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CLINICAL THERAPEUTICS

Explorative Randomized Phase II Clinical Study of the Efficacy and Safety of Finafloxacin versus Ciprofloxacin for Treatment of Complicated Urinary Tract Infections

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ABSTRACT The broad-spectrum C-8-cyano-fluoroquinolone finafloxacin displays enhanced activity under acidic conditions. This phase II clinical study compared the efficacies and safeties of finafloxacin and ciprofloxacin in patients with complicated urinary tract infection and/or pyelonephritis. A 5-day regimen with 800 mg finafloxacin once a day (q.d.) (FINA05) had results similar to those of a 10-day regimen with 800 mg finafloxacin q.d. (FINA10). Combined microbiological and clinical responses at the test-of-cure (TOC) visit were 70% for FINA05, 68% for FINA10, and 57% for a 10-day ciprofloxacin regimen (CIPRO10) in 193 patients (64 for FINA05, 68 for FINA10, and 61 for CIPRO10) of the microbiological intent-to-treat (mITT) population. Additionally, the clinical effects of ciprofloxacin on patients with an acidic urine pH (80% of patients) were reduced, whereas the effects of finafloxacin were unchanged. Finafloxacin was safe and well tolerated. Overall, 43.4% of the patients in the FINA05 group, 42.7% in the FINA10 group, and 54.2% in the CIPRO10 group experienced mostly mild and treatment-emergent but unrelated adverse events. A short-course regimen of 5 days of finafloxacin resulted in high eradication and improved clinical outcome rates compared to those for treatment with ciprofloxacin for 10 days. In contrast to those of ciprofloxacin, the clinical effects of finafloxacin were not reduced by acidic urine pH. Hospitalized adults were randomized 1:1:1 to finafloxacin treatment (800 mg q.d.) for either 5 or 10 days or to ciprofloxacin treatment (400 mg/500 mg b.i.d.) for 10 days with an optional switch from intravenous (i.v.) to oral administration at day 3. The primary endpoint was the combined microbiological and clinical response at the TOC visit in the microbiological intent-to-treat population. (This study has been registered at ClinicalTrials.gov under identifier NCT01928433.)

KEYWORDS acidic urine, complicated urinary tract infection, finafloxacin, pyelonephritis, treatment duration

Urinary tract infections (UTIs) are common diseases in outpatient as well as institutional health care settings, and they account for a large part of antibiotic administrations (1, 2). Fluoroquinolones are considered among the first-choice treatments for these conditions due to their activity against bacterial pathogens causing complicated UTIs (cUTIs) and high levels of excretion in the urine following oral and intravenous (i.v.) administration (1, 3). However, many currently prescribed fluoroquinolones exhibit reduced antibacterial activity at low pH, which suggests reduced activity in infected urinary tracts in which an acidic pH prevails. *In vitro* results show that finafloxacin

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achieves optimum activity under acidic conditions (4–6) similar to those usually found in urine, particularly infected urine (7, 8). This suggests an improved potency of finafloxacin against cUTI pathogens compared to those of currently prescribed fluoroquinolones such as ciprofloxacin or levofloxacin.

Finafloxacin, an investigational fluoroquinolone suitable for intravenous and oral administration, is being developed as sequential therapy for bacterial infections, including the treatment of UTIs (9). This compound exhibits essential features required to successfully treat such infections: good activity against Gram-positive, Gram-negative, and anaerobic pathogens with a bactericidal mechanism of action (4); a high level of excretion in the urine (10, 11); and increased potency at acidic pH (4, 5). Fluoroquinolones inhibit the activity of bacterial type II topoisomerases, i.e., DNA gyrase and topoisomerase IV. Despite the affinity of most expanded-spectrum fluoroquinolones for both targets, they usually inhibit one enzyme, preferentially facilitating the development of bacterial resistance. Methoxy-quinolones, however, inhibit both enzymes at almost the same concentrations, which may potentially limit the emergence of resistance. However, the theory of dual targeting is discussed controversially (12–15). Finafloxacin is also characterized by the balanced inhibition of both enzymes, but it inhibits bacterial type II topoisomerases at ≥3-fold-lower concentrations than those of methoxy-quinolones and other previous fluoroquinolones (16). The high target affinity and enhanced activity of finafloxacin under acidic conditions resulted in a higher activity of finafloxacin than that of ciprofloxacin, levofloxacin, or moxifloxacin against double mutant strains also expressing plasmid-mediated quinolone resistance (5).

This explorative phase II study aimed to evaluate the safety and efficacy of finafloxacin, initially administered intravenously and subsequently administered orally to patients with cUTI, for a total of either 5 or 10 days, compared with sequential 10-day therapy with ciprofloxacin. A group administered finafloxacin for 5 days was included in this study to evaluate if a shorter treatment duration would be as effective as a 10-day treatment regimen with finafloxacin or ciprofloxacin. The study was powered to estimate the eradication rate with a precision of 9.0% or lower (precision equals the half-width of the 95% confidence interval [CI]) in each group, assuming an expected rate of 0.85.

RESULTS

Study population. In total, 225 patients (intent-to-treat [ITT] population) were enrolled in the study. These patients were recruited in Germany ($n = 33$; 14.7%) and Poland ($n = 192$; 85.3%). The safety (SAF) population consisted of 223 patients who received at least one study drug administration and who were assigned to one of three treatment arms: 76 patients in the group receiving finafloxacin for 5 days (FINA05), 75 in the group receiving finafloxacin for 10 days (FINA10), and 72 in the group receiving ciprofloxacin for 10 days (CIPRO10). A total of 193 patients met the criteria for the microbiological ITT (mITT) population. Of the randomized subjects, 64 patients were allocated to the FINA05 arm, 68 patients were allocated to the FINA10 arm, and 61 patients were allocated to the CIPRO10 arm (Table 1 and Fig. 1).

Demographic and baseline characteristics were similar for the three groups, and no relevant differences between the treatment groups were observed. All patients were Caucasians, 82.1% ($n = 183$) were female, 61.9% ($n = 138$) had a diagnosis of uncomplicated acute pyelonephritis, 8.1% ($n = 18$) had a diagnosis of complicated acute pyelonephritis, and 30.0% ($n = 67$) had complicated UTI. The mean age of females was 51.8 ± 19.5 years, and the mean age of males was 43.8 ± 14.4 years (Table 1).

Analysis of efficacy. (i) Primary endpoint. The treatment success rates (combined clinical and microbiological response [primary endpoint]) for the mITT population at the test-of-cure (TOC) visit on day 17 were 70.3% (95% CI, 57.6% to 81.1%) for the FINA05 group, 67.6% (95% CI, 55.2% to 78.5%) for the FINA10 group, and 57.4% (95% CI, 44.1% to 70.0%) for the CIPRO10 group. Finafloxacin dosed for 5 or 10 days showed higher treatment success rates than did ciprofloxacin dosed for 10 days (Table 2). This

TABLE 1 Summary of demographic and baseline characteristics[a]

Parameter	No. (%) of patients			
	FINA05	FINA10	CIPRO10	Total
Patients	76 (100.0)	75 (100.0)	72 (100.0)	223 (100.0)
Caucasian race	76 (100.0)	75 (100.0)	72 (100.0)	223 (100.0)
Gender				
Male	12 (15.8)	13 (17.3)	15 (20.8)	40 (17.9)
Female	64 (84.2)	62 (82.7)	57 (79.2)	183 (82.1)
Age group (yr)				
≤35	17 (22.4)	14 (18.7)	23 (31.9)	54 (24.2)
36–≤65	36 (47.4)	30 (40.0)	27 (37.5)	93 (41.7)
≥66	23 (30.3)	31 (41.3)	22 (30.6)	76 (34.1)
Diagnosis				
cUTI	24 (31.6)	22 (29.3)	21 (29.2)	67 (30.0)
uPN	47 (61.8)	45 (60.0)	46 (63.9)	138 (61.9)
cPN	5 (6.6)	8 (10.7)	5 (6.9)	18 (8.1)
mITT population	64 (84.2)	68 (90.7)	61 (84.7)	193 (86.6)

[a]Race, gender, age group, and diagnosis are given for the safety population for patients receiving 800 mg finafloxacin once daily for 5 days (FINA05) or 10 days (FINA10) or 400/500 mg ciprofloxacin for 10 days (CIPRO10); mITT, microbiological intent to treat; cUTI, complicated urinary tract infection; uPN, uncomplicated acute pyelonephritis; cPN, complicated acute pyelonephritis.

explorative phase II study was not powered to demonstrate a statistically significant difference or noninferiority between one of the finafloxacin groups and the ciprofloxacin group.

(ii) Secondary endpoints. Finafloxacin dosed for 5 or 10 days showed higher treatment success rates than did ciprofloxacin dosed for 10 days for the composite response (combined microbiological and clinical success) as well as for the clinical and microbiological responses for patients in the mITT population at the early time point (day 3) and at the end of the study (day 24) (Table 2). Both finafloxacin and ciprofloxacin dosed for 10 days yielded similar effects on the composite response but different clinical and microbiological responses at the end of therapy (Table 2).

(iii) Additional study results for the mITT population. *Escherichia coli* was the most common pathogen among the isolates in the patients (83.4%) of the mITT population. Eradication rates for patients with *E. coli* infections were 71.7% for the FINA05 group, 73.7% for the FINA10 group, and 58.8% for the CIPRO10 group at the

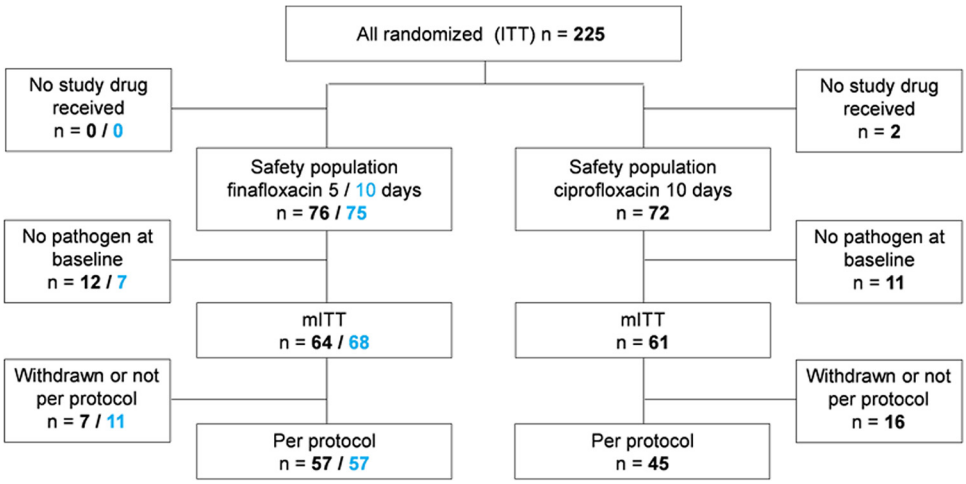

FIG 1 Study design and patient disposition. The flow diagram displays the patient disposition of the 225 enrolled patients for the three different study arms. ITT, intent-to-treat population; mITT, microbiological intent-to-treat population.

TABLE 2 Time course of clinical and microbiological responses (mITT population)[a]

Endpoint	No. of patients (% of patients [95% CI])		
	FINA05	FINA10	CIPRO10
Total	64 (100.0)	68 (100.0)	61 (100.0)
Visit 2 (day 3)			
Combined endpoint	39 (60.9 [47.9–72.9])	40 (58.8 [46.2–70.6])	33 (54.1 [40.8–66.9])
Clinical success	40 (62.5 [49.5–74.3])	42 (61.8 [49.2–73.3])	35 (57.4 [44.1–70.0])
Microbiological eradication	57 (89.1 [78.8–95.5])	60 (88.2 [78.1–94.8])	48 (78.7 [66.3–88.1])
End of therapy (day 10)			
Combined endpoint	49 (76.6 [64.3–86.2])	49 (72.1 [59.9–82.3])	44 (72.1 [59.2–82.9])
Clinical success	56 (87.5 [76.8–94.4])	55 (80.9 [69.5–89.4])	49 (80.3 [68.2–89.4])
Microbiological eradication	49 (76.6 [64.3–86.2])	53 (77.9 [66.2–87.1])	45 (73.8 [60.9–84.2])
Test of cure (day 17) (primary endpoint)			
Combined endpoint	45 (70.3 [57.6–81.1])	46 (67.6 [55.2–78.5])	35 (57.4 [44.1–70.0])
Clinical success	51 (79.7 [67.8–88.7])	57 (83.8 [72.9–91.6])	44 (72.1 [59.2–82.9])
Microbiological eradication	46 (71.9 [59.2–82.4])	48 (70.6 [58.3–81.0])	36 (59.0 [45.7–71.4])
End of study (day 24)			
Combined endpoint	47 (73.4 [60.9–83.7])	42 (61.8 [49.2–73.3])	34 (55.7 [42.4–68.5])
Clinical success	52 (81.3 [69.5–89.9])	53 (77.9 [66.2–87.1])	43 (70.5 [57.4–81.5])
Microbiological eradication	48 (75.0 [62.6–85.0])	44 (64.7 [52.2–75.9])	36 (59.0 [45.7–71.4])

[a]Numbers of patients, percentages of patients, and 95% confidence intervals for the mITT population are given as a combined endpoint (both clinical and microbiological success) and with clinical success and microbiological eradication separately. The presented data are grouped by visit for patients receiving 800 mg finafloxacin once daily for 5 days (FINA05) or 10 days (FINA10) or 400/500 mg ciprofloxacin for 10 days (CIPRO10).

TOC visit (day 17). Clinical success was recorded for 81.1% of patients in the FINA05 group, 87.7% in the FINA10 group, and 72.5% in the CIPRO10 group, while the composite responses were 69.8%, 71.9%, and 56.9%, respectively (data not shown).

Overall, 83.6% of the patients of the mITT population who provided a valid urine pH measurement ($n = 145$) at study entry had a urine pH below 7 at screening. An early microbiological response was recorded for 45 (90.0%) patients in the FINA05 group, 44 (86.3%) patients in the FINA10 group, and 33 (73.3%) patients in the CIPRO10 group for patients with acidic urine at visit 2 (day 3) (Table 3). For patients with an alkaline urine pH, a microbiological response was noted for 11 (91.7%) patients in the FINA05 group, 12 (92.3%) patients in the FINA10 group, and 11 (91.7%) patients in the CIPRO10 group at visit 2. The microbiological eradication rate for ciprofloxacin was lower in the patient group with an acidic urine pH than in those with an alkaline urine pH, while the microbiological eradication rate for finafloxacin was equally high at either pH range, as determined by the microbiological response on day 3 (Table 3).

Safety and tolerability. The safety profiles for the 3 treatment groups were equivalent (Table 4), and the majority of the adverse events (AEs) was mild to moderate in severity and regarded as being unrelated to the study medication (Table 5). The most common AEs (threshold of ≥3% of patients per treatment group) for the finafloxacin-treated patients were headache, diarrhea, nausea, increased blood pressure, insomnia,

TABLE 3 Microbiological eradication at day 3 by urine pH at study entry[a]

Group	No. of patients with pH of <7.0	No. (%) of patients with microbiological eradication with urine pH of <7.0	No. of patients with pH of ≥7.0	No. (%) of patients with microbiological eradication with urine pH of ≥7.0
FINA05	50	45 (90.0)	12	11 (91.7)
FINA10	51	44 (86.3)	13	12 (92.3)
CIPRO10	45	33 (73.3)	12	11 (91.7)

[a]Numbers and percentages of patients are shown for the mITT population. A total of 10 subjects of the mITT population had a missing urine pH value at study entry; urine pH was determined at the screening visit. Patients received 800 mg finafloxacin q.d. for 5 days (FINA05) or 10 days (FINA10) or 400/500 mg ciprofloxacin for 10 days (CIPRO10).

TABLE 4 Summary of AEs occurring in ≥3% of patients per treatment group (safety population)[a]

AE (preferred term)	FINA05		FINA10		CIPRO10	
	n_{AE}	n_S (%)	n_{AE}	n_S (%)	n_{AE}	n_S (%)
Headache	7	6 (7.9)	3	3 (4.0)	9	6 (8.3)
Diarrhea	5	4 (5.3)	6	4 (5.3)	5	5 (6.9)
Nausea	5	5 (6.6)	1	1 (1.3)	1	1 (1.4)
Abdominal pain	2	2 (2.6)	1	1 (1.3)	3	3 (4.2)
Increased blood pressure	0	0	5	4 (5.3)	3	2 (2.8)
Insomnia	4	3 (3.9)	2	2 (2.7)	1	1 (1.4)
Hypokalemia	3	3 (3.9)	0	0	2	2 (2.8)
Superficial thrombophlebitis	0	0	1	1 (1.3)	3	3 (4.2)
Vomiting	3	3 (3.9)	0	0	1	1 (1.4)
Prolonged QT interval on electrocardiogram	3	3 (3.9)	0	0	0	0
Skin reaction	0	0	0	0	3	3 (4.2)

[a]Shown are data for patients who received at least one administration of the study drug. Displayed are numbers of adverse events (n_{AE}) and numbers of subjects (n_S). Patients received 800 mg finafloxacin q.d. for 5 days (FINA05) or 10 days (FINA10) or 400/500 mg ciprofloxacin for 10 days (CIPRO10).

hypokalemia, vomiting, and a prolonged QT interval, while those for the ciprofloxacin-treated group were headache, diarrhea, abdominal pain, superficial thrombophlebitis, and skin reactions.

Withdrawals due to adverse events. Overall, 156 (70.0%) out of 223 patients of the SAF population completed the study: 56 patients (73.7%) in the FINA05 group, 54 patients (72.0%) in the FINA10 group, and 46 patients (63.9%) in the CIPRO10 group. In total, 12 (5.4%) patients were prematurely withdrawn due to an AE: 5 patients (6.6%) in the FINA05 group, 2 patients (2.7%) in the FINA10 group, and 5 patients (6.9%) in the CIPRO10 group.

Adverse events. A total of 202 individual AEs were reported during the study course: 191 were treatment-emergent AEs (TEAEs) (starting during or after the first administration of the study drug). Overall, for 104 patients (46.6%), at least one TEAE was reported: 33 patients (43.4%) in the FINA05 group, 32 patients (42.7%) in the FINA10 group, and 39 patients (54.2%) in the CIPRO10 group.

Five patients (6.6%) in the FINA05 group, 2 patients (2.7%) in the FINA10 group, and 5 patients (6.9%) in the CIPRO10 group were withdrawn from the study due to adverse events. There were no deaths in the study. In the FINA05 group and in the FINA10 group, a total of three drug-related serious adverse events (SAEs) were recorded: 1 case of diarrhea (FINA05 group) and 2 cases of *Clostridium difficile* infections (FINA10 group).

DISCUSSION

The present study was conducted as an exploratory study of hospitalized male and female patients to compare finafloxacin with ciprofloxacin for the treatment of cUTI or complicated/uncomplicated acute pyelonephritis. Fluoroquinolones are considered

TABLE 5 Summary of TEAEs by intensity and relationship to the study medication (safety population)[a]

TEAE property	FINA05		FINA10		CIPRO10		Total	
	n_{AE}	% of patients with AE	n_{AE}	% of patients with AE	n_{AE}	% of patients with AE	n_{AE}	% of patients with AE
Intensity								
Mild	54	77.1	28	54.9	49	70.0	131	68.6
Moderate	15	21.4	22	43.1	19	27.1	56	29.3
Severe	1	1.4	1	2.0	2	2.9	4	2.1
Relationship to study medication								
Unrelated	49	70.0	37	72.5	53	75.7	139	72.8
Related	21	30.0	14	27.5	17	24.3	52	27.2

[a]Shown is a summary of treatment-emergent adverse events per treatment group and total for the safety population (patients who received at least one administration of the study drug). Displayed are the numbers of adverse events (n_{AE}). Patients received 800 mg finafloxacin q.d. for 5 days (FINA05) or 10 days (FINA10) or 400/500 mg ciprofloxacin for 10 days (CIPRO10).

among the first-choice treatments for these conditions due to their activity against cUTI pathogens and high urinary excretion following oral and/or parenteral administration (1). Finafloxacin (800 mg) administered once daily (q.d.) for either 5 or 10 days resulted in comparable clinical and microbiological response rates as well as composite response rates at the TOC visit on day 17. Overall, finafloxacin success rates were higher than those for 10-day treatment with ciprofloxacin. This finding demonstrates that short-course therapy with finafloxacin for 5 days for patients with complicated UTIs or acute pyelonephritis was numerically at least comparable to standard 10-day regimens. Likewise, high-dose short courses with levofloxacin (17–20) and ciprofloxacin in immediate-release (21, 22) and extended-release (23–27) formulations, respectively, were equally as effective in the treatment of cUTIs and acute pyelonephritis as 10-day regimens. Furthermore, it has been demonstrated that 7-day ciprofloxacin treatment of female patients with uncomplicated pyelonephritis was as effective as a 14-day course with trimethoprim-sulfamethoxazole (28). Short-course treatment may minimize the potential emergence of resistance without compromising clinical efficacy. Appropriate minimum durations of antibiotic therapy have been investigated only for specific bacterial infections, whereas the duration of therapy for common sites of infection such as the urinary tract has not been assessed in well-controlled trials (29–33).

A follow-up visit 7 days after the TOC visit on day 24 revealed that patients receiving treatment with finafloxacin for 5 days did not have an increased risk of relapses due to the shortened treatment duration. In fact, cure rates in this group were even further improved at the later visit and appeared to be higher than those in the patient group receiving finafloxacin for 10 days. Since the effects of both finafloxacin treatment durations were very similar at all other evaluation visits, it is currently unclear if this is an effect caused by the rather small sample size or by a less-pronounced effect on the human microbiome affecting the resident flora less markedly following short-course therapy than a 10-day regimen. This hypothesis is supported by the findings that antibacterial therapy affects gut and urine microbiota moderately during the first 3 to 5 days of treatment, thus keeping barrier and/or defense mechanisms intact, whereas longer durations of therapy exert pronounced effects on the microbiome (34–36).

In agreement with the bacterial etiology of cUTIs and acute pyelonephritis (2, 37), approximately 84% of the patients enrolled in this study were infected with *E. coli*; other Gram-negative organisms were isolated from 9% of the samples, and Gram-positive organisms were isolated from 7% of the samples. Eradication of bacterial pathogens was defined prospectively as the presence of $\leq 10^3$ CFU/ml of the uropathogen(s) at assessment. Eradication of approximately 90% of the pathogens was achieved within 3 days of finafloxacin treatment, compared to 78.7% in the ciprofloxacin treatment arm. In a separate phase II study with patients with uncomplicated UTI (uUTI), the speed of eradication of pathogens from patients' urine specimens during the first 24 h of treatment was analyzed in a small subset of the patient population. Finafloxacin eradicated susceptible pathogens from all tested patients within 2 h after the administration of the first dose, whereas the eradication of these pathogens by ciprofloxacin took up to 8 h (38). The use of an early endpoint at day 3 is more focused on the impact of antibacterial treatment on the microbiological response while minimizing the impact of extraneous factors such as immune responses supporting bacterial eradication on the one hand and pathoadaptive effects like morphological plasticity and/or the synthesis of pathogenicity factors, etc., subverting host defense mechanisms on the other hand (2). Therefore, the microbiological response at day 3 likely represents an actual treatment effect. The early response rates were much higher than the response rates recorded at the TOC visit. This finding is in agreement with data generated in 27 comparative, well-powered clinical trials of cUTI. As summarized recently, the microbiological and clinical response rates were higher following short-term follow-up (5 to 9 days) than those at long-term follow-up (4 to 6 weeks) (39). A comparison of data from these studies is compromised by a variety of factors, e.g., the exclusion of resistant pathogens in the previous studies (whereas resistant isolates were included in this study), different endpoints, or a lack of blinding, but still, data generated in this study

and those generated previously indicate that efficacy rates analyzed at an early time point are more favorable than those analyzed later. The clinical and pathophysiological backgrounds for these differences have to be elucidated.

In contrast to ciprofloxacin, the *in vitro* activity of finafloxacin is not negatively affected by an acidic and hyperosmolar environment as it prevails in urine (4–6). Human urine contains high concentrations of divalent cations and is acidic in most UTI patients (7, 8); in this study, the urine pH was also <7 in almost 80% of the patients. To test the effect of urine pH on ciprofloxacin and finafloxacin activities, the microbiological efficacy on day 3 was analyzed by stratification of the patients by urine pH at screening (Table 3). This analysis revealed that finafloxacin eradicated pathogens more effectively than did ciprofloxacin in patients with a low urine pH, whereas the efficacies of both drugs were comparable at a urine pH at or above 7. The increased activity of finafloxacin but the decreased activity of ciprofloxacin or levofloxacin under acidic conditions has been demonstrated in a number of *in vitro* and *in vivo* studies (5, 6, 40). Tubular reabsorption of finafloxacin is minimal at the acidic pH of urine, so finafloxacin is increasingly available at the site of infection in the urinary tract (9). In contrast, ciprofloxacin (41) and levofloxacin (42) are known to undergo tubular reabsorption in humans; ciprofloxacin had a 12-fold-higher affinity for a putative renal transporter than that of levofloxacin (33). A unique feature of finafloxacin compared to all currently marketed fluoroquinolones is its intracellular accumulation in bacterial cells under acidic conditions, resulting in a significantly increased activity of finafloxacin against intracellular bacteria (40). Thus, the increased antibacterial activity of finafloxacin at acidic pH as well as its high concentrations at the focus of infection, in contrast to the characteristics of levofloxacin or ciprofloxacin, likely contribute to its pronounced clinical efficacy in patients with cUTIs or acute pyelonephritis. It is noteworthy that 14 and 23 subjects treated with ciprofloxacin and finafloxacin, respectively, showed ciprofloxacin-resistant uropathogens, and the early rates of eradication of these pathogens were 35.7% and 69.6% for ciprofloxacin and finafloxacin, respectively (44), Finafloxacin was also found to be generally safe and well tolerated for both 5 and 10 days at the study dose. Overall, 12 (5.4%) patients were prematurely withdrawn from the study (7/151 [4.6%] finafloxacin-treated subjects and 5/72 [6.9%] ciprofloxacin-treated subjects). Out of a total number of 191 treatment-emergent AEs, the majority of the AEs (131 [68.6%]) were of mild intensity (56 [28.7%] moderate and 4 [1.9%] severe AEs). A total of nine SAEs were reported during the course of the study: eight for finafloxacin and one for ciprofloxacin. Three of the SAEs for finafloxacin were assessed as being related to the study medication. There were no deaths reported during treatment.

In summary, these results strongly suggest that finafloxacin given for 5 days is a viable treatment option for the rapid resolution of major signs and symptoms of cUTI or acute pyelonephritis. Furthermore, the data suggest that bacteriological eradication is obtained within the first 3 days of therapy. Importantly, posttreatment evaluation on day 24 did not indicate that a shorter treatment duration resulted in an increased rate of relapse. Shorter treatment regimens of antibiotics could lead to less collateral damage to the microbiome, shorter hospital stays, and, hence, lower hospital costs. However, these results need to be confirmed in a larger patient population.

MATERIALS AND METHODS

Patient population. Male and female patients ≥18 years of age with cUTI and/or acute pyelonephritis requiring hospitalization were enrolled in this study if they had at least two of the following acute signs and symptoms: chills, rigors, or warmth associated with fever (e.g., oral temperature of >38.0°C); flank pain (pyelonephritis) or pelvic pain (cUTI); nausea or vomiting; dysuria, urinary frequency, or urinary urgency; and/or costovertebral angle tenderness (pyelonephritis) upon physical examination.

The patients must have provided one adequate pretreatment positive urine sample. A positive urine culture was defined as a culture having $\geq 10^5$ CFU/ml of one causative pathogen in the case of cUTI or $\geq 10^4$ CFU/ml of one causative pathogen in the case of acute pyelonephritis. Patients also must have had pyuria, with at least 10 blood cells/μl urine.

Study design. This study was an explorative, multicenter, double-blind, double-dummy, active-control, randomized clinical trial, which examined finafloxacin (i.v. and orally) for a total of 5 days (FINA05) or for a total of 10 days (FINA10) versus ciprofloxacin (i.v. and orally) for a total of 10 days (CIPRO10) for the treatment of cUTI and/or acute pyelonephritis. Patients were randomized 1:1:1 into one

of the three treatment arms. Patients randomized to finafloxacin treatment for a total of 5 days received placebo dummies only on days 6 to 10. The total duration of therapy was 10 days. Physicians could switch from the initial i.v. dosing to oral dosing after day 3. The study lasted 24 ± 2 days, with examinations on day 3, on day 10 ± 2 days, and on day 17 ± 2 days (TOC visit).

The primary endpoint of this study was the combined clinical and microbiological response of patients with cUTI or acute pyelonephritis to treatment with 800 mg finafloxacin q.d. for 5 days versus 800 mg finafloxacin q.d. for 10 days versus 400 mg (i.v.)/500 mg (oral) ciprofloxacin twice a day (b.i.d.) for 10 days as a reference comparator at the TOC visit (day 17) in the mITT population. The mITT population included all randomized patients who were positive for a baseline bacterial pathogen upon culture of urine that causes UTI against which the investigational drug has antibacterial activity. Subjects were excluded from this population based upon events that occurred after randomization (e.g., loss to follow-up).

Clinical response was defined as complete resolution of cUTI or resolution of cUTI to baseline symptoms with no new symptoms developing. Microbiological response was defined as the elimination or reduction of the study entry pathogen(s) to $\leq 10^3$ CFU/ml upon urine culture.

Secondary endpoints were the clinical and microbiological responses at the on-therapy visit (day 3), the clinical and microbiological responses at the end-of-therapy visit (day 10), the clinical and microbiological responses at the end-of-study visit (day 24), separate analyses for all time points for the two outcome variables clinical responder and microbiological responder, and the safety and tolerability in patients with cUTI of multiple doses of finafloxacin for both 5 days and 10 days (i.v. and orally), compared to those of ciprofloxacin (i.v. and orally) for 10 days. Safety and tolerability assessments were done with the safety population (223 subjects), which included all randomized patients who received at least one administration of the study drug.

Statistical analysis. The FINA-007 study (ClinicalTrials.gov identifier NCT01928433) was designed as an exploratory dose-range-finding phase 2 study to prove if a short duration of treatment with finafloxacin (FINA05) is comparable to a standard duration of treatment (FINA10). This study was not powered to demonstrate a statistically significant difference between the finafloxacin and ciprofloxacin treatment groups in terms of noninferiority or superiority. A minimum of 180 evaluable subjects for the microbiological intent-to-treat population (anticipating a 30% early-withdrawal rate due to a negative urine culture/ciprofloxacin-resistant pathogen) was targeted. A sample size of at least 180 subjects for the microbiological intent-to-treat population is considered large enough to estimate the eradication rate with a given precision of 9.0% or better (precision is the half-width of the 95% CI) in each arm. Additionally, the sample size is considered large enough for all relevant adverse events (incidence of >5%) to occur at least once in each arm with a given probability of 98%.

For the primary and key secondary endpoints, the responder rates were calculated, and the exact Clopper-Pearson method was used to calculate the corresponding 95% CIs (43). In addition, Fisher's exact test was used to calculate *P* values for pairwise comparisons between the treatment groups to describe treatment differences (explorative analyses).

The study started on 11 December 2012 (first patient and first visit), and the last patient completed the study on 15 June 2014 (last patient and last visit).

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