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A Phase I Study to Determine Safety, Tolerability and Pharmacokinetics (PK) of Finafloxacin (FIN) in Healthy Subjects

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Revised abstract

Introduction: FIN is a novel fluoroquinolone (FQ) under early clinical development. FIN exhibits optimal activity at slightly acidic pH (pH 5.0 - 6.0). A combined Phase I study protocol was designed to evaluate safety, tolerability and PK of single and multiple ascending oral doses of FIN in healthy adult subjects.

Methods: The study was designed as a single-center, inpatient, double-blind, randomized, placebo-controlled, not weight-adjusted, single and multiple escalating dose study of FIN oral tablets. 75 (64 males, 11 females) subjects were included, 3 of which received a single dose of 25 mg, 40 of which (in groups of 6+2) received single doses of 50 - 800 mg FIN/placebo under fasting conditions (part A). A further 32 were given doses of 150, 300, 600 or 800 mg for 7 consecutive days (part B). The study also included one cohort to evaluate 600 mg multiple dose of 7 days in 20 *H. pylori* carriers (part C). 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: All enrolled subjects completed the study. No significant changes in laboratory test parameters were observed. Adverse events were recorded for 50 of the 95 subjects including (but not limited to): headache (14 incidents), tiredness (11), feeling of pressure in the head (7), diarrhoea (8) and nausea (3). No serious adverse events were reported. At 400 and 800 mg single doses the plasma $t_{1/2}$ of FIN was 10.1 and 10.5h, C_{max} [µg/mL] was 5.1 and 9.5; and $AUC_{0\text{-}inf}$ [h*µg/mL] was 14.2 and 24.8 respectively. FIN was readily absorbed with peak plasma concentration achieved at 0.5 - 2h after dosing. The systemic exposure ($AUC_{0\text{-}tlast}$) of FIN increased linearly from 25 to 800 mg. For 400 mg and 800 mg, mean urinary excretion was 28.3% and 33.4%, respectively.

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 a novel, 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 bacteria *in vitro* [3] and in a wide range of rodent infection models [4,5]. Additionally, FIN displayed an excellent safety profile in a wide range of predictive, *in vitro,* toxicity assays [6]. Here, the results of pharmacokinetics, safety and tolerability in healthy subjects in a phase I study is reported. These attributes suggest that FIN warrants further clinical investigation for bacterial infections that are associated with low pH such as urinary tract infection and *Helicobacter pylori* eradication.

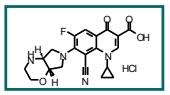


Figure 1. Finafloxacin hydrochloride.

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 finafloxacin hydrochloride administered orally to healthy male and female subjects, aged between 18 and 55 years. Subjects received single doses of 25, 50, 100, 200, 400 or 800 mg. For the multiple dose study, subjects received 7 daily doses of 150, 300, 600 or 800 mg.

ECG rhythm measurements were made from the time of dosing and up to 4 h post-dosing and then at 8h and at 24 h.

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 till 48 h post dose for pharmacokinetic analysis. Urinary bactericidal activity was determined for 200 and 800 mg single dose. See poster F1-2049 for further details.

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 reported and assessed as mild, moderate or severe.

Results and Discussion

ECG: No clinically relevant abnormalities were observed.

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.

Plasma pharmacokinetics (PK) for single dose:

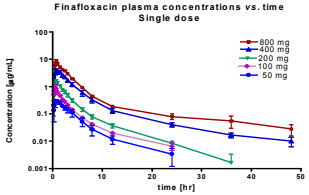
The PK values for subjects receiving single doses are tabulated in Figure 2. Plasma concentration *vs.* time profile of escalating single dose is shown in Figure 3.

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

Dose	100 mg	200 mg	400 mg	800 mg
C_{max} [µg/mL]	1.0 ± 0.5	1.9 ± 0.7	5.1 ± 2.1	9.5 ± 2.6
$AUC_{0\text{-}inf}$ [h*µg/mL]	2.2 ± 0.6	4.1 ± 1.0	14.2 ± 4.4	24.8 ± 5.8
$t_{1/2}$ [h]	5.8 ± 2.6	5.0 ± 2.6	10.1 ± 4.5	10.5 ± 2.7

Results and Discussion

Figure 3. Log concentration vs. time curve for single dose of FIN.

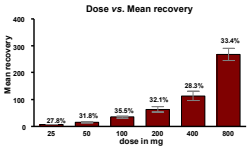


FIN absorption was rapid, with t_{max} values of 0.5 to 2 hour. C_{max} & $AUC_{0\text{-}inf}$ increased almost linearly with dose. The median value of total oral body clearance was 28.0 and 35.8 L/hr for 400 mg and 800 mg dose, respectively.

Urine pharmacokinetics for single dose:

Urinary recovery median values ranged from 26.99% to 34.75%. The absence of clear differences between doses show that urine excretion of unchanged FIN is a relevant elimination route. Figure 4 shows mean urinary recovery after single dose.

Figure 4. Mean urinary recovery for single dose of FIN.



The mean (median) maximum concentration of FIN in urine was 120 (85.2) mg/L at 2 to 4 hours following 400 mg dose and 150 (137) mg/L at 4 to 8 hours following 800 mg dose. The median value of renal clearance was 7.5 and 11 L/hr following 400 mg and 800 mg dose, respectively.

Plasma pharmacokinetics for multiple dose in healthy subjects:

Figure 5 shows plasma concentration *vs.* time curve for 7 day multiple dosing. The PK values for subjects receiving single oral dose of FIN for 7 consecutive days is described in Figure 6.

Figure 5. Log concentration vs. time curve for multiple dose of FIN.

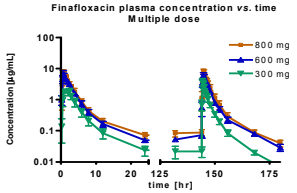


Figure 6. Non-compartmental PK parameters determined as mean ± standard deviation in the subjects on day 7 receiving multiple doses of FIN.

Dose	300 mg	600 mg	800 mg
C_{max} [µg/L]	4.0 ± 2.3	6.8 ± 2.2	9.0 ± 3.1
$AUC_{0\text{-}inf}$ [h*µg/L]	8.9 ± 4.2	20.2 ± 6.7	27.8 ± 9.3
$t_{1/2}$ [h]	6.5 ± 2.7	8.7 ± 3.1	13.8 ± 5.4

Steady state was reached at day 4. The median value of total oral body clearance was 32.4 and 32.2 L/hr for 600 mg and 800 mg dose, respectively.

Safety & Tolerability:

- The subjects enrolled in single and multiple dose group were comparable with regard to age, weight and body mass index.
- The tolerability of FIN / Placebo tablets given as a single dose or in multiple doses over 7 days was considered to be good.
- There was no serious adverse event or death and no discontinuation due to adverse events (AEs).
- No clear dose dependency on the number of subjects reporting AEs per cohort could be detected and none of the reported AEs increased in number or intensity with increasing doses.
- No clear difference of AEs experienced by subjects taking FIN or placebo was observed.
- Figure 7 shows the AEs experienced by single dose, multiple dose and placebo dose group. The most frequent AEs were headache, diarrhoea, nausea, back pain. Flatulence (GI) was more common in *H. pylori* carriers.
- CNS and RTI adverse events were found more frequently in placebo group, where as GI related adverse events were more for subjects taking FIN.

Figure 7. Adverse events reported in subjects receiving single and multiple oral dose of FIN and placebo.

Body system	Part A n = 33	Part B n = 24	Part C n = 20	FIN Total n = 77	Placebo n = 18
	n (%)	n (%)	n (%)	n (%)	n (%)
CNS	13 (39)	9 (37)	4 (20)	26 (34)	8 (44)
Cardiovascular	1 (17)	-	-	1 (1)	-
GI	5 (15)	5 (21)	11 (55)	21 (27)	1 (6)
Musculoskeletal	-	7 (29)	-	7 (9)	1 (6)
RTI	1 (3)	3 (12)	1 (5)	5 (6)	4 (22)
General	2 (6)	1 (4)	1 (5)	4 (5)	1 (6)
Skin	-	-	3 (15)	3 (4)	1 (6)
Eye	-	1 (4)	-	1 (1)	-

Part A = Single dose Part B = Multiple dose in healthy subjects
Part C = Multiple dose in *Helicobacter pylori* carriers

CNS; Central nervous system, RTI; Respiratory tract infection, GI; Gastrointestinal

Conclusions

- This FIN Phase I study in healthy subjects revealed a favorable pharmacokinetics profile with high C_{max} and long half life.
- FIN was well tolerated following single dose and when given for seven days at a range of doses up to 800 mg. Human safety data do not suggest any quantitatively higher or qualitatively different toxicity for FIN as compared with placebo.
- Overall, these findings indicate that the risk of serious adverse reactions to finafloxacin hydrochloride can be expected to be very low. Given the possible therapeutic effects of FIN, further clinical development of the drug appears justified and can be recommended.

Literature

[1] Wohlert *et al.*, 48th ICAAC, Washington DC 2008, Poster No. F1-2036.
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