Pharmacokinetics of Ulfloxacin, a Fluoroquinolone for Bacterial Gastroenteritis Treatment, in Healthy Subjects After Oral Dosing of the Prodrug Pruliloxacin at Three Supratherapeutic Dose Levels

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Abstract

Purpose: Pruliloxacin is a prodrug for ulfloxacin. The objective of this study was to assess ulfloxacin PK, safety and tolerability in healthy adult subjects equivalent to 2×, 4×, and 6× the daily therapeutic dose (300 mg) used in Phase II clinical trials of pruliloxacin as therapy for bacterial gastroenteritis. The data were utilized to determine an appropriate supratherapeutic dose level to be used in a later though QT interval prolongation study.

Methods: This was a randomized, placebo-controlled, safety and tolerability (PK) study. Three groups were randomized to receive a single dose of 1200, 2400 or 3600 mg pruliloxacin, respectively. Each group contained 6 active and 2 placebo subjects. Plasma and urine samples were collected over 24 hours post dosing and were analyzed for ulfloxacin concentrations using validated HPLC–MS/MS assays. PK parameters were determined using standard model independent methods.

Results: Following pruliloxacin oral dosing, ulfloxacin was measured in plasma with median Tm values ranging from 1.18 to 1.50 hours. Cmax values were 2415, 2040 and 2470 ng/mL, and AUC0-24 values were 12000, 10250 and 24200 ng·h/mL for pruliloxacin-doses of 1200, 2400 and 3600 mg, respectively. Tmax ranged from 6.0 to 7.30 hours. Ulfloxacin was recovered in urine. The elimination rate of ulfloxacin in urine appeared to be comparable to that of the plasma. The mean T1/2, % dose excreted values were 15.7%, 12.2% and 11.6% and CLR were 183, 221 and 189 mL/min for respective pruliloxacin doses. All 3 doses were well tolerated.

Conclusions: Following pruliloxacin oral dosing, pruliloxacin was absorbed and converted to ulfloxacin. In general, ulfloxacin exposure in plasma and urine increased as a function of pruliloxacin dose in a less than proportional fashion. Ulfloxacin CLR values exceeded the glomerular filtration rate (>2×), which indicates that tubular secretion markedly contributes to the renal elimination of ulfloxacin. All 3 doses were well tolerated and the 1800 mg dose was selected as an appropriate supratherapeutic level for the QT interval prolongation study.

To assess PK of ulfloxacin in a study that evaluated the safety of the prodrug pruliloxacin when administered as a single dose of 1200 mg, 2400 mg, or 3600 mg (equivalent to 2×, 4×, or 6× the therapeutic dose). The data were utilized to determine the appropriate supratherapeutic dose level to be used in a later though QT interval prolongation study.

Introduction

Pruliloxacin, a new broad-spectrum fluoroquinolone antibacterial agent, is being developed by Optimer Pharmaceuticals to treat bacterial gastroenteritis. Following an oral dose, pruliloxacin is absorbed and rapidly metabolized by an N-demethylation (detoxification) to the active form, ulfloxacin [Kouba et al., 2009; Knecht and Perry, 2004; Patel et al., 2005].

Ulfloxacin displayed a potent in vivo activity against the most common gastroenteritis-producing bacterial pathogens, with an antibacterial activity generally 2–4× more potent than ciprofloxacin [Fritsche et al., 2009].

Phruliloxacin, when given once daily for 3 days at a dose level of 850 mg/d, was shown to be superior to placebo in two Phase II trials of pruliloxacin as therapy for bacterial gastroenteritis [Dupont et al., 2009; Steffen et al., 2008]. Pruliloxacin has been approved for multiple indications, including various infectious diarrheas in Japan.

This poster presents the PK of ulfloxacin in a study that evaluated the safety of pruliloxacin when administered once daily at 2×, 4×, or 6× therapeutic dose.

Materials and Methods

A. Study

A Phase I randomized, placebo-controlled study of the safety and tolerability of pruliloxacin at three supratherapeutic dose levels in healthy volunteers.

B. Dose

Three groups were randomized to receive a single dose of 1200, 2400 or 3600 mg pruliloxacin, respectively. Each group contained 6 active and 2 placebo subjects.

C. Analytical Method

The plasma and the urine samples were analyzed for ulfloxacin by validated HPLC–MS/MS assays.

D. PK Analysis

Plasma PK parameters (Cmax, Tmax, AUC0-24, AUC0-∞, and AUC0-12 h) and urine PK parameters (AUC0-24, ωt<sub>12</sub> less than the urine concentration-time area, % Ex, 24 hour cumulative excretion, % N or amount, mg, secreted, F<sub>lin</sub> (maximum urinary excretion rate, Tmax) rate to reach AUC<sub>12</sub> and ωt<sub>12</sub> clearance) were determined using WinNonlin Professional 5.2.1 (Pharsight Corp., Mountain View, CA).

Results and Discussion

Following single oral dosing of the prodrug pruliloxacin, ulfloxacin was readily produced in human plasma with median T<sub>m</sub> value less than 2 hours (Figure 1 Table 1).

Ulfloxacin plasma exposure (C<sub>max</sub> and AUC<sub>0-24</sub>) increased as function of pruliloxacin dose in a less than proportional fashion (Figures 1 and 2 Table 1). Ulfloxacin’s mean T<sub>m</sub> values ranged from 6.0 to 7.30 hours and did not change with pruliloxacin doses increases (Figure 1 and Table 1).

Ulfloxacin was readily measurable at high concentrations in the urine with % dose values observed during 0–8 hours and increased as a function of pruliloxacin doses (Figures 5 and Table 2). Ulfloxacin 24 hours urinary recovery (% dose) ranged from 11.6% to 17.5% (Figure 4 and Table 2). The CLR<sub>0</sub> of ulfloxacin ranged from 160 to 221 mL/min. There was no statistically significant difference of ulfloxacin CLR<sub>0</sub> among the treated groups (p < 0.05) (Figure 6).

Conclusions

Ulfloxacin exposure in plasma and urine increased as a function of pruliloxacin dose in a less than proportional fashion. Ulfloxacin CLR values exceeded the glomerular filtration rate (GFR) or > 2×, which indicates that tubular secretion markedly contributes to the renal elimination of ulfloxacin. All 3 doses were well tolerated and the 1800 mg dose was selected as an appropriate supratherapeutic level for the QT interval prolongation study.

Figure 1

Chemical Structure of the Prodrug Pruliloxacin and its Active Metabolite, Ulfloxacin

Figure 2

Mean Plasma Concentration-Time Profiles of Ulfloxacin in Human Subjects Following Oral Administration of Single Doses of Pruliloxacin

Figure 3

Mean C<sub>max</sub> and AUC<sub>0-24</sub> of Ulfloxacin in Human Subjects Following Oral Administration of Single Doses of Pruliloxacin

Figure 4

Mean Cumulative Urinary Excretion (mg or % Total Dose) of Ulfloxacin in a Human Subject Following Dosing of Single Doses of Pruliloxacin

Figure 5

Mean Urine Excretion Rates (mg/hr) of Ulfloxacin Following Oral Administration of Single Doses of Pruliloxacin

Figure 6

Summary of Mean Urine PK Parameters of Ulfloxacin Following Oral Administration of Single Doses of Pruliloxacin

References


*fe(0-24) = 100 x [Ae(0-24)/(pruli oxacin (349.38 g/mole) and MWp is the molecular weight of pruli oxacin (461.46 g/mole).