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Safety and Efficacy of Finafloxacin versus Ciprofloxacin in the Treatment of Hospitalized Patients with complicated Urinary Tract Infections and Pyelonephritis Determined in a Phase 2 Clinical Study

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Abstract

Background: The novel C-8-cyano fluoroquinolone finafloxacin has potent antimicrobial activity against a broad range of pathogens, with increased activity under acidic conditions. We present data from the first clinical phase 2 study with finafloxacin in patients with cUTI and pyelonephritis.

Methods: Safety and efficacy of finafloxacin were investigated in a double-blind, double-dummy phase 2 study at 18 sites in Poland and Germany. Adult Patients diagnosed with cUTI and acute pyelonephritis were randomized to receive finafloxacin (800 mg o.d. i.v. or oral) either for a total of 5 (FINA 5 days) or 10 days (FINA 10 days) or ciprofloxacin (400 mg b.i.d. i.v. or 500 mg b.i.d. oral) for 10 days (CIPRO 10 days) with a potential switch from initial i.v. to oral administration on day 3 or later. Primary endpoint was to determine the combined clinical and microbiological response at Test of Cure (ToC) on day 17 for the microbiological intention-to-treat (mITT) population.

Results: 225 patients were enrolled in the study. Finafloxacin was found to be safe, with few adverse events observed. The data indicate that

- finafloxacin dosed for 5 days is as efficient as a 10 day regimen.
- combined clinical and microbiological response as primary endpoint at ToC for finafloxacin were 70 % when dosed for 5 days and 68% for 10 days vs. 57% for 10 days with ciprofloxacin.
- compared to either CIPRO 10 days or FINA 10 days, FINA 5 days did not result in an increased rate of relapses on day 24.
- in patients from the CIPRO 10 days group with an acidic urine pH (n=45) 73% of the pathogens were eradicated on day 3 compared to 92 % if the urine pH was ≥7 (n=12). In contrast, finafloxacin activity was not influenced by the urine pH: 92% (n=102) eradication at urine pH ≥7 vs. 88% eradication at urine pH <7 (n=25).

Conclusions: Results from this phase 2 study indicate that patients treated with a high-dose, short course regimen with finafloxacin once daily for just 5 days had higher, more rapid and more sustainable levels of microbiological eradication and showed improved clinical outcomes than those treated with ciprofloxacin twice daily for 10 days. In contrast to ciprofloxacin, the activity of finafloxacin was not reduced by acidic urine pH.

Introduction

UTIs are among the most prevalent infectious diseases in ambulatory and hospitalized populations, with a substantial financial burden on society. In the US the treatment of UTI accounts for about 15% of all community-prescribed antibiotics and UTIs result in more than 100,000 hospital admissions each year. Finafloxacin is a novel fluoroquinolone, being developed as a systemic treatment for bacterial infections including the treatment of urinary tract infections (Bartoletti *et al.* Expert Opin Investig Drugs. 2015; 24:957-63). Finafloxacin combines essential features required to successfully treat such infections: good activity against Gram positive, Gram negative and anaerobic pathogens with a bactericidal mechanism of action and increased potency at acidic pH.

Methods

Study design
Multi-dose, double-blind, double-dummy, active-control, randomized clinical trial for the treatment of lower complicated urinary tract infection (cUTI) and/or acute pyelonephritis.

Patient population
Male and female patients ≥18 years with symptoms of cUTI or pyelonephritis requiring hospitalization.

Dosing regimens

FINA 5 days:	800 mg (i.v. or oral) finafloxacin once daily for a total of 5 days
FINA 10 days:	800 mg (i.v. or oral) finafloxacin once daily for a total 10 days
CIPRO 10 days:	400 mg (i.v.) or 500 mg (oral) ciprofloxacin twice daily for 10 days

Physicians could switch from the initial i.v. to oral dosing after day 3.

Primary endpoint
The combined Clinical and Microbiological Response of patients in the microbiological intent-to-treat population (mITT) at the Test of Cure (ToC) visit on day 17. Clinical Response is the resolution of the disease symptoms and no new symptoms developed. Microbiological Response is the elimination or reduction of study entry pathogens to $\leq 10^3$ CFU /mL in a urine culture.

Secondary endpoints
•The Clinical and Microbiological Response at day 3 and the Clinical and Microbiological Response at the End of Study (EoS) visit on day 24.
•The Clinical and Microbiological Response at the End of Therapy (EoT) visit on day 10.
•The safety and tolerability throughout the full course of the study until the EoS visit on day 24.

Results

Recruitment

225 patients were enrolled in Germany (n=33) and Poland (n=192), from which 223 patients received study medication (safety population). 30 % of the safety population had cUTI and 70% had pyelonephritis. The most frequent pathogen was *E. coli* (80%). 20% of all isolated pathogens at study entry were resistant against ciprofloxacin.

Figure 1 Patient disposition

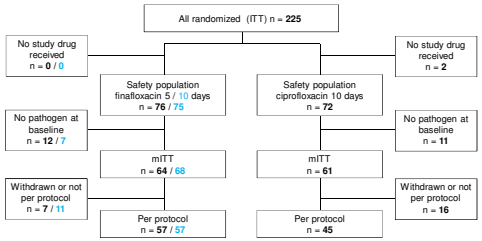


Table 1 Demographic and patient characteristics (safety population)

Characteristic	FINA 5 days	FINA 10 days	CIPRO 10 days
Gender male, n (%)	12 (15.8)	13 (17.3)	15 (20.8)
Gender female, n (%)	64 (84.2)	62 (82.7)	57 (79.2)
Race Caucasian, n (%)	76 (100.0)	75 (100.0)	72 (100.0)
Age, in years, mean (SD)	54.6 (19.6)	58 (19.3)	51 (21.0)
Age group			
Age ≤ 35 years, n (%)	17 (22.4)	14 (18.7)	23 (31.9)
36 ≤ Age ≤ 65 years, n (%)	36 (47.4)	30 (40.0)	27 (37.5)
Age ≥ 66 years, n (%)	23 (30.3)	31 (41.3)	22 (30.6)
Body mass index, kg/m^2, mean (SD)	28.0 (5.9)	26.9 (5.5)	26.7 (5.2)
Primary diagnosis			
complicated Urinary Tract Infection, n (%)	24 (31.6)	22 (29.3)	21 (29.2)
uncomplicated Pyelonephritis, n (%)	47 (61.8)	45 (60.0)	46 (63.9)
complicated Pyelonephritis, n (%)	5 (6.6)	8 (10.7)	5 (6.9)

Safety and tolerability

- The safety profiles of the 3 treatment arms were equivalent.
- The majority of AEs were mild to moderate in severity.
- 5 patients (6.6%) of the FINA 5 days group, 2 patients (2.7%) of the FINA 10 days group and 5 patients (6.9%) of the CIPRO 10 days group were withdrawn from the study due to adverse events.
- There were no deaths in the study. In the FINA 5 days group and in the FINA 10 days group a total of three drug related serious adverse events were recorded: 1 case of diarrhoea (FINA 5 days) and 2 cases of *C. difficile* infections (FINA 10 days).

Table 2 Summary of drug-related adverse events occurring in ≥1% of patients in either treatment group (safety population)

AE (Preferred Term)	FINA 5 days			FINA 10 days			CIPRO 10 days		
	N_{AE}	N_S (%)		N_{AE}	N_S (%)		N_{AE}	N_S (%)	
Nervous system disorders	2	2	(2.6%)	0	0		1	1	(1.4%)
Gastrointestinal disorders	6	6	(7.9%)	2	2	(2.7%)	2	2	(2.8%)
Skin disorders	3	1	(3.9%)	2	2	(2.7%)	4	4	(5.6%)
Vascular disorders	0	0		1	1	(1.3%)	4	4	(5.6%)
Injection site irritation	0	0		2	2	(2.7%)	2	2	(2.8%)
Drug hypersensitivity	1	1	(1.3%)	0	0		2	2	(2.8%)
Hepatic enzyme increase	0	0		1	1	(1.3%)	0	0	
Reproductive system and breast disorders	0	0		1	1	(1.3%)	1	1	(1.4%)
Blood pressure increase	1	1	(1.3%)	1	1	(1.3%)	0	0	0
Electrocardiogram QT prolonged	1	1	(1.3%)	0	0		0	0	
Decreased appetite	1	1		0	0		0	0	0

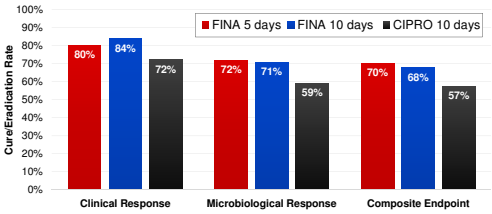
N_{AE} – Number of events; N_S Number of subjects

Efficacy

The data for the primary endpoint are displayed in figure 2. At the Test of Cure (ToC) visit on day 17 finafloxacin dosed for 5 or 10 days was more efficient than ciprofloxacin dosed for 10 days for the Composite Response for patients in the mITT (70% FINA 5 days vs. 68% FINA 10 days vs. 57% CIPRO 10 days). Similarly finafloxacin dosed for 5 or 10 days was more efficient than ciprofloxacin dosed for 10 days for both the Clinical (80% FINA5 days vs. 84% FINA 10 days vs. 72% CIPRO 10 days) and Microbiological Response (72% FINA 5 days vs. 71% FINA 10 days vs. 59% CIPRO 10 days) for patients in the mITT.

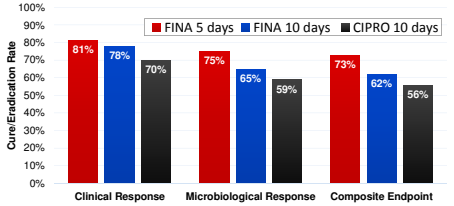
The comparison of both finafloxacin dosing regimens revealed that finafloxacin dosed for 5 days was as efficient as finafloxacin dosed for 10 days. This indicates that a shortened treatment period of 5 days is sufficient to treat patients with lower complicated urinary tract infection (cUTI) and/or acute pyelonephritis.

Figure 2 Primary endpoint: Clinical, Microbiological and Composite Response of patients in the mITT at day 17



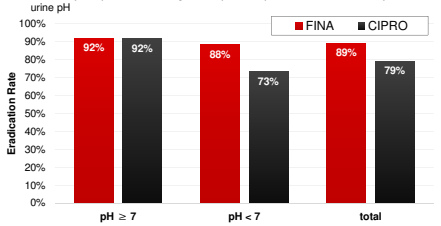
A short treatment course with 800 mg o.d. finafloxacin does not result in an increased number of relapses based on the Clinical, Microbiological and Composite Response of patients in the mITT at the End of Study visit on day 24 (Fig. 3).

Figure 3 Secondary endpoint: Clinical, Microbiological and Composite Response of patients in the mITT at day 24



Approx. 80% of the patients had a urine pH below 7 at screening. Ciprofloxacin was less active in the patient group with urine pH <7 compared to those with urine pH ≥7, while finafloxacin activity was equally strong at either pH range as determined by the Microbiological Response on day 3 in the mITT. Already after 3 days of treatment finafloxacin showed high efficacy with eradication rates of 89% (Fig. 4).

Figure 4 Secondary Endpoint: Microbiological Response of patients in the mITT at day 3 based on urine pH



Conclusions

- A 800 mg high-dose, short course once daily regimen with finafloxacin for the treatment of cUTI/pyelonephritis patients for 5 days is as efficient as the same treatment regimen with finafloxacin for 10 days.
- A 800 mg high-dose, short course once daily regimen with finafloxacin for the treatment of cUTI/pyelonephritis patients for 5 days is more efficient than a 400 mg (i.v.) / 500 mg (oral) b.i.d. treatment regimen with ciprofloxacin for 10 days.
- Finafloxacin eradicated pathogens efficiently (89%) within 3 days and with that at a higher rate than ciprofloxacin (77%).
- Ciprofloxacin activity was negatively affected by an acidic urine pH (<7) found in 80% of the patients whereas finafloxacin activity was comparably high in patients with acidic or basic urine pH.
- A 5 day treatment regimen with finafloxacin did not result in an increased frequency of relapses when compared to the more extended 10 day treatment regimens with finafloxacin or ciprofloxacin.
- Both 800 mg high-dose finafloxacin treatment regimens, for 5 as well as 10 days, were safe and well tolerated.