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A PHASE 1, OPEN-LABEL STUDY OF THE EFFECT OF DELAFLOXACIN (DLX) ON THE PHARMACOKINETICS (PK) OF A SINGLE ORAL DOSE OF MIDAZOLAM (MID)

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ABSTRACT

Background: DLX is an anionic fluoroquinolone with activity against methicillin-resistant *Staphylococcus aureus* and susceptible gram-negative bacteria currently in Phase 3 development. This Phase 1 study was performed to determine the impact of DLX treatment on the sensitive CYP substrate, MID.

Methods: Twenty-two male and female subjects were enrolled in this single sequence, single group study. A single 5 mg oral dose of MID was given to fasted subjects on Days 1 and 8. Subjects received oral DLX (450 mg) twice daily on Days 3 - 8. Plasma samples were analyzed for DLX, MID, and 1-hydroxymidazolam (1-OH-MID) concentrations with validated LC-MS/MS methods. Analysis of variance was performed on the ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} of MID and 1-OH-MID to estimate the ratio of geometric least squares (LS) means between treatments and their 90% confidence interval (CI).

Results: Co-administration of DLX with MID did not alter the PK of MID as the 90% CI of geometric mean ratios of C_{max} (ng/mL) and AUC (h•ng/mL) values were within 80 to 125% acceptance criteria. The 1-OH-MID AUC values were also not affected by co-administration, whereas 1-OH-MID C_{max} values were slightly increased. The statistical analyses of plasma non-compartmental PK parameters of MID and 1-OH-MID (MID/1-OH + DLX vs. MID alone) are presented:

Parameter	Substrate	Ratio (%) of Geometric LS Means	90% CI of the Ratio (%)
$AUC_{0\text{-}t}$	MID	89.4	(83.2, 96.1)
$AUC_{0\text{-}\infty}$		89.4	(83.2, 96.0)
C_{max}		93.6	(83.7, 104.6)
$AUC_{0\text{-}t}$	1-OH-MID	106.6	(98.8, 114.9)
$AUC_{0\text{-}\infty}$		105.7	(97.7, 114.3)
C_{max}		116.1	(101.7, 132.4)

DLX reached steady state by Day 7 after 4 days of dosing. A similar C_{max} was observed on Days 3 and 7, and terminal elimination half-life was 2.5 and 2.9 hours, respectively. Five subjects (22.7%) reported at least 1 mild treatment-emergent adverse event (TEAE), and no deaths, serious AEs or TEAEs leading to study discontinuation were reported. All TEAEs resolved by study end.

Conclusion: DLX did not affect the C_{max} and $AUC_{0\text{-}\infty}$ of MID/1-OH-MID, and minimal effect was indicated for 1-OH-MID C_{max}. DLX was shown to have no clinically significant interaction with CYP3A substrate MID in a Phase 1 study.

INTRODUCTION

Delafloxacin is an investigational anionic fluoroquinolone antibiotic with a broad spectrum of activity. Delafloxacin is active against an array of bacteria, including gram-positive organisms, gram-negative organisms, atypical organisms, and anaerobes (1). Delafloxacin is being developed as a sterile 300-mg lyophilized formulation for intravenous (IV) administration as well as an oral 450-mg tablet formulation.

The FDA Draft Guidance on Drug Interaction Studies (2, DHHS 2012) recommends PK interactions be defined during drug development. Human radiolabeled ADME studies indicated that oxidative metabolism is not an important pathway for elimination of delafloxacin. *In vitro* studies conducted with human liver microsomes have shown that delafloxacin was not an inhibitor of common CYP enzymes. Although not an inducer of CYP1A2 or CYP2B6, delafloxacin was a mild inducer of CYP3A in cultures of human hepatocytes. As delafloxacin may be co-administered with drugs that are substrates of CYP3A4, this study evaluated the effect of repeated doses of oral delafloxacin on the PK profile of a single oral dose of midazolam.

METHODS

- This study was a single sequence, single group study of 22 male and female subjects. Each subject received a single oral 5-mg dose of midazolam on Day 1, oral delafloxacin (450 mg) twice-daily (every 12 hours [q12h]) doses on Days 3 to 8, and co-administered a single 5-mg oral dose of midazolam in the morning on Day 8.
- The study consisted of a screening period (Days –28 to –2), check-in (Day –1), 1 treatment period (Days 1 to 8), and end-of-study/early termination assessments (Day 9).
- Subjects were screened to determine eligibility within 28 days before dosing. Subjects were admitted to the clinical unit on Day –1 for baseline assessments. On Day 1, subjects received midazolam after overnight fast of at least 10 hours. Subjects fasted for 4 hours after study drug administration on Day 1. During fasting, no fluids were allowed except water; however, water was not allowed from 1 hour before dosing to 1 hour after dosing (except for 240 mL of tap water required to be taken to swallow delafloxacin or midazolam). Subjects then received 450-mg delafloxacin q12h on Days 3 through 8. Delafloxacin morning doses on Days 3 through 7 were administered after overnight fast, and subjects continued fasting for at least 2 hours after the morning dose. Midazolam was co-administered in the morning on Day 8 after overnight fast of at least 10 hours, and subjects continued fasting for 4 hours after study drug administration. Subjects could not lie down for 4 hours after the morning dose on Days 1, 3, 7 and 8.
- Serial blood samples for PK analysis were drawn from all subjects before dosing and for up to 24 hours after dosing on Days 1, 3, 7, and 8. Blood samples were also collected just before the morning dose of delafloxacin on Days 4, 5, and 6.
- Plasma samples were processed by SLE extraction and quantitated using a validated LC-MS/MS method with a calibration range of 5 to 5000 ng/mL. Plasma concentration data was analyzed by non-compartmental methods. Pharmacokinetic parameters determined for midazolam and 1-OH midazolam included C_{max}, $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, AUC_{last}, AUC_{inf}, CL and Vz. Actual sample times were used.
- Subjects were confined to the clinic until Day 9 and safety and tolerability were assessed by monitoring and recording of AEs; clinical laboratory results including hematology, coagulation, serum chemistry, and urinalysis; vital sign (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) and pulse oximetry measurements; 12-lead ECG results; and physical examination findings.

SUMMARY OF SUBJECT DISPOSITION

Analysis Population	Overall (N=22)
Total Number of Subjects, n (%)	22 (100%)
Safety Population[a]	22 (100%)
Midazolam Pharmacokinetic (PK) Population[b]	22 (100%)
Delafloxacin Pharmacokinetic (PK) Population[b]	22 (100%)
Subjects Completed	22 (100%)
Subjects Discontinued	0 (0%)

Note: Percentages were based on the number of all subjects overall.
[a]Safety population included all subjects who received at least 1 dose of study drug.
[b]The midazolam or delafloxacin PK population included subjects with at least 1 dose of midazolam with sufficient concentration data to support accurate estimation of at least 1 primary PK parameter.

RESULTS

SUMMARY OF SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Overall (N=22)
Age (years)	
Mean (SD)	37.1 (10.4)
Minimum, Maximum	18, 50
Sex, n (%)	
Female	8 (36.4)
Male	14 (63.6)
Race, n (%)	
Black or African American	10 (45.5)
White	12 (54.5)
Ethnicity, n (%)	
Hispanic or Latino	11 (50.0)
Not Hispanic or Latino	11 (50.0)
Height (cm)	
Mean (SD)	170.2 (12.0)
Minimum, maximum	148.8, 192.8
Body mass index (kg/m^2)	
Mean (SD)	25.6 (2.8)
Minimum, maximum	19.9, 30.7

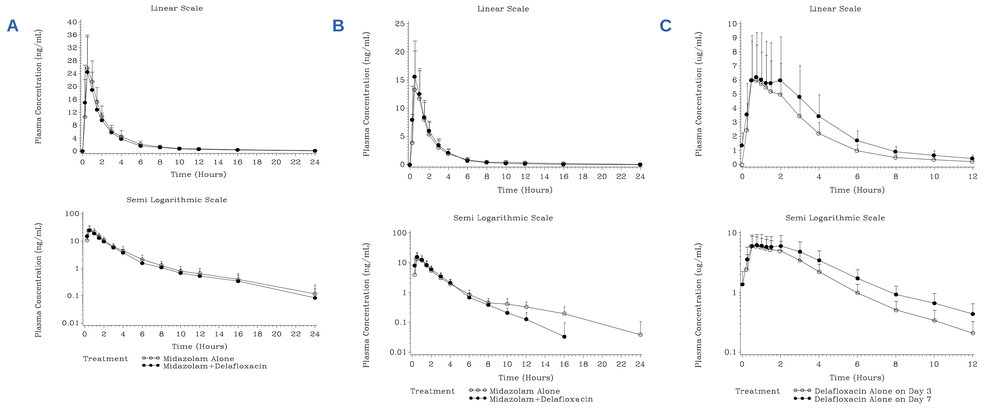
Note: Percentages were based on the number of all subjects overall.

MEAN (CV) PLASMA PHARMACOKINETIC PARAMETERS OF MIDAZOLAM, 1-OH MIDAZOLAM, AND DELAFLOXACIN BY TREATMENT (MIDAZOLAM OR DELAFLOXACIN PK POPULATION)

Parameter (unit)	Midazolam PK Parameters		1-OH Midazolam PK Parameters		Parameter (unit)	Delafloxacin PK Parameters		
	Midazolam Alone (N=22)	Midazolam + Delafloxacin (N=22)	Midazolam Alone (N=22)	Midazolam + Delafloxacin (N=22)		Day 3 Single Dose (N=22)		Day 7 Steady State[d] (N=22)
$AUC_{0\text{-}t}$ (h•ng/mL)	64.44 (31.2)	57.56 (29.4)	31.07 (36.9)	32.29 (28.2)	$AUC_{0\text{-}t}$ (h•µg/mL)	22.70 (27.4)	$AUC_{0\text{-}12,ss}$ (h•µg/mL)	30.75 (37.1)
$AUC_{0\text{-}24}$ (h•ng/mL)	64.72 (31.0)	57.87 (28.9)	31.57 (36.2)	32.60 (28.2)	$AUC_{0\text{-}12}$ (h•µg/mL)	22.70 (27.4)	$AUC_{0\text{-}12,ss}$ (h•µg/mL)	30.75 (37.1)
$AUC_{0\text{-}inf}$ (h•ng/mL)	65.85 (31.7)	58.76 (29.3)	31.58 (37.9)[b]	32.84 (28.1)	$AUC_{0\text{-}inf}$ (h•µg/mL)	23.49 (26.1)	$C_{max,\ ss}$ (µg/mL)	7.45 (42.4)
C_{max} (ng/mL)	27.51 (35.7)	25.76 (37.9)	15.13 (42.3)	16.69 (32.8)	C_{max} (µg/mL)	7.17 (28.1)	$C_{trough,ss}$ (µg/mL	1.36 (63.5)
T_{max} (h)[a]	0.50 (0.25, 1.00)	0.50 (0.25, 1.50)	0.50 (0.50, 1.00)	0.50 (0.50, 1.50)	T_{max} (h)[a]	0.75 (0.50, 4.00)	$T_{max,\ ss}$ (h)[a]	1.00 (0.50, 6.00)
$t_{1/2}$ (h)	4.67 (28.5)	4.63 (26.3)	4.95 (34.1)[b]	2.68 (33.2)	$t_{1/2}$ (h)	2.46 (20.9)	$t_{1/2}$ (h)	2.92 (25.5)[c]
CL/F (L/h)	82.66 (30.6)	92.58 (31.7)	-	-	CL/F (L/h)	20.61 (29.4)	CL_{ss}/F (L/h)	16.81 (38.9)
V_z/F (L)	535.4 (31.0)	597.6 (29.7)	-	-	V_z/F (L)	74.4 (41.0)	V_z/F (L)	70.8 (47.9)[c]

Abbreviations: CV, coefficient of variation; PK, Pharmacokinetic; h, hours. Note: Values below the limit of quantification were set to zero for summary statistics.
[a] For T_{max} and $T_{max,ss}$, the median (minimum, maximum) values are presented. [b] n = 20. [c] n = 21. [d] PK Parameters are at steady state.

MEAN (+SD) PLASMA CONCENTRATIONS OF MIDAZOLAM (A), 1-OH MIDAZOLAM (B) OR ORAL DELAFLOXACIN (C) VERSUS TIME ON LINEAR AND SEMILOGARITHMIC SCALES (MIDAZOLAM OR DELAFLOXACIN PHARMACOKINETIC POPULATION)



CONCLUSION

- **Pharmacokinetics**
  - Delafloxacin did not affect the C_{max} and $AUC_{0\text{-}inf}$ of midazolam. Delafloxacin did not affect the $AUC_{0\text{-}inf}$ of 1-OH midazolam. There was a minimal effect indicated for the C_{max} of 1-OH midazolam.
  - Steady state for almost all subjects appeared to have been reached by the Day 7 dosing of delafloxacin.
  - Delafloxacin does not appear to have a clinically significant effect on CYP3A, and these results suggest that Delafloxacin may be co-administered with CYP3A substrates without concern for any drug-drug interactions.
- **Safety**
  - Delafloxacin, administered as repeated oral 450-mg doses and co-administered with midazolam, was generally well tolerated by the healthy subjects in this study.
  - A total of 5 subjects (22.7%) reported at least 1 TEAE; 1 subject (4.5%) after receiving midazolam alone, 4 subjects (18.2%) after receiving delafloxacin alone, and no subjects after receiving midazolam co-administered with delafloxacin. All TEAEs were mild in severity.
  - The most frequently reported TEAE overall was diarrhea (3 subjects, 13.6%), reported after administration of delafloxacin alone, were mild, and did not lead to treatment discontinuation.
  - There were no deaths, SAEs, or TEAEs leading to study discontinuation.
  - One subject, Subject 108, was discontinued from study treatment on Day 8 due to a mild, possibly related TEAE of increased blood creatinine noted after administration of delafloxacin on Day 7; the subject completed the study. All TEAEs resolved by the end of the study.
  - With the exception of increased blood creatinine in 1 subject, there were no clinically significant findings noted or TEAEs reported resulting from clinical laboratory assessments, vital sign measurements, physical examination findings, or ECG results.

REFERENCES

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