Pharmacokinetics (PK) and Safety of Single Doses of Delafloxacin Administered Intravenously in Healthy Subjects

Laura Lawrence1, Michael Benedicic1, James Hart2, Allan Hawkins2, Danping Li3, Matthew Bedrick1, Scott Hopkins1, and Eric Burak1

1Rib-X Pharmaceuticals, New Haven, CT; 2PD Phase I Clinic, Austin, TX; 3Theraxis, New York, NY

Abstract

Introduction

Delafloxacin (RX-3341) is an investigational fluoroquinolone (FQ) with potent activity against Staphylococcus aureus and other gram-positive organisms, including methicillin-resistant Staphylococcus aureus (MRSA) and Enterococcus faecalis. Its tobramycin-like clinical activity against MRSA has been observed in single-dose clinical studies of 300 mg delafloxacin. The objective of this study was to evaluate the pharmacokinetics (PK), tolerability, and safety of single intravenous (IV) doses of 300, 450, 600, 750, and 900 mg of delafloxacin, and a 1200 mg IV dose in healthy subjects. Study subjects received the single IV dose of delafloxacin as a 20 minute infusion, and blood samples were collected prior to and post-dose up to 8 hours. The PK and tolerability results of the study were compared and analyzed for dose-related effects.

Methods

This was a double-blind, placebo-controlled study conducted at the New Haven, Connecticut Clinical Research Unit in New Haven, Connecticut, USA. Subjects were eligible if they were healthy adult males or females aged 18-55 years with a body mass index (BMI) of 18-30 kg/m2. Subjects were admitted to the unit overnight the day before dosing and were required to fast for at least 8 hours before dosing. Subjects were fasted overnight for at least 8 hours before dosing and continued to fast for 4 hours after dosing. Standard meals were provided while subjects were confined to the clinical unit. Blood for plasma was withdrawn from each subject at specific time points after dosing, and plasma and urine samples were analyzed.

Results

Delafloxacin was rapidly absorbed following IV administration with a median time to maximum concentration (tmax) of 0.25 hours (range: 0.25-1.0 hours). The median area under the plasma concentration-time curve (AUC0-8) was 12,591 ng·h/mL (range: 9,949-16,724 ng·h/mL) for the 900 mg dose group, demonstrating linear PK characteristics over the dose range studied. The median steady-state volume of distribution (Vss) was 23,752 L (range: 17,413-31,084 L). The median half-life (t1/2) was 7.4 hours (range: 5.8-9.2 hours), indicating that delafloxacin is eliminated slowly from the body. The median total body clearance (CL) was 3.5 L/hr (range: 2.9-4.0 L/hr). The median maximum concentration (Cmax) was 11.7 mg/L (range: 7.7-15.6 mg/L) for the 900 mg dose group, with a 90% confidence interval of 1.03-1.05 mg/L for the area under the curve from 0 to 8 hours (AUC0-8).

Conclusions

Delafloxacin was rapidly absorbed following IV administration, with a median tmax of 0.25 hours. The median AUC0-8 was 12,591 ng·h/mL for the 900 mg dose group, demonstrating linear PK characteristics over the dose range studied. Delafloxacin was eliminated slowly from the body, with a median t1/2 of 7.4 hours and median CL of 3.5 L/hr. No dose-related effects were observed in the tolerability profile of delafloxacin. Delafloxacin was well tolerated at all doses studied, with no serious adverse events reported. The study results provide evidence of the safety and tolerability of delafloxacin at single IV doses of 300-900 mg in healthy subjects.

References


Figure 1 - Structure of Delafloxacin

Figure 2 - Study Design