similar to the eradication rates observed for ciprofloxacin IR. The high eradication rates are consistent with the predictions of pharmacokinetic/pharmacodynamic studies with ciprofloxacin ER in healthy volunteers that showed single-dose and steady-state urinary concentrations of ciprofloxacin that substantially exceeded the ciprofloxacin MICs for common causative pathogens of uUTI over the 24-hour dosing interval. The urinary concentrations, as well as the area under the plasma concentration-time curve/MIC and maximum plasma concentration/MIC ratios following single-dose and steady-state administra-

TABLE 5. Most frequent adverse events occurring while patients were on study drug: safety population

Preferred term (MedDRA) ^b	No. (%) of events ^a		P value ^c
	Ciprofloxacin ER, 500 mg QD for 3 days (n = 518)	Ciprofloxacin IR, 250 mg BID for 3 days (n = 509)	
At least one event	66 (12.7%)	75 (14.7%)	NS
Gastrointestinal system	15 (2.9%)	26 (5.1%)	0.080
Nausea	3 (0.6%)	11 (2.2%)	0.033
Diarrhea	1 (0.2%)	7 (1.4%)	0.037
Nervous system	11 (2.1%)	15 (2.9%)	NS
Headache	7 (1.4%)	10 (2.0%)	NS

^a Includes adverse events reported by >1% of patients in either group during double-blind treatment and for 3 days following treatment.
^b MedDRA, Medical Dictionary for Regulatory Activities.
^c NS, not significant.

tion, were comparable for ciprofloxacin ER and ciprofloxacin IR (16).

The frequency of new infections observed in this study for both treatment groups was high compared to previous studies. A majority of the new infections were caused by *Enterococcus*, which is not associated with uUTI, and most of the patients with new infections had no clinical symptoms and did not require additional therapy. The frequency of new infections associated with gram-negative rods is more consistent with the frequency of new infections reported in the literature (23).

The clinical-cure rate with ciprofloxacin ER (85.7%) was similar and noninferior to the rates observed for the ciprofloxacin IR group (86.1%) at the test-of-cure visit. These results indicate consistency between the clinical-cure and the microbiological-eradication rates, consistent with the significant positive correlation between microbiological-eradication and clinical-cure rates at this visit. In addition, approximately 93% of patients in the ciprofloxacin ER group and 96% in the ciprofloxacin IR group rated their treatment as successful in resolving their uUTI.

Ciprofloxacin ER was safe and well tolerated in this study. The low frequencies of adverse events (12.7% for ciprofloxacin ER and 14.7% for ciprofloxacin IR) are similar to the approximately 15% frequency reported for ciprofloxacin IR in previous studies conducted in the United States (27). The rates for a marketed once-daily extended-release formulation of ciprofloxacin are approximately the same as for ciprofloxacin IR (13). The most common adverse events occurred in the gastrointestinal and nervous systems, consistent with previous reports for ciprofloxacin (7, 27).

An important safety finding in this study was the low frequency of nausea and diarrhea in the ciprofloxacin ER group, consistent with the trend observed in an earlier phase II clinical trial with ciprofloxacin ER (4). Although not significant statistically, the frequency of all GI adverse events in the ciprofloxacin ER group (2.9%) was 43% lower than the frequency of GI adverse events in the ciprofloxacin IR group (5.1%). These results support the earlier hypothesis that ciprofloxacin ER is likely to be associated with a reduced risk of GI adverse events compared to ciprofloxacin IR. The frequency of GI adverse events in the ciprofloxacin IR group is consistent with the approximately 5% frequency observed for ciprofloxacin IR in previous worldwide phase II/III clinical trials ($n = 9,473$) (7). Furthermore, the frequencies of nausea and diarrhea for ciprofloxacin IR treatment (2.2% and 1.4%) are similar to the frequencies of 2.5% and 1.6%, respectively, observed previously from clinical investigations ($n = 49,038$) of all formulations, all dosages, and all drug therapy durations and for all indications of ciprofloxacin IR (1).

The precise mechanism of this reduced frequency of GI adverse events with ciprofloxacin ER treatment is not known but may be attributable to the extended-release properties of ciprofloxacin ER. This extended-release profile results in approximately 175 mg of the 500-mg dose being released into the GI tract in the first 2 h after dosing (manufacturer's dissolution data) compared to 200 mg of a 250-mg dose released within the first 30 min for ciprofloxacin IR. This corresponds to an approximately fourfold reduction in the amount of drug released into the GI tract in the first 30 min after dosing with ciprofloxacin ER, which could account for the reduced frequency of

nausea. The reduced concentrations of drug in the lower GI tract, resulting from reduced drug delivery and release in the colon, with a lower concentration relative to the MIC for the colonic flora, may be responsible for the reduced frequency of diarrhea.

In conclusion, ciprofloxacin ER, 500 mg QD for 3 days, is a safe and effective treatment for acute uncomplicated UTIs in women and is associated with significantly reduced frequencies of nausea and diarrhea. The convenience of once-daily dosing and the reduced GI adverse-event profile with ciprofloxacin ER may potentially result in improved patient compliance and decreased costs.

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