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# A Phase I Study to Determine Safety, Tolerability and Pharmacokinetics (PK) of Intravenous Doses of Finafloxacin HCl in Healthy Subjects

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## Revised abstract

**Introduction:** Finafloxacin (FIN) ($C_{20}H_{19}FN_4O_4$. HCl, molar mass 434.9) is a novel fluoroquinolone (FQ) under clinical development. FIN exhibits optimal activity at slightly acidic pH (pH 5.0 - 6.0). Safety, tolerability and PK of single and multiple ascending intravenous doses of FIN in healthy adult subjects were evaluated in a combined phase I study protocol.

**Methods:** A single-center, inpatient, randomized, double-blind, placebo-controlled, not weight-adjusted, single and multiple escalating dose phase I study was conducted to evaluate the safety, tolerability and PK profiles of FIN intravenously administered in healthy subjects. 58 subjects were included, 18 of which received single doses of 200 - 1000 mg FIN or placebo (in groups of 6+3) in a cross-over design. The remaining 40 subjects were given FIN doses of 600 - 1000 mg or placebo (in groups of 8+2) once daily for 7 consecutive days. Laboratory safety assessment, vital signs and ECGs were evaluated. Plasma and urine samples for the determination of the PK were collected over a period of 48h post dose.

**Results:** No clinically relevant changes in safety laboratory test parameters were observed. Treatment Emergent Adverse events were recorded for 36 of the 58 subjects including (but not limited to): musculo-skeletal disorders (10 incidents), headache (9), diarrhoea (6), administration site disorders (7). No serious adverse events were reported. At 800 and 1000 mg single doses the mean $C_{max}$ [µg/mL] was 13.7 and 21.0; and the mean $AUC_{0-24}$ [h*µg/mL] was 31.2 and 47.1, respectively. For the corresponding multiple doses the mean $C_{max}$ [µg/mL] was 11.9 and 18.9; and mean $AUC_{0-24}$ [h*µg/mL] on day 7 was 37.1 and 67.8, respectively. The systemic exposure ($AUC_{0-tlast}$) of FIN increased in a dose-dependent manner.

**Conclusions:** Single and multiple doses were very well tolerated at all evaluated doses. Based on the good safety, tolerability and PK profile, FIN warrants further clinical evaluation.

## Introduction

Finafloxacin (FIN, Figure 1) is an investigational broad spectrum fluoroquinolone (FQ) that belongs to a new 8-cyano subclass [1]. FIN contains a novel base component which confers improved antibacterial activity at slightly acidic pH (pH 5.0 – 6.0) under which other marketed FQs exhibit significantly reduced activity [2].

FIN exhibited superior activity to comparator FQs against adherent [3] and intracellular [4] bacteria *in vitro* and in a wide range of rodent infection models [5]. Additionally, FIN displayed an excellent safety profile in a wide range of predictive, *in vitro,* toxicity assays, *in vivo animal* models and in humans [6]. Here, the results of pharmacokinetics, safety and tolerability for intravenously administered FIN in healthy subjects in a phase I study are reported. These attributes suggest that FIN warrants further clinical investigation for bacterial infections that are associated with low pH such as urinary tract and lung infection.

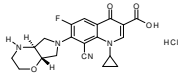


**Figure 1** Finafloxacin hydrochloride

## Methods

The study was an inpatient, randomized, double-blind, placebo-controlled, dose-escalating study to evaluate the safety, tolerability and pharmacokinetic profiles of single and multiple doses of FIN administered intravenously to healthy male and female subjects, aged between 18 and 55 years. Subjects received single doses of 200, 400, 600, 800 or 1000 mg and for the multiple dose study, subjects received 7 daily doses of 600, 800 or 1000 mg.

Blood and urine samples were collected prior to the study, at entry and at the end of evaluation for clinical chemistry, haematology and urinalysis. Plasma and urine samples were collected at various intervals from pre-dose until 48 h after initiation of dosing for pharmacokinetic analysis.

FIN concentrations were estimated in plasma and urine samples by a validated LC/MS-MS method. The lower quantification limit was 5 ng/mL in plasma and 100 ng/mL in urine. Pharmacokinetic parameters were evaluated using non-compartmental analysis. PK parameters, urinary recovery and renal clearance were determined.

All adverse events were coded according to MedDRA, reported and assessed as mild, moderate or severe. Test results of clinical laboratory, vital sign measurements, and ECG rhythm measurements (at screening, pre-dose, at various time points post-start infusion and 5-7 days post-dosing) were listed as actual results and changes from the baseline.

## Results

**Clinical laboratory evaluations:**

Isolated, minor deviations from the normal ranges were observed for various haematology, blood chemistry and / or urinalysis parameters at various time points during the study. None of these deviations were considered clinically significant and no treatment or dose related trends were detected.

**Plasma pharmacokinetics (PK) for single dose:**

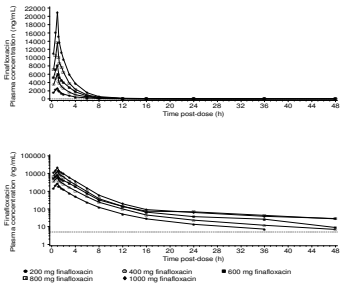
The PK values for subjects receiving single doses are tabulated in Figure 2. Plasma concentrations *vs.* time profiles of escalating single doses are shown in Figure 3.

**Figure 2.** Non-compartmental PK parameters determined as mean ± standard deviation in the subjects receiving single doses of FIN intravenously.

| Dose | 200 mg | 400 mg | 600 mg | 800 mg | 1000 mg |
|---|---|---|---|---|---|
| $C_{max}$ [µg/mL] | 2.6 ± 0.3 | 6.1 ± 10.4 | 8.1 ± 1.4 | 13.7 ± 23.6 | 21.0 ± 6.3 |
| $AUC_{0-24}$ [h*µg/mL] | 6.6 ± 0.7 | 14.3 ± 1.9 | 21.2 ± 2.3 | 31.2 ± 11.8 | 47.1 ± 16.3 |
| $t_{1/2}$ [h] | 12.1 ± 6.0 | 12.5 ± 3.7 | 10.3 ± 1.4 | 19.9 ± 9.8 | 20.6 ± 13.5 |

## Results

**Figure 3.** Plasma concentration over time for single dose of FIN




$C_{max}$ and $AUC_{0-24}$ increased almost linearly with dose. The median value of total body clearance was 27.2 and 24.9 L/hr for 400 mg and 800 mg dose, respectively.

**Figure 4.** Plasma concentration over time for multiple doses of FIN

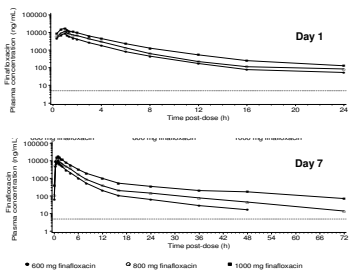



**Figure 5.** Non-compartmental PK parameters determined as mean ± standard deviation in the subjects on day 7 receiving multiple doses of FIN.

| Dose | 600 mg | 800 mg | 1000 mg |
|---|---|---|---|
| $C_{max}$ [µg/L] | 9.3 ± 1.7 | 11.9 ± 2.7 | 18.9 ± 6.3 |
| $AUC_{0-24}$ [h*µg/L] | 25.0 ± 6.7 | 37.1 ± 13.1 | 67.8 ± 22.6 |
| $t_{1/2}$ [h] | 22.1 ± 7.7 | 23.6 ± 4.6 | 32.4 ± 25.6 |

Steady state was reached at day 4, 72 h after first infusion. The median value of total oral body clearance was 24.6 and 15.6 L/hr for 600 mg and 1000 mg dose, respectively.

The majority of FIN renally eliminated as unchanged drug was excreted within 0 to 8 hours post-start of infusion. The mean fraction of the dose excreted in the urine ranged from 29.9% to 44.2% for single doses and 31.8 – 35% for multiple doses on day 7 of FIN.

**Safety & Tolerability:**

- Single (200 to 1000 mg) and multiple IV doses (600 to 1000 mg o.d. for 7 days) of FIN were considered to be safe and well tolerated by healthy volunteers.
- Overall, 85 treatment emergent adverse events (TEAEs) were reported in the study. 52 (37 for FIN and 15 for placebo) of those were suspected to be study-drug related (Figure 7). No dose-related trends were observed and a similar distribution of TEAEs was recorded for the different FIN dose groups or placebo (Figure 6). All adverse events with the exception of one were resolved without treatment.
- No deaths or serious adverse events were reported. One adverse event in the placebo dose group led to discontinuation.
- No treatment or dose-related trends in the 12-lead ECG parameters were noted. In particular, there was no evidence of prolongation of QTc interval at each dose level of FIN. There were no clinically important findings in the morphology of the 12 lead ECG for individual subjects at each dose level of FIN.

**Figure 6.** Summary of Treatment Emergent Adverse Events

| Dose (mg) | Placebo | 200 | 400 | 600 | 800 | 1000 |
|---|---|---|---|---|---|---|
| Part A | 3 (20%) [4] | 1 (17%) [1] | 2 (33%) [2] | 0 (0%) [0] | 2 (33%) [2] | 2 (33%) [2] |
| Part B | 5 (63%) [18] | - | - | 9 (56%) [17] | 6 (75%) [20] | 6 (75%) [19] |

Number of Subjects (%) with Adverse Events; [Number of Adverse Events]

**Figure 7**. Study drug related adverse events reported for subjects receiving single and multiple IV doses of FIN and placebo.

| Body system | Part A FIN n = 18 | Part A Placebo n = 15 | Part B FIN n = 32 | Part B Placebo n = 8 |
|---|---|---|---|---|
| CNS | 0 (0%) [0] | 0 (0%) [0] | 9 (28%) [12] | 3 (38%) [3] |
| GI | 4 (22%) [4] | 1 (7%) [1] | 5 (16%) [8] | 4 (50%) [5] |
| Musculoskeletal | 0 (0%) [0] | 0 (0%) [0] | 2 (6%) [4] | 2 (25%) [3] |
| General | 0 (0%) [0] | 0 (0%) [0] | 4 (13%) [4] | 0 (0%) [0] |
| Infections | 0 (0%) [0] | 0 (0%) [0] | 1 (3%) [1] | 0 (0%) [0] |
| Metabolism | 0 (0%) [0] | 0 (0%) [0] | 1 (3%) [1] | 0 (0%) [0] |
| Psychatric | 0 (0%) [0] | 0 (0%) [0] | 0 (0%) [0] | 1 (13%) [1] |
| Respiratory | 0 (0%) [0] | 0 (0%) [0] | 1 (3%) [1] | 0 (0%) [0] |
| Skin | 1 (6%) [1] | 0 (0%) [0] | 0 (0%) [0] | 1 (13%) [1] |
| Vascular | 0 (0%) [0] | 0 (0%) [0] | 1 (3%) [1] | 0 (0%) [0] |
| Renal | 0 (0%) [0] | 1 (7%) [1] | 0 (0%) [0] | 0 (0%) [0] |

Part A = Single dose Part B = Multiple dose in healthy subjects
n = Number of subjects [Number of Adverse Events]
CNS = Central nervous system, GI = Gastrointestinal

## Conclusions

- This FIN Phase I study in healthy subjects revealed a favorable pharmacokinetics profile with high values for $C_{max}$ and $t_{1/2}$. Appr. 30-40% of FIN were renally eliminated as unchanged drug.
- FIN was well tolerated following single dose and when given for seven days at a range of doses up to 1000 mg. Human safety data do not suggest any quantitatively higher or qualitatively different toxicity for FIN as compared with placebo and no dose-related trends were observed.
- Overall, these findings indicate that the risk of serious adverse reactions to FIN can be expected to be very low. Given the possible therapeutic effects of FIN, further clinical development of the drug appears to be justified and can be recommended.

## Literature

[1] Wohlert *et al.*, 48th ICAAC, Washington DC 2008, Poster No. F1-2036
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[6] Patel *et al.*, AAC 55 (2011) 4386-93