**Efficacy of the Investigational Fluoroquinolone Finafloxacin in a Murine Inhalational Model of Melioidosis**

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**Abstract**

Background: Finafloxacin (FIN) is a novel fluorquinolone (FQ) in clinical development. It has the unique property of being a broad-spectrum agent with activity against clinically relevant Gram-negative and -positive bacteria, including strains known to be resistant to other FQs. However, FIN exhibits a high degree of resistance against Stenotrophomonas maltophilia, the causative agent of melioidosis and Burkholderia pseudomallei, which are intracellular pathogens that can replicate within host organelles when the local pH is acidic. Other FQs have reduced antibacterial activity at lower pHs and therefore FIN may offer greater efficacy in the treatment of intracellular infections, especially since it has been shown that FINs is efficiently accumulated within cells in an acidic environment. The study was performed to determine the efficacy of FIN N in murine intralobular model of melioidosis.

**Methods:** The efficacy of FIN against Burkholderia pseudomallei (B. pseudomallei) was investigated. This activity was determined in vitro using a panel of 14 strains of B. pseudomallei from an international challenge group. The intracellular efficacy was compared with that of levofloxacin. The intracellular model used was the murine liver macrophage cell line RAW264.7. The bacteria were inoculated into the RAW264.7 cells to an MOI of 5. The bacteria were cultured for 4 h before addition of drugs and 24 h post-drug administration. The drug media was removed and the cell media was cultured for 7 days. The remaining viable bacteria were enumerated using a 96-well plate. The intracellular efficacy was compared with that of levofloxacin. The intracellular model used was the murine liver macrophage cell line RAW264.7. The bacteria were inoculated into the RAW264.7 cells to an MOI of 5. The bacteria were cultured for 4 h before addition of drugs and 24 h post-drug administration. The drug media was removed and the cell media was cultured for 7 days. The remaining viable bacteria were enumerated using a 96-well plate. The intracellular efficacy was compared with that of levofloxacin.

**Results:** The study was an important, randomized, double-blind, placebo-controlled, dose-escalating study to evaluate the safety, tolerability and pharmacokinetic profiles of single and multiple IV doses of FIN administered intravenously to healthy male and female subjects aged between 18 and 50 years. Subjects received single doses of 200, 400, 600, 800 and 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 compared with marketed FQs.

**Conclusions:** Overall, these findings indicate that the risk of serious adverse reactions to FIN is minimal.

**References:**

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**Literature**


**Figure 1:** Finafloxacin hydrobromide

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

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

**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 receiving multiple doses of FIN.

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