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A PHASE 1, OPEN-LABEL, EVALUATION OF THE SINGLE-DOSE PHARMACOKINETICS OF DELAFLOXACIN (DLX) IN SUBJECTS WITH AND WITHOUT HEPATIC IMPAIRMENT

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ABSTRACT

Background: Delafloxacin (DLX) is an investigational broad spectrum fluoroquinolone with activity against methicillin-resistant *S. aureus* (MRSA) and susceptible gram-negative bacteria. DLX is in Phase 3 development for treatment of acute bacterial skin and skin structure infections (ABSSSI).

Methods: This was a Phase 1 pharmacokinetic (PK) study in subjects with mild, moderate, or severe hepatic impairment (n=6 per category). Healthy subjects (n=18) were closely matched with the impaired subjects for age, weight, and sex. DLX was given as a 300 mg, 1-hour IV infusion, and plasma DLX concentrations were determined by LC-MS/MS. The effects of hepatic impairment were assessed by ANOVA of log-transformed values for AUC, C_{max}, and systemic clearance, with hepatic group as a fixed effect. Each impairment group was compared with its matching healthy group, and also with pooled healthy subjects.

Results: Mean AUC_{inf} and C_{max} in each impairment group were not significantly different from the pooled healthy subjects (P>.05). The 90% confidence interval (CI) of the ratios of least-squares means did not indicate significant differences between the impairment groups and pooled healthy subjects. No significant trend was observed for any PK parameter versus the ordered normal and impairment categories (P>.05). AUC_{inf} and C_{max} for the impairment groups were similar to historic values in Phase 1 studies with healthy subjects. Treatment-emergent adverse events (TEAEs) were mild or moderate (10 out of 39 subjects).

AUC_{inf} (hr*µg/mL)						
Group	N	Geo LS Mean	90% CI of Geo LS Mean	Comp.	Ratio of Geo LS Means (%)	90% CI of the Ratio (%)
A: Mild impairment	6	23.25	(19.91, 27.14)	A/D	114.44	(95.57, 137.03)
B: Moderate impairment	6	23.32	(19.97, 27.22)	B/D	114.78	(95.86, 137.44)
C: Severe impairment	6	23.38	(20.02, 27.29)	C/D	115.09	(96.11, 137.80)
D: Combined match	17	20.31	(18.53, 22.27)	--	--	--

Conclusions: The exposure and clearance of DLX in subjects with mild, moderate, or severe hepatic impairment did not differ significantly from pooled, matched healthy subjects. No trend in DLX exposure was observed with increasing impairment. The exposure of DLX in subjects with hepatic impairment was similar to historic Phase 1 values. It is suggested that dose adjustment of DLX is not required for subjects with mild, moderate, or severe hepatic impairment.

INTRODUCTION

Delafloxacin is an investigational anionic fluoroquinolone antibiotic that is active against gram-positive and gram-negative bacteria, including methicillin-resistant strains of *Staphylococcus aureus* (MRSA). Delafloxacin is eliminated by both renal and hepatic pathways. This study was conducted to determine the effects of hepatic impairment on the pharmacokinetics (PK) of delafloxacin after single intravenous (IV) infusion.

METHODS

CLINICAL STUDY DESIGN

This was a Phase 1, multicenter, open-label, single-dose, PK study. The objectives were to evaluate the PK profile, safety, and tolerability of a single IV dose of delafloxacin in normal healthy subjects and in subjects with mild, moderate, or severe hepatic impairment. A total of 36 subjects were planned to be stratified into groups based on hepatic function: 3 impairment groups (mild, moderate, or severe, defined by Child-Pugh classes A, B, and C, respectively) with 6 subjects each, and a healthy subject group (D) with 18 subjects. Each healthy subject was matched with a subject with hepatic impairment with respect to age (±10 years), weight (±20%), and sex, and a reasonable attempt was also made to match the subjects in terms of smoking status and alcohol use.

The mild and moderate hepatic impairment groups were enrolled first. An interim analysis was performed after completion of the first 2 impairment groups and the matching healthy subjects, and enrollment of the severe impairment group was initiated after the interim analysis. In total, 39 subjects were enrolled (19 healthy subjects and 20 subjects with hepatic impairment). Of these subjects, 36 completed the study. Thirty-nine subjects were analyzed for safety, and 36 subjects were analyzed for PK.

DRUG ADMINISTRATION AND ANALYSES

A single, 1-hour IV infusion of delafloxacin 300 mg was administered. Blood samples were collected for the PK analysis of delafloxacin concentrations through 72 hours after dosing. Safety assessments included evaluations of adverse events (AEs), clinical laboratory results, vital sign measurements, 12-lead electrocardiogram measurements, and physical examination findings. Plasma samples for delafloxacin were processed by SLE extraction and quantitated using a validated LC-MS/MS method with a calibration range of 5-5000 ng/mL. Plasma concentration data were analyzed by noncompartmental methods. Pharmacokinetic parameters determined included C_{max}, AUC_{0-12}, AUC_{0-24}, AUC_{last1}, AUC_{inf}, CL, and Vss. Actual sample times were used in the calculations.

RESULTS

SUMMARY OF SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS (ALL SUBJECTS)

	A: Mild Impairment (n=7)	D: Mild Match (n=7)	B: Moderate Impairment (n=6)	D: Moderate Match (n=7)	C: Severe Impairment (n=6)	D: Severe Match (n=6)	D: Combined Match (n=20)	Overall (N=39)
Age (years), mean (SD)	54.4 (6.8)	51.7 (6.5)	56.8 (7.3)	56.4 (7.0)	54.3 (5.4)	53.7 (7.7)	54.0 (7.0)	54.5 (6.6)
Sex, n (%)								
Male	6 (85.7)	6 (85.7)	5 (83.3)	6 (85.7)	6 (100.0)	6 (100.0)	18 (90.0)	35 (89.7)
Female	1 (14.3)	1 (14.3)	1 (16.7)	1 (14.3)	0	0	2 (10.0)	4 (10.3)
Race, n (%)								
White	7 (100.0)	5 (71.4)	5 (83.3)	4 (57.1)	5 (83.3)	5 (83.3)	14 (70.0)	31 (79.5)
Black or African American	0	2 (28.6)	1 (16.7)	3 (42.9)	0	1 (16.7)	6 (30.0)	7 (17.9)
Multiracial	0	0	0	0	1 (16.7)	0	0	1 (2.6)
Ethnicity, n (%)								
Hispanic or Latino	4 (57.1)	5 (71.4)	4 (66.7)	3 (42.9)	4 (66.7)	4 (66.7)	12 (60.0)	24 (61.5)
Not Hispanic or Latino	3 (42.9)	2 (28.6)	2 (33.3)	4 (57.1)	2 (33.3)	2 (33.3)	8 (40.0)	15 (38.5)
Height (cm), mean (SD)	169.4 (9.5)	172.3 (8.6)	175.7 (12.1)	171.1 (8.0)	172.4 (6.7)	174.6 (7.1)	172.6 (7.7)	172.5 (8.5)
Weight (kg), mean (SD)	79.5 (7.1)	82.3 (11.6)	93.1 (17.5)	89.7 (7.1)	96.6 (25.8)	87.5 (13.7)	87.5 (13.7)	88.3 (16.1)
BMI (kg/m^2), mean (SD)	28.1 (5.2)	27.7 (3.5)	30.4 (6.0)	30.7 (3.0)	32.1 (6.5)	29.5 (4.7)	29.3 (3.7)	29.7 (4.8)
Child-Pugh class, mean (min, max)	5.7 (5, 6)	--	8.5 (8, 9)	--	10.8 (10, 12)	--	--	8.2 (5, 12)

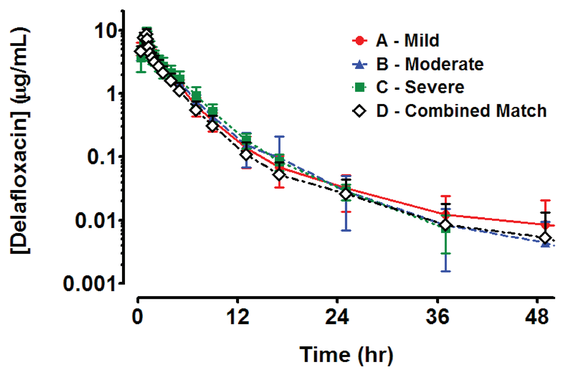
Abbreviations: SD, standard deviation; min, minimum; max, maximum; BMI, body mass index

Note: Percentages are based on the number of subjects in the safety population within each group and overall

PHARMACOKINETICS

During a single 1-hour infusion of delafloxacin 300 mg, mean plasma concentrations of delafloxacin rapidly increased. After the end of infusion, mean plasma concentrations of delafloxacin exponentially decreased. The overall shapes of the mean plasma concentration versus time profiles of delafloxacin were similar for each hepatic function group and pooled healthy subject group. Mean CL values were 13.07 L/h, 12.91 L/h, and 13.57 L/h for mild (Group A), moderate (Group B), and severe (Group C) hepatic impairment, respectively. Mean CL ranged between 13.22-17.85 L/h for the matched healthy subject groups. Vss ranged from 48.7-50.9 L in the hepatic impairment groups, and from 44.7-51.5 L in the matched healthy subject groups.

MEAN (SD) PLASMA CONCENTRATIONS FOR DELAFLOXACIN

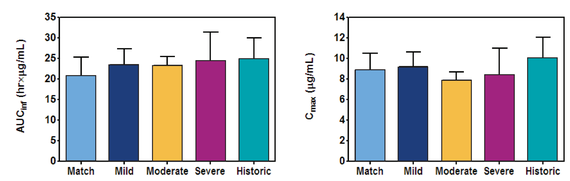


MEAN (CV) PLASMA PK PARAMETERS FOR DELAFLOXACIN

PK Parameter	A: Mild Impairment (n=6)	B: Moderate Impairment (n=6)	C: Severe Impairment (n=6)	D: Mild Match (n=6)	D: Moderate Match (n=6)	D: Severe Match (n=6)	D: Combined Match (n=18)
AUC_{0-12} (h*µg/mL), mean (CV%)	21.9 (13.8)	21.8 (6.1)	22.9 (29.1)	20.1 (14.3)	21.9 (20.4)	16.6 (15.5)	19.5 (20.1)
AUC_{0-24} (h*µg/mL), mean (CV%)	22.8 (15.0)	23.0 (8.4)	24.1 (28.6)	20.8 (15.5)	22.9 (20.1)	17.0 (15.0)	20.2 (20.7)
AUC_{last} (h*µg/mL), mean (CV%)	23.4 (16.3)	23.3 (9.2)	24.3 (28.8)	21.1 (16.3)	23.5 (19.9)	17.1 (15.2)	20.6 (21.3)
AUC_{inf} (h*µg/mL), mean (CV%)	23.5 (16.3)	23.4 (9.2)[a]	24.4 (28.7)	21.7 (17.3)	23.6 (19.9)	17.2 (15.2)	20.8 (21.9)[b]
C_{max} (µg/mL), mean (CV%)	9.22 (15.5)	7.92 (9.8)	8.42 (30.6)	9.26 (17.3)	9.01 (19.9)	8.33 (21.3)	8.86 (18.9)
CL (L/h), mean (CV%)	13.1 (17.9)	12.9 (9.1)[a]	13.6 (41.3)	14.1 (14.3)	13.2 (22.7)	17.9 (17.4)	15.1 (22.3)[b]
Vss (L), mean (CV%)	50.9 (20.2)	48.7 (20.2)[a]	49.7 (42.5)	44.7 (18.6)	51.5 (25.3)	47.9 (23.5)	48.3 (22.5)[b]

[a]n=5; [b]n=17

MEAN (SD) PLASMA AUC_{INF} AND C_{MAX} FOR DELAFLOXACIN



STATISTICAL ANALYSES

Compared with the pooled healthy subjects, AUC_{inf} for plasma delafloxacin was not significantly different for any hepatic impairment group, with mean ratios of approximately 115%, and 90% CIs of about 96% to 138%. Similarly, C_{max} was not significantly different for any hepatic impairment group compared with the pooled healthy subjects, with mean ratios of 90% to 105%, and 90% CI ranges that included 100% in every case.

Compared with matched healthy subjects, AUC_{inf} for plasma delafloxacin was not significantly different in subjects with mild (mean ratio 108%; 90% CI, 87% to 134%) or moderate hepatic impairment (mean ratio 101%; 90% CI, 82% to 123%). For subjects with severe hepatic impairment, AUC_{inf} was increased compared with matched healthy subjects (mean ratio 138%; 90% CI, 112% to 168%), but this appeared to be due to unusually low exposures in the severe match group subjects. C_{max} was not significantly different for any hepatic impairment group compared with the corresponding matched healthy subjects. An ordered trend analysis across pooled healthy subjects and the hepatic impairment groups was not significant, with P-values >.05 for both AUC_{inf} and C_{max}.

The results for the hepatic impairment groups were compared with historic means (SD, n) from pooled Phase 1 studies for AUC_{inf} (24.85 hr*µg/mL [5.21, 121]) and C_{max} (10.01 µg/mL [2.08, 193]). Analysis of variance (ANOVA) indicated no significant difference for the hepatic impairment groups versus the historic mean for AUC_{inf} (P>.05). Mean C_{max} for the mild and severe hepatic impairment groups was not different from the historic mean, whereas mean C_{max} for the moderate hepatic impairment group was slightly lower than the historic mean (P<.05).

STATISTICAL ANALYSIS OF PLASMA PK PARAMETERS OF DELAFLOXACIN FOLLOWING 300 MG IV INFUSIONS IN SUBJECTS WITH NORMAL AND IMPAIRED HEPATIC FUNCTION

Group	N	Geo LS Mean	90% CI of Geo LS Mean	Comparison	Ratio of Geo LS Means (%)	90% CI of the Ratio (%)
AUC_{inf} (hr*µg/mL)						
A: Mild impairment	6	23.25	(19.910, 27.140)	A/D	114.4	(95.6, 137.0)
B: Moderate impairment	6	23.32	(19.969, 27.220)	B/D	114.8	(95.9, 137.4)
C: Severe impairment	6	23.38	(20.022, 27.293)	C/D	115.1	(96.1, 137.8)
D: Combined match	17	20.31	(18.527, 22.270)			
C_{max} (µg/mL)						
A: Mild impairment	6	9.13	(7.931, 10.514)	A/D	104.8	(89.0, 123.3)
B: Moderate impairment	6	7.89	(6.849, 9.079)	B/D	90.5	(76.9, 106.5)
C: Severe impairment	6	8.05	(6.993, 9.270)	C/D	92.4	(78.5, 108.7)
D: Combined match	18	8.72	(8.036, 9.456)			

Group	N	Geo LS Mean	90% CI of Geo LS Mean	Comparison	Ratio of Geo LS Means (%)	90% CI of the Ratio (%)
AUC_{inf} (hr*µg/mL)						
A: Mild impairment	6	23.25	(20.135, 26.836)	A/D (mild)	108.2	(87.4, 133.8)
D: Mild match	5	21.50	(18.365, 25.157)			
B: Moderate impairment	6	23.32	(20.195, 26.916)	B/D (moderate)	100.7	(82.2, 123.4)
D: Moderate match	6	23.15	(20.253, 26.727)			
C: Severe impairment	6	23.38	(20.249, 26.987)	C/D (severe)	137.5	(112.2, 168.5)
D: Severe match	6	17.00	(14.726, 19.627)			
C_{max} (µg/mL)						
A: Mild impairment	6	9.13	(7.909, 10.542)	A/D (mild)	99.9	(81.5, 122.4)
D: Mild match	6	9.14	(7.916, 10.551)			
B: Moderate impairment	6	7.89	(6.830, 9.104)	B/D (moderate)	88.9	(72.6, 108.9)
D: Moderate match	6	8.87	(7.681, 10.238)			
C: Severe impairment	6	8.05	(6.974, 9.295)	C/D (severe)	98.5	(80.4, 120.7)
D: Severe match	6	8.17	(7.079, 9.435)			

SAFETY

Overall, 11 treatment-emergent adverse events (TEAEs) were reported and 10 of 39 subjects (25.6%) reported at least 1 TEAE after receiving the delafloxacin 300 mg IV dose. Treatment-emergent AEs were reported by 1 of 7 subjects (14.3%) in the mild hepatic impairment group; no subjects in the moderate hepatic impairment group; 2 of 6 subjects (33.3%) in the severe hepatic impairment group; and 7 of 20 subjects (35.0%) overall in the healthy subjects group. Within the healthy subjects group, 3 of 7 subjects (42.9%) in the mild hepatic impairment match group; 3 of 7 subjects (42.9%) in the moderate hepatic impairment match group; and 1 of 6 subjects (16.7%) in the severe hepatic impairment match group reported as least 1 TEAE.

In subjects who reported TEAEs, the majority had TEAEs that were considered unrelated to study drug by the investigator (5 of 39 subjects; [12.8%]). Fewer subjects reported TEAEs that were considered probably related to study drug (3 of 39 subjects [7.7%]) or possibly related to study drug (2 of 39 subjects [5.1%]). No TEAE was considered definitely related to study drug. With the exception of 2 moderate TEAEs, all TEAEs were of mild severity. Moderate TEAEs reported included headache and drug hypersensitivity. Three subjects (7.7%) discontinued due to TEAEs. One subject in the mild hepatic impairment group was discontinued due to a mild, probably related TEAE of drug hypersensitivity; 1 healthy subject in the mild hepatic impairment match group was discontinued due to a mild, possibly related TEAE of presyncope; and 1 healthy subject in the moderate hepatic impairment match group was discontinued due to a moderate, probably related TEAE of drug hypersensitivity. All TEAEs resolved by the end of the study.

CONCLUSIONS

- Delafloxacin IV infusion pharmacokinetic and plasma time/concentration profiles were not significantly affected in subjects with mild, moderate, or severe hepatic impairment
- No significant trend across the ordered normal hepatic impairment categories was observed for delafloxacin AUC_{inf} and C_{max}
- AUC_{inf} and C_{max} in the hepatic impairment subjects were generally similar to historical means for 300 mg IV delafloxacin in Phase 1 studies
- TEAEs were generally mild and all TEAEs resolved by the end of the study
- Delafloxacin IV dose adjustment does not appear to be indicated for subjects with hepatic impairment