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A Phase 1, Open-Label, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of a Single Dose of Oral Delafloxacin in Healthy Subjects

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Abstract

Background
Delafloxacin is a next-generation fluoroquinolone with broad-spectrum activity against methicillin-resistant *S. aureus* (MRSA), susceptible gram-negative bacteria including fluoroquinolone-resistant *N. gonorrhoeae*, and is in Phase III development for ABSSSI and uncomplicated gonorrhea.

Methods
This was a Phase 1, single-dose, randomized, open-label, 3-period, 6-sequence crossover study in 30 healthy subjects. After an overnight fast of at least 10 h, subjects received a 900 mg oral dose of delafloxacin in 1 of 6 treatment sequences comprised of 3 periods: fasting conditions (A), fed conditions (B), and fasting conditions with a high-fat meal 2 h post dose (C). Plasma samples were analyzed for delafloxacin concentrations with a validated LC-MS/MS method. Pharmacokinetic parameters were calculated using noncompartmental methods. To assess the effects of the fed states (Test) versus the fasted state (Reference), a linear mixed-effect model was performed on natural log-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 fasted state and both of the test states 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 in C_{max} was concluded between the fasted state and fasting with a meal 2 hours post dose, but not between the fasted and fed states.

Parameter (unit)	Treatment	N	Geometric LS Mean	Treatment Comparison	Ratio (%) of Geometric LS Means	90% CI of the Ratio
AUC0-t (hr*ug/mL)	A – Fasted	28	51.42	--	--	--
	B – Fed	29	52.34	B/A	101.8	95.71, 108.3
	C – Fed at 2 hr	25	45.91	C/A	89.3	83.82, 95.12
AUC0-inf (hr*ug/mL)	A – Fasted	9	49.48	--	--	--
	B – Fed	16	51.95	B/A	105.0	92.08, 119.7
	C – Fed at 2 hr	14	49.63	C/A	100.3	86.73, 116.0
Cmax (ug/mL)	A – Fasted	28	10.30	--	--	--
	B – Fed	29	8.19	B/A	79.5	73.19, 86.45
	C – Fed at 2 hr	24	10.45	C/A	101.4	93.02, 110.6

Conclusions
The AUCs of delafloxacin were equivalent between the fed and fasted states. Geometric mean C_{max} was reduced by 22% in the fed state. Because the PK/PD relationship for delafloxacin is AUC/MIC, the effect of food is not considered clinically significant.

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 study was a Phase 1, single-dose, randomized, open-label, 3-period, 6-sequence crossover study in 30 healthy subjects. Subjects who met all of the eligibility criteria were randomly assigned to 1 of 6 treatment sequences. Each sequence comprised 3 treatments of a single oral dose of 900 mg delafloxacin under fasting conditions for at least 10 hours (Treatment A), fed conditions of standardized FDA high-fat breakfast 30 minutes before dosing (Treatment B), and fasting conditions with a high-fat meal 2 hours after dosing (Treatment C). 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, and 48 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 was analyzed by non-compartmental methods. Pharmacokinetic parameters determined included C_{max}, T_{max}, AUC_{0-12}, AUC_{0-24}, AUC_t, AUC_{inf}, $T_{1/2}$, CL/F and Vz/F. Actual sample times were used.

Results

Figure 1. Structure of Delafloxacin

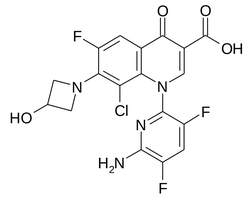

Table 1. Summary of Subject Demographics and Baseline Characteristics (All Subjects)

No. of subjects (%)	Overall (n = 30)
Mean age (years) (SD)	33.7 (10.2)
Min, max	22, 55
Gender, No. (%)	
Female	19 (63.3)
Male	11 (36.7)
Race, No. (%)	
White	24 (80.0)
Black or African American	6 (20.0)
Mean Weight (kg) (SD)	69.0 (12.1)
Min, max	51.0, 93.4
Mean BMI (kg/m^2) (SD)	25.3 (2.79)
Min, max	18.7, 29.3

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.

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

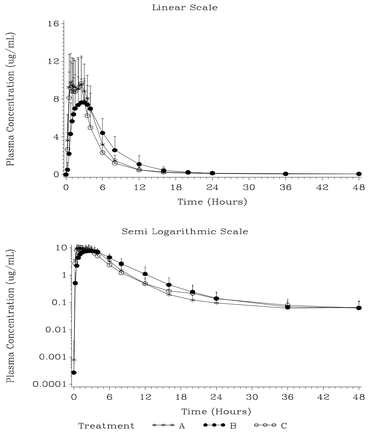

Table 2. Mean (CV) Plasma Pharmacokinetic Parameters of Delafloxacin 900 mg (Pharmacokinetic Population)

Parameter (Unit)	Fasted (A) (n = 28)	Fed (B) (n = 29)	Fed 2 hr Post-dose (C) (n = 25)
AUC_{0-12} (µg•h/mL)	52.1 (27.7)	49.9 (24.4)	44.5 (24.4)
AUC_{0-24} (µg•h/mL)	54.5 (27.5)	55.1 (25.3)	47.6 (24.6)
AUC_{0-t} (µg•h/mL)	56.2 (27.1)	57.1 (24.8)	49.8 (24.1)
AUC_{0-inf} (µg•h/mL)[a]	55.2 (24.8)	58.2 (19.6)	52.2 (24.0)
C_{max} (µg/mL)	11.5 (24.0)	9.14 (30.8)	11.8 (22.5)[c]
T_{max} (h)[b]	1.25 (0.50, 4.00)	2.50 (1.00, 6.00)	1.50 (0.50, 2.50)[c]
$t_{1/2}$ (h)[a]	14.1 (59.3)	12.9 (49.0)	12.0 (35.6)
CL/F (L/h)[a]	17.2 (23.6)	16.1 (21.4)	18.2 (23.3)
V_z/F (L)[a]	369 (76.3)	307 (58.5)	313 (42.6)

Abbreviations: CV, coefficient of variation.
Note: Two subjects experienced emesis and were excluded from the pharmacokinetic analysis for the respective periods. Collection samples were missing for Subject 118 Treatment C and Subject 128 Treatment C around the median T_{max} of the treatment group. These subjects' observed C_{max} and T_{max} were excluded from the pharmacokinetic analysis since these were not true parameters.
[a] n = 9, 16, and 14 for Treatments A, B, and C, respectively, for parameters AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F.
[b] For T_{max}, the median (minimum, maximum) values are presented.
[c] n = 23 for C_{max} and T_{max} following Treatment C.

Results

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

System Organ Class Preferred Term, No. (%)	Fasted (n = 28)	Fed (n = 29)	Fed 2 hr post-dose (n = 27)	Overall (n = 30)
Total number of TEAEs	5	12	11	28
Number of subjects with at least 1 TEAE	4 (14.3)	6 (20.7)	7 (25.9)	14 (46.7)
Gastrointestinal disorders	2 (7.1)	6 (20.7)	5 (18.5)	10 (33.3)
Diarrhoea	1 (3.6)	4 (13.8)	2 (7.4)	5 (16.7)
Nausea	1 (3.6)	2 (6.9)	2 (7.4)	4 (13.3)
Vomiting	0	0	2 (7.4)	2 (6.7)
Abdominal discomfort	0	0	1 (3.7)	1 (3.3)
Abdominal distension	0	0	1 (3.7)	1 (3.3)
Nervous system disorders	1 (3.6)	1 (3.4)	2 (7.4)	4 (13.3)
Presyncope	1 (3.6)	0	2 (7.4)	3 (10.0)
Headache	0	1 (3.4)	0	1 (3.3)
Infections and infestations	1 (3.6)	1 (3.4)	1 (3.7)	3 (10.0)
Vaginal infection	1 (3.6)	1 (3.4)	0	2 (6.7)
Nasopharyngitis	0	0	1 (3.7)	1 (3.3)
Skin and subcutaneous tissue disorders	1 (3.6)	1 (3.4)	0	2 (6.7)
Pruritus	1 (3.6)	0	0	1 (3.3)
Skin reaction	0	1 (3.4)	0	1 (3.3)
General disorders and administration site conditions	0	1 (3.4)	0	1 (3.3)
Fatigue	0	1 (3.4)	0	1 (3.3)
Metabolism and nutrition disorders	0	1 (3.4)	0	1 (3.3)
Decreased appetite	0	1 (3.4)	0	1 (3.3)
Respiratory, thoracic, and mediastinal disorders	0	1 (3.4)	0	1 (3.3)
Cough	0	1 (3.4)	0	1 (3.3)

Note: The total number of TEAEs counted 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 or she reported 1 or more events. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 16.1. Percentages were based on the number of subjects in the safety population within each treatment and overall.

Conclusions

- Total exposure (AUC_{0-t} and AUC_{0-inf}) of delafloxacin was not affected by administration under fed conditions.
- Peak exposure (C_{max}) of delafloxacin was reduced by 20.5% when administered under fed conditions versus fasted conditions.
- Median T_{max} of delafloxacin administered under fed conditions was delayed by 1.25 hours compared to administration under fasted conditions.
- Meals fed 2 hours after dosing did not have a statistically significant effect on delafloxacin plasma AUC_{0-inf}, C_{max}, or T_{max} following a 900-mg dose.

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