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CLINICAL THERAPEUTICS

Early Clinical Assessment of the Antimicrobial Activity of Finafloxacin Compared to Ciprofloxacin in Subsets of Microbiologically Characterized Isolates

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ABSTRACT Two phase II studies were performed with patients with uncomplicated urinary tract infections (uUTIs) and complicated urinary tract infections (cUTIs) or acute pyelonephritis (PN) to compare finafloxacin (300 mg twice a day [b.i.d.] orally for uUTI and 800 mg once a day [q.d.] intravenously [i.v.] for cUTI/PN) and ciprofloxacin (250 mg b.i.d. orally for uUTI and 400 mg b.i.d. i.v. for cUTI/PN). The early response to the study medications was evaluated in the microbiological intent-to-treat population (mITT) at day 3. A total of 21% of the isolates were ciprofloxacin resistant, 13.7% were primed pathogens carrying a mutation(s) potentially fostering fluoroquinolone resistance development, and 7.1% produced extended-spectrum β-lactamases (ESBLs). Finafloxacin demonstrated very good early clinical activity, with microbiological eradication rates of 88.6% ($n = 132$), compared to 78.7% ($n = 61$) for ciprofloxacin, and 69.6% ($n = 23$), compared to 35.7% ($n = 14$) for ciprofloxacin, in patients with ciprofloxacin-resistant uropathogens; 94.1% ($n = 17$), compared to 80.0% ($n = 10$) for ciprofloxacin, in patients infected with uropathogens primed for fluoroquinolone resistance uropathogens; and 91.7% ($n = 11$), compared to 0% for ciprofloxacin, in patients infected with ESBL producers. Finafloxacin demonstrated early and rapid activity against uropathogens, including fluoroquinolone-resistant and/or multiresistant pathogens or ESBL producers, while ciprofloxacin was less active against this subset of resistant pathogens. Susceptibilities of pathogens were quantitated by broth microdilution. Isolates were subgrouped according to their susceptibility patterns, in particular first-step quinolone resistance, quinolone resistance, and ESBL production. Eradication was defined as the elimination or reduction of study entry pathogens to $<10^3$ CFU/ml in urine culture. (The studies described in this paper have been registered at ClinicalTrials.gov under identifiers NCT00722735 and NCT01928433.)

KEYWORDS antimicrobial agents, clinical trials, early eradication, finafloxacin, fluoroquinolone, urinary tract infection

Traditional primary efficacy endpoints for clinical and microbiological response rates of antibacterial treatment of urinary tract infections are documented at the test-of-cure visit, i.e., approximately 7 days after the last treatment day (1, 2). Clinical and microbiological responses to antibiotic therapy at this time are the composite effect of innate and adaptive immune responses and antibacterial treatment, respectively, as well as adaptive responses of the pathogen. The use of an early primary endpoint or an interim analysis on day 3 of treatment, however, provides a more focused analysis of the antibacterial activity of an antibiotic, as the impacts of confounding factors, such as an immune response supporting bacterial eradication on the one hand and adaptive effects of the pathogen supporting adhesion, colonization, and invasion on the other

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TABLE 1 Velocity of the reduction of viable counts from uropathogens in urine specimens of uUTI patients, determined in a phase II study[a]

Ciprofloxacin MIC of isolate (mg/liter)	Medication	CFU/ml			
		Predose	2 h	4 h	8 h
0.008	Finafloxacin	1.7×10^7	—	—	—
0.012	Finafloxacin	1.0×10^6	—	—	—
0.012	Finafloxacin	2.7×10^5	—	—	—
0.19	Finafloxacin	2.8×10^5	—	—	—
>32	Finafloxacin	1.5×10^8	3.6×10^6	2.5×10^4	—
0.008	Ciprofloxacin	1.4×10^5	—	—	—
0.012	Ciprofloxacin	2.3×10^6	2.0×10^3	—	—
0.19	Ciprofloxacin	3.4×10^7	6.1×10^4	2.7×10^3	—

[a]Viable counts of pathogens isolated from urine specimens of uUTI patients were determined before and 2, 4, and 8 h after treatment with a single oral dose of 250 mg ciprofloxacin or 300 mg finafloxacin. —, no growth was detected.

hand, are minimized (3). The U.S. Food and Drug Administration (FDA) has defined a new primary endpoint for the assessment of clinical efficacy in the treatment of skin and skin structure infections (4). The clinical response should be based on a quantitative measure of lesion size 48 to 72 h after the commencement of ongoing antibiotic therapy compared to the baseline (4). However, this guideline has been discussed controversially (5), and early responses may not correlate with clinical and microbiological responses at the test-of-cure visit, which is the ultimate goal of antibiotic therapy. However, a recent quantitative analysis of microbiological and/or pharmacodynamic parameters as well as recent clinical trials have confirmed that early evaluation of patients prevented inappropriate or ineffective therapy (6, 7). It was demonstrated previously that the more rapid and more pronounced bactericidal *in vitro* activity of amoxicillin than that of ampicillin is clinically relevant. It was shown by fractionated sampling of urine from cystitis patients that one dose of amoxicillin reduced viable counts of uropathogens more rapidly than ampicillin (8, 9). A review of historical and modern data came to the conclusion that antimicrobial treatment effects are most apparent early in therapy, although later outcomes provide important supportive information (10).

Furthermore, short and efficacious treatment regimens help to minimize side effects and reduce resistance development (11). To support such an approach, a drug should achieve pathogen eradication within a short period of time.

The subanalysis of the clinical phase II studies described in this publication aimed to evaluate the early response of patients with uncomplicated urinary tract infections (uUTIs) and complicated urinary tract infections (cUTIs) or acute pyelonephritis (PN) to finafloxacin treatment to focus on the antibacterial action of the agent while minimizing the impact of confounding factors such as the host immune response. Ciprofloxacin served as a comparator.

RESULTS

Phase II in uUTI. In a proof-of-concept phase II study, the efficacies of oral doses of finafloxacin (300 mg twice a day [b.i.d.]) and the comparator ciprofloxacin (250 mg b.i.d.) in the treatment of patients with uUTI were evaluated. The eradication rate in the microbiological intent-to-treat (mITT) population at the end of treatment on days 4 to 6 was 100% for both treatment groups.

To examine if the velocity of the antibacterial activity of finafloxacin *in vitro* could be verified in patients, the reduction of viable counts of pathogens (*Escherichia coli* only) was monitored in a subset of 8 patients within the first 8 h after they were dosed with the initial oral dose of the antibiotic. Five of these patients received finafloxacin, and 3 patients were dosed with ciprofloxacin. Eradication of the uropathogens was achieved within 2 h after the initial 300-mg dose of finafloxacin for all quinolone-susceptible pathogens (MICs of 0.08 to 0.19 mg/liter) (Table 1). A highly finafloxacin-resistant *E. coli* strain (ciprofloxacin MIC of >32 mg/liter) was eradicated within 8 h after the first

TABLE 2 Uropathogens isolated from the urine specimens of cUTI and pyelonephritis patients at the screening visit[a]

Isolate at screening	Frequency of isolation (%) (no. of isolates)		
	Finafloxacin (n = 134)	Ciprofloxacin (n = 64)	Total (n = 198)
Escherichia coli	83.5 (111)	78.1 (50)	81.7 (161)
Klebsiella pneumoniae	6 (8)	6.3 (4)	6.1 (12)
Proteus mirabilis	2.3 (3)	3.1 (2)	2.5 (5)
Enterococcus faecalis	0.8 (1)	4.7 (3)	2.0 (4)
Streptococcus agalactiae	1.5 (2)	1.6 (1)	1.5 (3)
Acinetobacter baumannii	1.5 (2)	0 (0)	1.0 (2)
Citrobacter koseri	0.8 (1)	1.6 (1)	1.0 (2)
Klebsiella oxytoca	0.8 (1)	1.6 (1)	1.0 (2)
Morganella morganii	0.8 (1)	1.6 (1)	1.0 (2)
Citrobacter freundii	0.8 (1)	0 (0)	0.5 (1)
Enterobacter cloacae	0.8 (1)	0 (0)	0.5 (1)
Pseudomonas aeruginosa	0.8 (1)	0 (0)	0.5 (1)
Staphylococcus aureus	0 (0)	1.6 (1)	0.5 (1)
Staphylococcus saprophyticus	0.8 (1)	0 (0)	0.5 (1)

[a]The frequencies of different bacterial species isolated from the urine specimens of cUTI and pyelonephritis patients at the screening visit in a phase II study were determined. Data for the mITT population are shown.

finafloxacin dose. In comparison, all patients in the ciprofloxacin treatment group were infected with ciprofloxacin-susceptible pathogens, which were eradicated within 2 h (MIC of 0.08 mg/liter), 4 h (MIC of 0.012 mg/liter), and 8 h (MIC of 0.19 mg/liter) after the initial ciprofloxacin dose, respectively (Table 1).

Phase II in cUTI or pyelonephritis. (i) Characterization of the pathogens. For patients with cUTI or acute pyelonephritis, 198 baseline uropathogens were isolated from the urine samples of 193 patients in the mITT population. A total of 81.7% of these pathogens were *E. coli*, 7.1% were *Klebsiella* spp., 2.5% were *Proteus mirabilis*, and 6.1% and 2.5% were other Gram-negative and Gram-positive bacterial species, respectively. The few isolated Gram-positive bacteria were excluded from further analysis because of nonsignificant numbers of isolates (Table 2). Resistance to different test antibiotics that were used to characterize the isolated uropathogens was determined (Table 3). Resistance to ampicillin (59.2%), nalidixic acid (31.9%), trimethoprim (30.7%), ciprofloxacin (21%), and amoxicillin-clavulanic acid (co-amoxiclav) (20.7%) was most common among the isolates. Isolated uropathogens with resistance to one of the tested nonfluoroquinolone antibiotics in general showed high levels of coresistance with ciprofloxacin,

TABLE 3 Characterization of pathogens isolated in phase II from cUTI and pyelonephritis patients[a]

Antibiotic	No. of tested pathogens	% resistant pathogens	MIC_{50} (mg/liter)	MIC_{90} (mg/liter)	% of pathogens with additional ciprofloxacin coresistance	Proportion of pathogens with both resistances treated with ciprofloxacin (%)	Proportion of pathogens with both resistances treated with finafloxacin (%)
Ampicillin	179	59.2	>32	>32	33.0	22.8	18.0
Cefadroxil	179	12.3	NA	NA	54.5	7.0	6.6
Cefepime	179	3.4	<1	<1	100.0	3.5	3.3
Cefotaxime	179	9.5	<1	>2	58.8	5.3	5.7
Co-amoxiclav	179	20.7	4	16	51.4	14.0	9.0
Gentamicin	179	7.8	<1	2	92.9	10.5	5.7
Imipenem	179	0.6	0.19	>0.19	0.0	0.0	0.8
Amdinocillin	179	10.1	1	>1	38.9	3.5	4.1
Nitrofurantoin	179	11.7	<16	128	42.9	7.0	4.1
Piperacillin-tazobactam	179	2.8	1.5	4	80.0	1.8	2.5
Trimethoprim	179	30.7	<0.5	>16	50.9	15.8	15.6
Nalidixic acid	185	31.9	4	>128	66.1	24.1	19.7
Ciprofloxacin	186	21.0	≤0.03	32	NA	NA	NA
Finafloxacin	186	NA	0.12	32	NA	NA	NA

[a]The resistance profiles of the Gram-positive pathogens isolated from the urine specimens of cUTI and pyelonephritis patients at the screening visit in a phase II study were determined. The frequencies of resistance to 14 antibiotics, MIC_{50} values, and MIC_{90} values are shown. In addition, the frequencies of pathogens with resistance to the listed antibiotic and ciprofloxacin are shown together with the frequencies of such strains in the different treatment arms of the clinical trial. NA, not applicable.

TABLE 4 Eradication of pathogens from the urine specimens of patients with cUTI/pyelonephritis on day 3 of a phase II clinical study (mITT population)[a]

Pathogen type	% eradication (no. of specimens with pathogen eradicated out of total no. of specimens)	
	Finafloxacin	Ciprofloxacin
All pathogens	88.6 (117 out of 132)	78.7 (48 out of 61)
ESBL producers	91 (10 out of 11)	0 (0 out of 3)
Ciprofloxacin resistant	69.6 (16 out of 23)	35.7 (5 out of 14)
Ciprofloxacin sensitive	92.0 (92 out of 100)	90.7 (39 out of 43)
Primed for FQ resistance	94.1 (16 out of 17)	80.0 (8 out of 10)

[a]The rates of eradication of pathogens from the urine of cUTI and pyelonephritis patients 3 days after the start of treatment in a phase II study were determined. FQ, fluoroquinolone.

varying from 33.0% (ampicillin-resistant pathogens) to 92.9% (gentamicin-resistant pathogens) (Table 3). A total of 7.1% of the isolates produced extended-spectrum β-lactamases (ESBLs), 31.9% of the pathogens isolated at the screening visit were nalidixic acid resistant, and 66.1% of these nalidixic acid-resistant strains were also ciprofloxacin resistant.

MIC_{50} and MIC_{90} values for the predominant species *E. coli* were 0.12 mg/liter and 32 mg/liter for finafloxacin and $\leq$0.03 mg/liter and 32 mg/liter for ciprofloxacin, respectively; MIC_{50} and MIC_{90} values of both drugs for all other pathogens were 0.5 mg/liter and 32 mg/liter, respectively (all MICs were determined at pH 7.2).

(ii) Analysis of efficacy. To examine the velocity of the antibacterial activity of finafloxacin in cUTI and pyelonephritis patients, the presence of pathogens in the urine specimens of the mITT study population was analyzed on the third day after the initiation of antibiotic therapy. Overall, pathogens were eradicated from the urine of 88.6% of patients treated with finafloxacin at day 3, compared to 78.7% of patients treated with ciprofloxacin (Table 4). Finafloxacin (eradication in 92 of 100 patients; 92.0%) and ciprofloxacin (eradication in 39 of 43 patients; 90.7%) displayed similar efficacies against ciprofloxacin-susceptible pathogens. However, finafloxacin showed a very rapid antimicrobial effect against fluoroquinolone-resistant pathogens: ciprofloxacin-resistant pathogens were eradicated by finafloxacin by day 3 in 16 of 23 patients (69.6%), whereas ciprofloxacin eradicated the pathogens in 5 of 14 patients (35.7%). Interestingly, the levels of ciprofloxacin resistance were not equally distributed among the different age groups in the patient population: 24% of pathogens isolated from patients aged >35 years (76% of the patient population; average MIC, 6.4 mg/liter) were resistant to ciprofloxacin, whereas the level of ciprofloxacin resistance was 7% in patients aged $\leq$35 years (24% of the patient population; average MIC, 2 mg/liter). The higher rate of fluoroquinolone resistance in this older patient population had a negative effect on the antibacterial activity of ciprofloxacin, resulting in 73% pathogen eradication on day 3, whereas finafloxacin showed pronounced efficacy in this patient group (90% eradication).

The activity of finafloxacin against ESBL-producing bacteria was high: finafloxacin eradicated ESBL producers from the urine samples of 10 out of 11 patients (91%) on day 3 of the study. In comparison, ciprofloxacin did not show a positive microbiological effect in any of the three patients infected with ESBL producers. In general, ciprofloxacin showed lower activity than finafloxacin against strains with resistance against 1 of 11 tested nonfluoroquinolone antibiotics. In contrast to ciprofloxacin, finafloxacin eradicated pathogens that were resistant to cephalosporins, imipenem, amdinocillin, aminoglycosides, nitrofurantoin, and trimethoprim at a higher rate by day 3 of treatment (Fig. 1). Finafloxacin also showed higher efficacy in patients infected with pathogens that were resistant to either of these agents as well as those with ciprofloxacin resistance (Fig. 1 and Table 3). The difference in the activities of finafloxacin and ciprofloxacin was especially obvious in patients infected with ciprofloxacin-resistant pathogens carrying cephalosporin (cefadroxil, cefepime, or cefotaxime) coresistance (Table 2). For doubly ciprofloxacin- and cephalosporin-resistant pathogens isolated

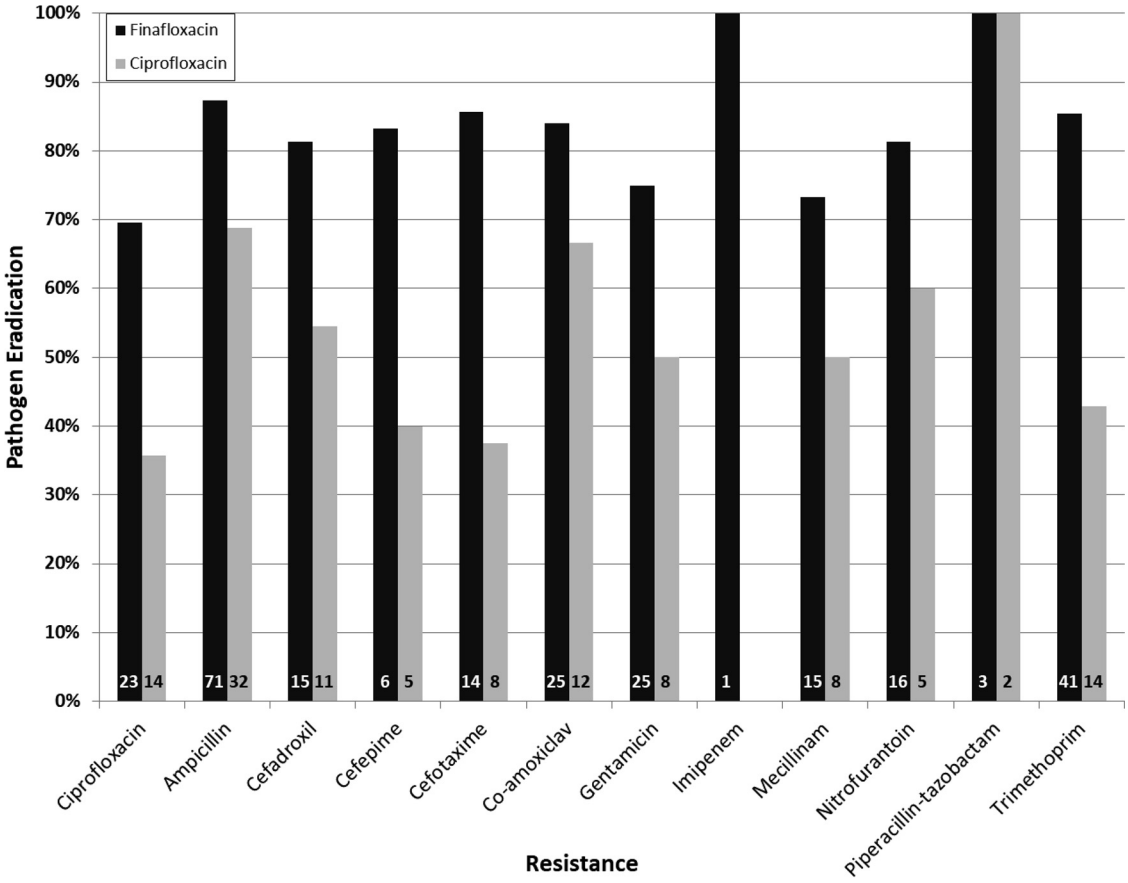

FIG 1 Pathogen eradication from the patients' urine specimens on day 3 of therapy with finafloxacin (dark columns) or ciprofloxacin (light columns) in the mITT population. Numbers in the columns show the numbers of patients in the different study arms, with uropathogens resistant to each of the antibiotics displayed at the bottom.

from urine samples, pathogens in 16 out of 19 (84.2%) patients were eradicated by finafloxacin, and pathogens in only 1 out of 12 (8.3%) patients were eradicated by ciprofloxacin.

Finafloxacin and ciprofloxacin eradicated 94.1% (16 out of 17) and 80% (8 out of 10), respectively, of primed pathogens that carried a mutation(s) potentially fostering fluoroquinolone resistance development (all pathogens with nalidixic acid resistance [MIC of >16 mg/liter]) but that were still ciprofloxacin susceptible (MIC of <4 mg/liter) (Table 4).

DISCUSSION

Data generated by the interim analysis on day 3 of treatment of patients with cUTI and acute pyelonephritis demonstrated the following. First, finafloxacin exerted rapid and pronounced antibacterial activity. This is supported by the data from patients with uUTI furnishing the proof of the elimination of pathogens from the patients' urine specimens within the first 2 h after the first oral dose of finafloxacin for fluoroquinolone-susceptible uropathogens and within 8 h for highly fluoroquinolone-resistant (ciprofloxacin MIC of >32) uropathogens. Furthermore, the study with patients with cUTI and acute pyelonephritis showed that viable counts in the urine were rapidly reduced by finafloxacin irrespective of whether the pathogens were fluoroquinolone susceptible, resistant, or borderline susceptible, due to either a single mutation in the quinolone-resistance-determining region or a plasmid-mediated quinolone resistance mechanism. These mutants are difficult to detect, as fluoroquinolone MICs remain below the resistance breakpoint so that such strains pass susceptibility testing unnoticed but are primed to mutate further. In this study, 13.7% of the pathogens

isolated from cUTI and pyelonephritis patients were characterized as primed strains. They not only appear to be broadly present in the patient population in general but also were even isolated from fluoroquinolone-naive patients (reviewed in references 12 and 13). Therefore, it is important to identify such strains, for example, by using nalidixic acid as an indicator of the acquisition of a first mutation with the aim of evaluating whether finafloxacin and/or ciprofloxacin may by active against this subgroup of isolates. This study revealed that finafloxacin was more active than ciprofloxacin against primed as well as fluoroquinolone-resistant strains. Finafloxacin eradicated 94.1% and 69.6% of primed and ciprofloxacin-resistant pathogens, respectively, in cUTI/pyelonephritis patients on day 3 of an 800-mg once daily schedule versus 80% and 35.7% eradications achieved by ciprofloxacin with a 400-mg b.i.d. schedule (Table 4). Furthermore, ciprofloxacin-resistant isolates that were coresistant to aminopenicillins, cephalosporins, gentamicin, and also trimethoprim-sulfamethoxazole were eradicated more effectively by finafloxacin than by ciprofloxacin (Table 4 and Fig. 1). The difference is particularly evident for cephalosporin-resistant isolates, thus indicating that ESBL production may contribute to the better activity of finafloxacin than of ciprofloxacin against resistant subpopulations. Finafloxacin eradicated 91% of ESBL producers on day 3 of treatment, whereas ciprofloxacin was not active against ESBL-positive strains. This result is in agreement with previous findings showing that finafloxacin was active against Gram-negative bacteria, including strains expressing *qepA*, *qnrA1*, *qnrB1*, *qnrS1*, and *aac(6′)-Ib-cr*, alone or in combination with chromosomal fluoroquinolone resistance mutations, as well as non-CTX-M ESBL-producing *Enterobacteriaceae* (14), and exhibited rapid and pronounced bactericidal activity against TEM- and SHV-type ESBL-producing *Enterobacteriaceae* in a pharmacodynamic *in vitro* model, whereas even high doses of ciprofloxacin and levofloxacin were inactive against such ESBL producers (15). Likewise, the activity of finafloxacin against methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, and ciprofloxacin-resistant staphylococci was higher than that of other fluoroquinolones tested, such as ciprofloxacin, levofloxacin, and moxifloxacin (14, 16–19), and it has been reported that finafloxacin overcomes efflux-mediated fluoroquinolone resistance in *Burkholderia pseudomallei* (20).

Second, elderly patients harbored more ciprofloxacin-resistant strains than did younger patients. Considerable age-specific variation in fluoroquinolone resistance levels has been described by others as well, while for other drug classes, either no or a marginal clinically significant age-related difference in susceptibilities was noted (21–23). The pronounced activity of finafloxacin against ciprofloxacin-resistant uropathogens is mirrored by its higher activity against this subset of strains isolated from elderly patients. Finafloxacin (MIC range from $\leq$0.03 to $>$32) had eradicated 90% of these isolates at day 3 of therapy, whereas ciprofloxacin (MIC range from $\leq$0.03 to $>$32) eradicated 73% of resistant isolates. This difference between finafloxacin and ciprofloxacin may be due to the fact that susceptibility testing was performed under standard conditions at pH 7.2, while in a pathophysiologically relevant acidic medium enriched with divalent cations, ciprofloxacin loses whereas finafloxacin gains activity (14, 15).

Third, finafloxacin eradicated uropathogens, in particular the resistant ones, more rapidly than did ciprofloxacin. While the different eradication rates may have an impact on not only clinical or microbiological outcomes but also economic outcomes, this is beyond the scope of this phase II study. Based on the clinical finding that ciprofloxacin eradicated Gram-negative respiratory pathogens rapidly from bronchoalveolar lavage fluid sampled daily from severely ill elderly patients (24), whereas β-lactams required longer treatment periods to eliminate the respiratory pathogen, as the *in vitro* and, in particular, *in vivo* bacterial killing rates are lower with β-lactams than with fluoroquinolones (25), two other clinical studies revealed that severely ill, hospitalized patients responded to treatment with ciprofloxacin earlier and more markedly than those who were treated with imipenem (26, 27). Also, frequencies of subsequent infections were lower in the ciprofloxacin group than in the imipenem group so that both treatment

and posttherapy costs were lower for the ciprofloxacin group than for the imipenem group (27). These findings are remarkable insofar as at the test-of-cure visit, both regimens were equally effective, with the only difference being the more-rapid and more-pronounced eradication of pathogens from the foci of infection. Moxifloxacin was also found to exert more-rapid and more-marked bactericidal activity *in vitro*, in pharmacodynamic infection models, and in experimental animals than β-lactams or macrolides (28–30). Pharmacoeconomic evaluations revealed that these differences in bactericidal activities, confirmed in clinical studies, resulted in higher cost-effectiveness (31, 32). Likewise, in preclinical as well as clinical studies, daptomycin exhibited rapid and marked bactericidal activity against Gram-positive bacteria, whereas vancomycin acted almost bacteriostatically (33–35). The more-rapid bactericidal action of daptomycin, causing more-rapid resolution of symptoms and higher clinical cure rates than those with vancomycin, resulted in cost savings (36).

The interim analysis of early response rates reported in this publication indicates that there are differences between patients treated with the fluoroquinolones finafloxacin and ciprofloxacin. Further clinical and preclinical analyses will be conducted to evaluate the rapid treatment effect of finafloxacin seen in these early phase II studies. These studies also clearly demonstrate that rapid bactericidal *in vitro* activities and pronounced bactericidal activity in pharmacodynamic infection models and in experimental animals can be translated into the clinical arena, thus potentially resulting in cost savings, even if, in some studies, clinical efficacy at the final test-of-cure visit was not different between the study drug and comparators. This has to be evaluated and confirmed in a larger phase III study to determine if finafloxacin may represent an alternative to ciprofloxacin and probably levofloxacin in terms of safety, efficacy, and pharmacoeconomic needs.

Conclusion. Finafloxacin could be a suitable agent for the treatment of UTIs due to (i) its activity even against fluoroquinolone-resistant uropathogens and those primed to mutate further and (ii) its maintained activity at an acidic pH and in urine (conditions which reduce the efficacy of ciprofloxacin or levofloxacin).

MATERIALS AND METHODS

Design of clinical studies. Two phase II studies were performed to evaluate the clinical efficacy and antibacterial activity of finafloxacin compared to ciprofloxacin for the treatment of uUTI and cUTI/PN. Both trials have been designed as randomized, double-blind, double-dummy studies. Clinical and microbiological responses at the primary and secondary endpoints are reported in a companion article (37). In this communication, we report the early microbiological response rates on day 3 only.

Phase IIa study: treatment of uncomplicated urinary tract infections. In 7 study centers located in Germany or Singapore, 36 female patients between 19 and 52 years of age with uUTI were randomized to receive either 300 mg finafloxacin orally administered b.i.d. or 250 mg ciprofloxacin orally administered b.i.d. for 3 days. The primary efficacy endpoint was bacterial eradication, i.e., a reduction of the initial counts to $\leq 10^3$ CFU/ml, at the end of the treatment visit on days 4 to 6 in both treatment groups.

In addition, the rate of reduction of viable counts of the causative pathogen was determined for a subset of patients by fractionated two-hourly sampling of urine on the first day of treatment after the administration of the first dose. Only data generated for this subgroup of patients are presented in this communication.

Phase II study: complicated urinary tract infections/acute pyelonephritis. A total of 225 patients were enrolled in 18 sites in Poland and Germany. Adult patients diagnosed with cUTI and PN were randomized to receive finafloxacin (800 mg once a day [q.d.] intravenously [i.v.]) or ciprofloxacin (400 mg b.i.d. i.v.). The early response to the study medications was evaluated in the mITT ($n = 193$) population at day 3 of the study, with pathogen eradication being defined as the elimination or reduction of study entry pathogens to $\leq 10^3$ CFU/ml in urine.

Microbiology. In general, patients enrolled in the uUTI as well as the cUTI studies collected a midstream specimen of urine. Urine specimens either were plated within 2 h after collection or, in cases where samples could not be plated within 2 h after collection, were refrigerated. Routine pathogen identification and susceptibility testing according to CLSI guidelines were performed at local laboratories. All isolates were shipped to a central reference laboratory (IHMA, Monthey/VS, Switzerland) for confirmatory identification and susceptibility testing. The latter results were used for data analysis. Susceptibility testing of the isolated pathogens was performed by broth microdilution, and pathogens were classified by susceptible and resistant breakpoints according to CLSI guidelines (38). Susceptibility testing and MIC determinations were performed at pH 7.2.

Detection of ESBLs in *Enterobacteriaceae*. Screening for ESBLs in *Enterobacteriaceae* was performed in accordance with guidelines issued by the EUCAST and CLSI by using cefotaxime and cefpodoxime with

a breakpoint of >1 mg/liter for either agent (39, 40). Phenotypic confirmation was based on the *in vitro* inhibition of ESBL activity by clavulanic acid.

Characterization of isolates primed for fluoroquinolone resistance. Detection of strains with only one mechanism of resistance to quinolones, such as a single mutation in the quinolone-resistance-determining region or a plasmid-mediated quinolone resistance mechanism, is difficult, as fluoroquinolone MICs remain below the resistance breakpoint. Therefore, nalidixic acid was used as an indicator of reduced fluoroquinolone susceptibility. Isolates with a nalidixic acid MIC of >16 mg/liter were defined as being primed for fluoroquinolone resistance (41, 42).

Statistical analysis. The clinical studies analyzed in this publication were designed as exploratory dose-range-finding phase II studies. These studies were not powered to demonstrate a statistically significant difference between the different treatment groups in terms of noninferiority or superiority.

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