2 SYNOPSIS

Title of the study:	A double-blind, double-dummy, prospective, randomized multiple-site study of oral Finafloxacin 300 mg b.i.d. *versus* oral Ciprofloxacin 250 mg b.i.d. in patients with lower uncomplicated UTI (uUTI) with a treatment duration of 3 days. **F**inaf**l**oxacin in **UT**I: FLUT study.
Investigator(s):	Dr. Jasper Hein, Gisselbergerstr. 2, 35037 Marburg, Germany
Study center(s):	6 active centers in Germany, 1 active center in Singapore
Study period:	Overall duration: 8 months Screening duration per patient: 188 days Treatment duration: 3 days Study start: OCT 2008 Study end: MAY 2009 First patient enrolled: 08-OCT-2008 Last patient completed: 14-MAY-2009 Clinical phase duration: 218 days Period per patient: 38 days
Study phase:	IIa
Objectives:	The primary objective was to compare the bacteriological eradication rates of Finafloxacin and Ciprofloxacin in female patients with uUTI. The secondary objectives were: 1). to assess the following treatment outcomes according to the study definitions: superinfection, eradication with relapse/reinfection, failure, clinical cure, clinical improvement, and clinical failure; 2). To assess the safety of the study medication by recording of the Adverse Events (AEs), Serious Adverse Events (SAEs), laboratory evaluation, vital signs, electrocardiogram (ECG), concomitant medication, and physical examination.
Methodology:	Proof-of-concept multicenter study, 2:1 randomized, double-blind, double-dummy, prospective

Number of patients:	Screened:	36
	Randomized:	36
	Intention-To-Treat (ITT):	36
	Modified ITT (MITT)	18
	Per Protocol (PP):	18

Study population:

Inclusion criteria:

1. Female patients between 18 and 55 years with uUTI.
2. Two of the following sign and symptoms of uUTI: dysuria, frequency, urgency, miction pain, suprapubic pain, gross hematuria, turbid urine or malodorous urine.
3. Able to supply a mid-stream, clean catch urine sample for microbiological analysis.
4. The result of the dipstick should indicate a high probability of the required number of bacteria.
5. Be able to communicate with the study personnel.
6. Has given written consent to participate in the study.

Exclusion criteria:

1. Female patients having signs and symptoms of upper Urinary Tract Infection (e.g. fever, flank pain) indicating complicated UTI.
2. Male patients.
3. History or evidence of other functional or anatomical abnormalities of the urinary tract (e.g. acute pyelonephritis), diabetes mellitus and immunosuppression.
4. Recurrent cystitis with more than 3 episodes in the past 12 months.
5. Clinical symptoms for more than 7 days before baseline.
6. Psychiatric, neurological or behavior disorders.
7. Clinically significant serious unstable physical illness.
8. Known uncontrolled condition of hypertension or symptomatic hypotension, known ischemic heart disease or history of myocardial infarction (within 12 months prior to study enrollment), coronary artery bypass surgery or Percutaneous Transluminal Coronary Angioplasty (PTCA).
9. Existence of any surgical or medical condition which

might interfere with the distribution, metabolism or excretion of the drug, i.e. impaired renal or hepatic function, diabetes mellitus, chronic symptoms of pronounced constipation or diarrhea or conditions associated with total or partial obstruction of the urinary tract.

10. Antibiotic intake 2 weeks before study enrollment.
11. Failed UTI therapy within 2 months before study inclusion.
12. Expectancy of concomitant administration of antibiotics, sucralfate or divalent and trivalent cations such as iron or antacids containing magnesium, aluminium or calcium intake during the course of the study.
13. Clinically abnormal vital signs, ECG findings and safety laboratory results at baseline.
14. Known hypersensitivity or contraindication to the use of fluoroquinolones.
15. History of tendon lesions or ruptures during quinolone treatment.
16. Any malignant disease or a history of malignant neoplasm other than carcinoma in situ of the cervix or basal cell carcinoma of the skin, within the last 5 years before baseline.
17. Current diagnosis or history of substance abuse.
18. Exposure to any of the investigational drugs 30 days prior to baseline.
19. Pregnant or nursing woman, or woman of childbearing potential who is not using an effective contraceptive method during the study, e.g. oral (stable doses for at least 3 months prior to baseline) or injectable (stable doses for at least 2 months prior to baseline) contraceptives, intrauterine devices (for at least 2 months prior to baseline), double-barrier method, contraceptive patch, female sterilization or condoms.
20. The patient, planned to be enrolled is an employee of any involved study investigator or any involved institution including the study sponsor.
21. Inability or lacking motivation to participate in the study.

Sample size	**A total of 36 patients were randomized to either Finafloxacin (28 patients) or Ciprofloxacin (8 patients) treatment arms. In Singapore, 8 patients were included in the Finafloxacin arm and 4 patients in the Ciprofloxacin arm.**	
Investigational Medicinal Product (IMP)/study medication:	Drug (INN):	Finafloxacin 50 mg tablets
	Dose/dosage:	300 mg b.i.d (6 X 50 mg tablets)
	Administration:	Oral
	Labeled batch number:	C0802001, expiry date: OCT 2009
	Batch number:	BX02R7H
study medication placebo:	Drug (INN):	Finafloxacin 50 mg placebo tablets
	Dose/dosage:	6 tablets b.i.d.
	Administration:	Oral
	Labeled batch number:	C0802001, expiry date: OCT 2009
	Batch number:	BX02H5P
IMP/reference medication:	Drug (INN):	Over-encapsulated Ciprofloxacin 250 mg capsules
	Dose/dosage:	250 mg b.i.d. (1x250 mg capsule)
	Administration:	Oral
	Labeled batch number:	C0802001, expiry date: OCT 2009
	Batch number:	C0801003
reference medication placebo:	Drug (INN):	Over-encapsulated Ciprofloxacin placebo 250 mg capsules
	Dose/dosage:	1 capsule b.i.d.
	Administration:	Oral
	Labeled batch number:	C0802001, expiry date: OCT 2009
	Batch number:	C0801002

Duration of treatment:	3 days
Criteria for evaluation:	
Efficacy/ Pharmacodynamics:	The primary efficacy variable of this study was the eradication (<10^3 cfu/ml) of the initial pathogen at Visit 3 in Finafloxacin (300 mg b.i.d) and Ciprofloxacin (250 mg b.i.d.) treatment groups, in female patients with uUTI. An additional primary variable for efficacy, for the Singapore sub-study only, was a comparison of the rate of bacterial killing in the Finafloxacin and Ciprofloxacin treatment groups. The secondary efficacy variables evaluated the rates of treatment outcomes in the following categories: • Superinfection • Relapse/Reinfection • Failure (microbiological) • Clinical cure • Clinical improvement • Clinical failure In addition, microbiological analyses and resistance rates of all isolated pathogens were determined for both treatment groups.
Safety:	The safety variables for both Finafloxacin and Ciprofloxacin were assessed by AEs, SAEs, clinical laboratory evaluation, vital signs, ECG, concomitant medications and physical examination.
Pharmacokinetics / Pharmacodynamics:	A pharmacokinetic (PK) sub-study was included for all patients enrolled in Singapore, the aim of which was to determine the rate of bacterial killing of Finafloxacin compared with Ciprofloxacin in the first 8 hours of treatment.
Pharmacokinetic sampling times and bioanalytical methods:	Plasma (PK) and urine (PK) were collected at pre-dose, 1, 2, 4, and 8 hours and urine (microbiology) at pre-dose, 2, 4, and 8 hours following dosing for the sub-study group of patients. All patients provided pre-dose and 1 hour PK and microbiology samples.
Statistical methods:	This study was designed as a proof of concept study to

show the efficacy of Finafloxacin, therefore sample size was not based on statistical power considerations.

Populations for analysis were:

Safety Evaluation Set (SAF) – patients that received at least one dose of study medication

Intention to Treat (ITT) – one dose of study medication and post-baseline data available

Modified ITT – all ITT patients with $\geq 10^5$ cfu/ml in the pre-dose culture, taken at least 5 doses of medication and had the primary endpoint measurement available at Visit 3

Per Protocol (PP) – all patients from the MITT set who complied with the protocol requirements

The analyses of primary variables were based on MITT/PP sets. The analyses of secondary variables were based on ITT and MITT/PP sets.

The analyses of safety variables were based on the SAF set.

Efficacy/ Pharmacodynamics: For the primary and secondary variables, comparison of treatment groups was provided by descriptive statistics: eradication rates and the respective 95% confidence intervals (CI) were presented by treatment group and also for the differences between treatment groups.

For the sub-study in Singapore patients, descriptive statistics for the rate of killing and bacterial concentration were presented. All evaluations were given overall and by treatment. For the comparison of treatment groups, the Wilcoxon rank sum test was used on an α-level of 5%. Additionally, the time required reaching bacterial eradication was analyzed.

Safety: Descriptive summary statistics by treatment group were presented for all safety variables. Shift tables were provided. AEs were analyzed according to intensity, causality assessment, and primary system organ class and preferred term of **MedDRA Version 11.1**.

Summary: A total of 36 patients were enrolled into the study, with all receiving at least one dose of study medication (Finafloxacin n=28; Ciprofloxacin n= 8).

Efficacy/ Pharmacodynamics In the MITT population, the eradication rate at Visit 3 was 100.0% in both treatment groups receiving either

results:

Finafloxacin or Ciprofloxacin therapy.

At Visit 4, the rate of clinical cure was 10 patients (76.9%) in the Finafloxacin arm and 5 patients in the Ciprofloxacin arm. At Visit 5 relapse/reinfection rates were 4 patients (30.8%) of the Finafloxacin arm and 1 patient (20.0%) of the Ciprofloxacin arm.

Two of the patients from the Finafloxacin arm who were classified as clinical failure at Visit 4 and relapse/reinfection at Visit 4 and 5 had taken additional antibiotics after Visit 3 and so qualified for these classifications in the absence of clinical or microbiological data. The remaining 1 case of clinical failure was not associated with relapse/reinfection and the remaining cases of relapse/reinfection were all clinically cured.

None of the patients enrolled in the study had superinfection as defined by the study conventions.

Bacterial isolates from 2 patients (15.4%) of the Finafloxacin group were resistant to Ciprofloxacin and associated with bacterial relapse/reinfection at Visit 5, still, both patients were clinically cured. None of the isolates from the Ciprofloxacin group were resistant to Ciprofloxacin. Bacterial isolates in 2 (15.4%) other patients of the Finafloxacin group and in 1 patient (20.0%) of the Ciprofloxacin group were susceptible to Ciprofloxacin but were also associated with bacterial relapse/reinfection at Visit 4 and/or Visit 5,

PK/PD analyses of the sub-cohort in Singapore, showed that 4 patients (80.0%) of the Finafloxacin arm reached bacterial eradication at 2 hours from the first administration of the study medication, and 1 other patient (20.0%) at 8 hours. In comparison, 1 patient each (33.3%) of the Ciprofloxacin arm reached bacterial eradication at 2, 4, and 8 hours. Thus, of the MITT population in Singapore, all 5 patients who were treated with Finafloxacin and all 3 treated with Ciprofloxacin reached bacterial eradication within the first 8 hours after the first dose.

Safety results:

Overall, 17 out of 36 patients of the safety set (47.2%) reported a total of 28 adverse events (AEs) during the treatment period. No Baseline AEs were reported. Treatment

emergent AEs (TEAEs) were documented in 16 patients (57.1%) receiving Finafloxacin, and in 1 patient (12.5%) receiving Ciprofloxacin therapy.

A total of 5 AEs were assessed as having been related to the study medication (17.9%) and were of mild or moderate intensity.

Of all 28 AE episodes, 9 (32.1%) were of moderate intensity, 18 (64.3%) were mild, and 1 (3.6%) was severe, (dysmenorrhea).

AEs, grouped by body system, which occurred in 2 or more patients of the Finafloxacin group were infections and infestations, nervous system disorders, immune system disorders, gastrointestinal disorders, reproductive system and breast disorders and vascular disorders.

The most often reported TEAEs by **MedDRA Version 11.1** preferred term in the Finafloxacin group were: headache (10.7%), urinary tract infection (10.7%) and dysmenorrhoea (7.1%).. In the Ciprofloxacin group, 1 episode of nasopharyngitis in 1 patient (12.5%) was documented.

One serious adverse event (SAE), was reported during this study, in which a patient was hospitalized for a hypersensitivity reaction following administration of the study drug. The patient recovered following treatment of the symptoms. This SAE was assessed as related to the intake of Finafloxacin, and the patient was withdrawn from the study.

Among the safety set, 3 AE episodes (8.3%), all occurring in the Finafloxacin group, led to premature patient discontinuation. However, with the exception of the SAE mentioned above, the other 2 events which led to patient discontinuation were not considered to have been related to the study medication. These 2 AEs were UTIs of moderate intensity which resolved after a period of 12 and 8 days, respectively. However, in 1 case, the event resolved with sequelae.

No clinically relevant changes in vital signs, ECG, and laboratory parameters were observed during the therapy. No patient died during this study.

Conclusions:

This study was conducted as an exploratory proof of concept study in female patients with uUTI infections.

Low recruitment rates resulted in the study being completed before the intended target of 48 patients could be entered into the study. Therefore, the overall treatment distribution was not in accordance with the planned 2:1 ratio of Finafloxacin to Ciprofloxacin, with a final 3.5:1 ratio being calculated.

The bacterial eradication rate was 100.0% in both groups (MITT/PP set). The calculation of confidence intervals was carried out according to the Newcombe-Wilson method. Importantly, the lower bound of the one-sided 95% confidence interval for the difference in rates between treatments exceeded the pre-defined non-inferiority margin of -0.200. The same applied to the lower bound of the calculated one-sided 90% confidence interval for the difference in rates between treatments. Thus, it was concluded that, within the predefined exploratory settings, the treatment with Finafloxacin was non-inferior to the reference therapy with Ciprofloxacin.

The difficulty in establishing a relationship between relapse/reinfection with clinical failure and also fluoroquinolone susceptibility with relapse/reinfection or clinical failure was compounded by the small number of MITT patients (18 in total, 13 in the Finafloxacin arm and 5 in the Ciprofloxacin arm). A study with a larger number of patients in each treatment arm will be required to fully explore and compare on the basis of these secondary efficacy variables.

Overall, Finafloxacin was found to be safe and well tolerated for 3 days at the study dose, with one patient being withdrawn from the study following a hypersensitivity reaction, previously unknown to the patient. The patient initially required hospitalization but recovered without sequelae. Hypersensitivity is a known class-effect of fluoroquinolones.

The results support Finafloxacin as an option for the resolution of major signs and symptoms of uUTI within 3 days, suggesting bacteriological eradication in the first 8 hours of the therapy. However, these findings would benefit from further investigation in a larger patient

population.

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