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Pharmacokinetics of a 900 mg Oral Formulation of Delafloxacin in Healthy Subjects Supporting a Gonorrhea Phase 3 Study

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Abstract

Background

Owing to drug resistance, a single (intramuscular) drug, ceftriaxone, remains as a CDC recommendation (STD treatment guidelines, 2012) for treatment of gonorrhea. Delafloxacin, a potent, investigational fluoroquinolone, has activity against multi-drug resistant Neisseria gonorrhoeae including ciprofloxacin-resistant strains. Tested against a 93-strain panel the MIC50/MIC90/MIC100 values for delafloxacin were 0.06/0.125/0.5 µg/mL, while for ciprofloxacin were 8/32/64 µg/mL. Delafloxacin is currently in Phase 3 clinical development for the treatment of uncomplicated gonorrhea using a single 900-mg oral dose.

Methods

In this Phase 1, open-label study, 20 healthy subjects received a single 900-mg dose of oral delafloxacin (2 x 450-mg tablets) after an overnight fast of 8 hours. Plasma was analyzed for delafloxacin concentrations with a validated LC-MS/MS method. Pharmacokinetic parameters were calculated using noncompartmental methods.

Results

Subjects ranged in age from 19 to 49 (Mean 30.6 years +/- 8.29 years), had a mean BMI of 25.96 kg/m2, and were 50% female. The arithmetic means (CV%) of delafloxacin for AUC0-t and AUC0 – inf (µg•h/mL) were 48.8 (35.9) and 44.1 (31.1). And mean C_{max} (µg/mL) (CV%) and median T_{max} (h) (range) were 10.4 (32.7) and 1.38 (0.50, 4.02), respectively. Three subjects reported 3 mild treatment-emergent adverse events: epistaxis (unrelated), diarrhea (unrelated), and nausea (possibly related). No other safety findings were observed. For quinolones, the free AUC0-24:MIC ratio is the most predictive PK/PD efficacy correlate. In a murine neutropenic MRSA thigh infection model, a 1-log kill was achieved with a mean free AUC0-24:MIC of 14.3. In this study, the 900-mg oral dose of delafloxacin produced a mean AUC0-24 (CV%) of 46.1 (34.7) µg•h/mL. The human plasma protein binding of delafloxacin is about 84%; therefore, the mean free AUC0-24 was approximately 7.38 µg•h/mL. Thus, the 900-mg oral delafloxacin dose should achieve sufficient antimicrobial coverage across the range of MICs of clinically encountered *N. gonorrhoeae* isolates.

Conclusions

The plasma exposure of the 900-mg was dose-proportional to previous clinical experience of the 450-mg oral dose. The delafloxacin 900-mg dose was well-tolerated, and the pharmacokinetic data provides support for this concentration in the Phase 3 gonorrhea clinical study.

Introduction

Gonorrhea is a sexually transmitted disease (STD) caused by infection with Neisseria gonorrhoeae and is the second most commonly reported notifiable disease in the United States, with more than 320,000 cases of gonorrhea reported to the Centers for Disease Control (CDC) in 2011 (CDC 2012b). Depending on the site of exposure, N. gonorrhoeae can cause urethritis, cervicitis, proctitis, and pharyngitis, and gonorrhea left untreated can cause serious and permanent health problems in both women and men (CDC 2012a; CDC 2013). Delafloxacin differs markedly from marketed quinolones in that it is highly active against all strains of *N. gonorrhoeae* tested to date, including those classified as multidrug-resistant. A 99-strain susceptibility panel, which was 70% ciprofloxacin resistant, was performed by the CDC in 2010 using specimens that were mostly isolated in the United States over the previous 10 years (Lawrence 2013). The MIC_{100} for delafloxacin was 0.5 µg/mL, and the MIC_{100} for ciprofloxacin was 64 µg/mL. These data suggest delafloxacin may be effective against N. gonorrhoeae infections that are resistant to currently marketed quinolones and in currently in a Phase 3 clinical study in the US.

Methods

Clinical Study Design

This study was a Phase 1 single dose, open-label, 1-period study in 20 healthy subjects. Subjects who met all of the eligibility criteria received a single 900-mg oral dose of delafloxacin (two 450-mg tablets) on Day 1 after an overnight fasting period of at least 8 hours. Subjects continued fasting for at least 4 hours after study drug administration. Subjects were confined to the clinical unit until discharge on Day 4 after all assessments were completed.. Safety assessments included monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, physical examination findings, and 12-lead electrocardiogram (ECG) results. Serial blood samples for the determination of plasma concentrations of delafloxacin were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48, and 72 hours after dosing.

Bioanalysis

Delafloxacin in plasma were quantitated using a validated LC-MS/MS method. Plasma samples for delafloxacin analysis were processed by SLE extraction. The processed samples were analyzed by an LC-MS/MS method with a calibration range of 5 to 5000 ng/mL.

Noncompartmental Pharmacokinetic Analysis

Plasma concentration data for delafloxacin was analyzed by noncompartmental methods. Pharmacokinetic parameters determined included C_{max}, T_{max}, C_{min}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL and Vz. Actual sample times were used.

Results

Figure 1. Structure of Delafloxacin

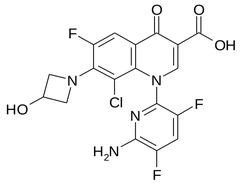

Figure 2. Mean (+SD) Plasma Concentrations of Delafloxacin (900 mg Oral) Versus Time

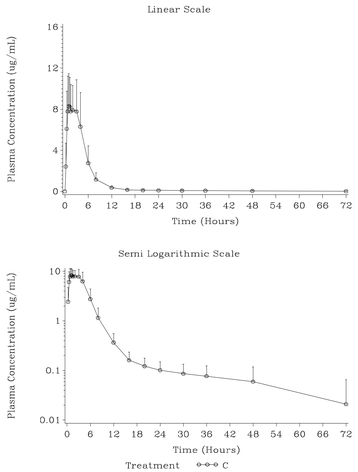

Table 1. Summary of Subject Demographics and Baseline Characteristics (Safety Population)

	Overall (n = 20)
Mean Age (years), (SD)	30.6 (8.29)
Minimum, maximum	19, 49
Gender, No. (%)	
Male	10 (50.0)
Female	10 (50.0)
Race, No. (%)	
White	12 (60.0)
Black or African American	6 (30.0)
Asian	1 (5.0)
Native Hawaiian or Other Pacific Islander	1 (5.0)
Mean Height (cm) (SD)	166.4 (9.7)
Minimum, maximum	147.5, 180.3
Mean Weight (kg) (SD)	72.5 (14.6)
Minimum, maximum	53.3, 98.2
Mean Body mass index (kg/m2) (SD)	26.0 (3.3)
Minimum, maximum	20.0, 30.6

Abbreviation: SD, standard deviation.
Note: Percentages were calculated based on the number of subjects in the safety population.

Results

Table 2. Mean (CV) Plasma Pharmacokinetic Parameters of Delafloxacin by Treatment (Pharmacokinetic Population)

Treatment: Delafloxacin Tablet (2 × 450 mg)	
Parameter (unit)	**(n = 20)**
$AUC_{0\text{-}tau}$ (µg•h/mL)	44.1 (35.5)
$AUC_{0\text{-}t}$ (µg•h/mL)	48.8 (35.9)
$AUC_{0\text{-}inf}$ (µg•h/mL)[a]	44.1 (31.1)
C_{max} (µg/mL)	10.4 (32.7)
T_{max} (h)[b]	1.375 (0.50, 4.02)
K_{el} (1/h)[a]	0.0497 (42.3)
$t_{1/2}$ (h)[a]	17.8 (58.8)

Abbreviation: CV, coefficient of variation.
[a] n = 14. Corresponding parameters were not calculated for some of the subjects because a linear regression could not be fitted through the terminal phase.
[b] For Tmax, the median (minimum, maximum) values are presented.

Table 3. Treatment-Emergent Adverse Events (TEAEs, Safety Population)

System Organ Class Preferred Term, No. (%)	Overall (n=20)
Total number of TEAEs	3
Number of subjects with at least 1 TEAE	3 (15.0)
Gastrointestinal disorders	2 (10.0)
Diarrhoea	1 (5.0)
Nausea	1 (5.0)
Respiratory, thoracic and mediastinal disorders	1 (5.0)
Epistaxis	1 (5.0)

Abbreviation: TEAE, treatment-emergent adverse event.
Note: The total number of adverse events counts all TEAEs for subjects in the safety population. Subjects could have had more than 1 TEAE per system organ class and preferred term. At each level of subject summarization, a subject was counted once if he/she reported 1 or more events. TEAEs were summarized by treatment at onset of the event. Adverse events were coded using MedDRA Version 16.0. Percentages were based on the number of subjects in the safety population within each treatment and overall.

Conclusions

- Mean total exposure ($AUC_{0\text{-}inf}$) and mean peak plasma concentration (C_{max}) of delafloxacin were 44.1 µg•h/mL and 10.4 µg/mL, respectively, following the administration of two 450 mg tablets
- Median T_{max} of delafloxacin occurred at 1.38 hours following the administration of the two 450 mg tablets
- Plasma exposure of the 900-mg was dose-proportional to previous clinical experience of the 450-mg oral dose.
- Delafloxacin was well tolerated with 3 TEAEs were considered possibly or unrelated to study drug administration.
- All TEAEs were mild and resolved by the end of the study. There were no deaths, SAEs, or TEAEs leading to study discontinuation.

References

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