Poster A-682
54th ICAAC
Washington, DC
September 5-9, 2014

Pharmacokinetics and Relative Bioavailability of Intravenous and Oral Formulations of Delafloxacin (DLX) in Healthy Subjects

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Abstract

Background
Delafloxacin, a novel fluoroquinolone, has activity against Gram-positive organisms including methicillin-resistant *S. aureus* (MRSA), and against susceptible Gram-negative organisms. Delafloxacin is currently in Phase 3 development for ABSSSI and uncomplicated gonorrhea.

Methods
This was a Phase 1, single dose, open-label, randomized, 2-period, 2-sequence crossover study, in which 56 healthy subjects received a single 450-mg dose of oral delafloxacin and a single 300-mg delafloxacin IV infusion in 1 of 2 treatment sequences. Plasma samples were analyzed for delafloxacin concentrations with a validated LC MS/MS method. Pharmacokinetic parameters were calculated using non-compartmental methods. To assess the relative exposures of the oral form (Test) to the IV form (Reference), a linear mixed-effect model was performed on the natural logarithm (ln)-transformed values of AUC_{0-t}, AUC_{0-inf}, and C_{max} with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

Results
Equivalence in AUC exposure between the oral and IV forms was concluded since the 90% CIs for the Test-to-Reference ratios of geometric means were entirely contained within the predefined criterion interval of 80% to 125% for AUC_{0-t} and AUC_{0-inf}. Equivalence for C_{max} was not concluded. 16 treatment-emergent AEs (TEAE) were reported, the most frequent of which were headache (5.4%), followed by diarrhea (3.6%). 2 TEAEs were considered moderate in severity, but the remainders were considered mild, and none led to study discontinuation.

Parameter (unit)	Treatment	N	Geometric LS Mean	Ratio (%) of Geometric LS Means (Test/Ref)	90% CI of the Ratio (Test/Ref)
AUC_{0-inf} (µg•h/mL)	450 mg Tablet	42	23.0	87.7	83.6, 92.0
	300 mg Infusion	49	26.2		
AUC_{0-t} (µg•h/mL)	450 mg Tablet	55	22.2	84.4	80.9, 88.2
	300 mg Infusion	55	26.3		
C_{max} (µg/mL)	450 mg Tablet	55	5.80	55.2	51.5, 59.1
	300 mg Infusion	55	10.5		

Conclusions
The plasma exposures of both formulations were similar to those observed in previous clinical experience. Delafloxacin doses were well-tolerated, and the pharmacokinetic data provides support for utilizing both formulations in Phase 3 IV-to-oral switch settings.

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), and left untreated can cause serious and permanent health problems in both women and men (CDC 2012a; CDC 2013). Delafloxacin is highly active against all strains of *N. gonorrhoeae* tested to date, including those classified as multidrug-resistant. In a 99-strain susceptibility panel (70% ciprofloxacin-resistant) performed by the CDC in 2010 using US specimens (Lawrence 2013), the MIC_{100}s for delafloxacin and ciprofloxacin were 0.5/64 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 was a Phase 1, single-dose, open-label, randomized, 2-period, 2-sequence crossover study in 56 healthy subjects. Subjects who met all of the eligibility criteria were randomly assigned in a 1:1 ratio to a single dose of oral delafloxacin (450-mg tablet; Treatment A) and IV delafloxacin (300 mg infused over 1 hour; Treatment B) in 1 of 2 treatment sequences. The study consisted of a screening period (Days –28 to –2), 2 check-ins (Day –1 of each period), 2 treatment periods (Days 1 to 4 of each period), and end-of-study/early termination assessments (Day 4 of Period 2). There was a minimum 7-day washout interval between doses in each period. 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, 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.

Non-compartmental Pharmacokinetic Analysis
Plasma concentration data for delafloxacin were analyzed by non-compartmental 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

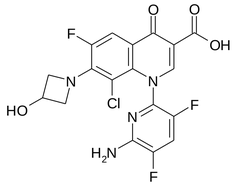

Figure 2. Mean (+SD) Plasma Concentrations of Delafloxacin (450-mg Oral and 300-mg IV Treatments) Versus Time (Pharmacokinetic Population)

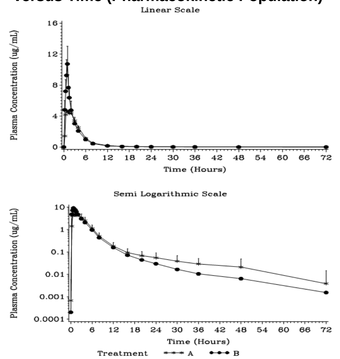

Table 1. Summary of Subject Demographics and Baseline Characteristics (All Subjects)

	Overall (n = 56)
Mean age (years) (SD)	36.2 (10.87)
Min, max	20, 61
Gender, No. (%)	
Female	28 (50.0)
Male	28 (50.0)
Race, No. (%)	
White	40 (71.4)
Black or African American	15 (26.8)
Asian	1 (1.8)
Mean Weight (kg) (SD)	75.3 (11.9)
Min, max	52.7, 97.7
Mean BMI (kg/m^2) (SD)	26.5 (3.10)
Min, max	19.2, 31.6

Abbreviation: SD, standard deviation. Min, minimum. Max, maximum. BMI, body mass index.

Note: Percentages were calculated based on the number of subjects in the safety population within each treatment sequence and overall.

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

	Treatment	
	Delafloxacin 450-mg Tablet	Delafloxacin 300-mg IV Infusion
Parameter (unit)	**(n = 55)**	**(n = 55)**
AUC_{0-tau} (µg•h/mL)	21.2 (29.7)	25.7 (21.5)
AUC_{0-t} (µg•h/mL)	23.3 (30.1)	26.9 (21.5)
AUC_{0-inf} (µg•h/mL)[a]	24.2 (26.6)	26.7 (22.6)
C_{max} (µg/mL)	6.12 (32.0)	10.7 (21.3)
T_{max} (h)[b]	0.817 (0.50, 4.00)	1.0 (0.75, 1.13)
K_{el} (1/h)[a]	0.0588 (43.0)	0.0804 (48.2)
$t_{1/2}$ (h)[a]	14.1 (42.0)	10.9 (54.6)
AUC_{0-tau}/Dose (µg•h/mL/mg)	0.0471 (29.7)	0.0856 (21.5)
AUC_{0-inf}/Dose (µg•h/mL/mg)[a]	0.0538 (26.6)	0.0889 (22.6)
AUC_{0-t}/Dose (µg•h/mL/mg)	0.0517 (30.1)	0.0896 (21.5)
C_{max}/Dose (µg/mL/mg)	0.0136 (32.0)	0.0358 (21.3)

Abbreviation: CV, coefficient of variation.

[a] n = 42 for Treatment A and n = 49 for Treatment B. Corresponding parameters were not calculated for some of the subjects because a linear regression could not be fitted through the terminal phase.

[b] For T_{max}, the median (minimum, maximum) values are presented.

Results

Table 3. Statistical Analysis of Plasma Pharmacokinetic Parameters of Delafloxacin Following 450-mg Oral and 300-mg IV Treatments (Pharmacokinetic Population)

Parameter (unit)	Treatment[a]	N	Geometric LS Means[c]	90% CI of the Geometric LS Means (A,B)	Ratio (%) of Geometric LS Means (A/B)[d]	90% CI of the Ratio (A/B)[e]
AUC_{0-t} (µg•h/mL)	A	55	22.2	(21.0, 23.6)	84.4	(80.9, 88.2)
	B	55	26.3	(24.9, 27.9)		
AUC_{0-inf} (µg•h/mL)	A	42	23.0	(21.6, 24.4)	87.7	(83.6, 92.0)
	B	49	26.2	(24.7, 27.8)		
C_{max} (µg/mL)	A	55	5.80	(5.44, 6.17)	55.2	(51.5, 59.1)
	B	55	10.5	(9.87, 11.2)		

Abbreviations: CI, confidence interval; CV, coefficient of variation; IV, intravenous; LS, least square.

Note: A linear mixed-effect model on the natural logarithms (ln) of AUC_{0-inf}, AUC_{0-t} and C_{max} was performed with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect.

[a] Treatment A = delafloxacin 450-mg tablet; Treatment B = delafloxacin 300 mg infused over 1 hour

Table 4. Treatment-Emergent Adverse Events (TEAEs, Safety Population)

System Organ Class Preferred Term, No. (%)	Delafloxacin 450-mg Tablet (n=55)	Delafloxacin 300-mg Infusion (n=55)
Total Number of TEAEs	5	11
Number of subjects with at least 1 TEAE	4 (7.3)	7 (12.7)
Gastrointestinal disorders	2 (3.6)	2 (3.6)
Diarrhoea	2 (3.6)	0
Abdominal discomfort	1 (1.8)	0
Infrequent bowel movements	0	1 (1.8)
Nausea	0	1 (1.8)
Vomiting	0	1 (1.8)
Nervous system disorders	1 (1.8)	3 (5.5)
Headache	1 (1.8)	2 (3.6)
Dizziness	0	1 (1.8)
Dysgeusia	0	1 (1.8)
Sinus headache	0	1 (1.8)
General disorders and administration site conditions	1 (1.8)	0
Energy decreased	1 (1.8)	0
Infections and infestations	0	1 (1.8)
Vulvovaginal candidiasis	0	1 (1.8)
Musculoskeletal and connective tissue disorders	0	1 (1.8)
Myalgia	0	1 (1.8)
Skin and subcutaneous tissue disorders	0	1 (1.8)
Pruritus	0	1 (1.8)

Conclusions

- Equivalence in total exposure of delafloxacin was concluded since the 90% CI of the geometric mean ratios was contained within the predefined criterion interval of 80% to 125% for AUC_{0-t} and AUC_{0-inf}.
- Median T_{max} of delafloxacin occurred at 0.82 hour following the administration of the 450-mg tablet and at 1.00 hour following 300 mg infused over 1 hour.
- 16 TEAEs were reported and 11 of 56 subjects (19.6%) experienced at least 1 TEAE. 7 of 55 subjects (12.7%) experienced TEAEs after delafloxacin 300 mg infused over 1 hour, and by 4 of 55 subjects (7.3%) after delafloxacin 450-mg tablet.
- The most frequently reported TEAE overall was headache followed by diarrhea. All TEAEs were considered either possibly related (6 subjects, 10.7%) or unrelated (5 subjects, 8.9%) to study drug. Most TEAEs were mild and all TEAEs resolved by the end of the study. There were no deaths, SAEs, or TEAEs leading to study discontinuation.

References

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