In Vivo Pharmacodynamics of ZTI-01 (Fosfomycin for Injection) in the Neutropenic Murine Thigh Infection Model Against ESBL-positive *E. coli* (EC), carbapenem-resistant (CR) *K. pneumoniae* (KPN), and *P. aeruginosa* (PSA)

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Background: ZTI-01 (fosfomycin for injection) is a broad-spectrum antibiotic with potent activity against MDR gram-negative rods (GNR), for which antimicrobial therapies are limited. ZTI-01 is currently under US development for the treatment of cUTI. We examined the PK/PD characteristics of ZTI-01 against a diverse group of GNRs, including those with ESBL- and CR- phenotype, using the neutropenic murine thigh infection model.

Methods: 5 EC (4 ESBL), 3 KPN (2 CR), and 2 PSA were used. MICs were determined by agar dilution. Single dose plasma PK was determined in mice after SC doses of 3.125, 12.5, 50, 200, 400 and 800 mg/kg. PK/PD index determination was performed using a dose fractionation (DF) study design. Efficacy was then examined against all 10 isolates (dose range 12.5 – 6400 mg/kg/24h). Organism burden after 24h was enumerated from each thigh infection. The dose-response data was analyzed using the Emax Hill equation. AUC/MIC and T>MIC targets associated with net stasis and 1 log kill were determined. A dose-ranging survival study using a single isolate was used to validate PD targets identified.

Results: MICs ranged from 1-16 mg/L. Single dose PK parameter ranges include: Cmax 0.6-42 mg/L, $AUC_{0-\infty}$ 1.4-87 mg*h/L, $T_{1/2}$ 0.51-1.1 h. PK/PD regression analysis from the DF study revealed: AUC/MIC R^2 0.70, Cmax/MIC R^2 0.51, T>MIC R^2 0.44. Dose-dependent cidal activity was demonstrated against every isolate. Maximal cidal activity was 2-3 log kill and commonly noted in isolates with lower fosfomycin MICs. The median static doses and associated AUC/MIC and T>MIC targets are shown in the table, as well as non-linear regression analysis of the PD indices. Median 1 log kill targets for *Enterobacteriaceae* group were AUC/MIC of 41.6 and T>MIC 75%. AUC/MIC exposures of 9-43 and T>MIC of 18-58% resulted in 100% survival.

	Static Dose (mg/kg/24 h)	Stasis AUC/MIC	Stasis T>MIC (%)	AUC/MIC Regression (R^2)	T>MIC Regression (R^2)
EC	256	19.3	37.7	0.72	0.55
KPN	1122	11.1	26.5	0.76	0.64
PSA	1920	14.6	29.0	0.92	0.87

Conclusions: ZTI-01 demonstrated in vitro and in vivo potency against EC, KPN and PSA including those with ESBL- and CR-phenotypes. PD index AUC/MIC was most closely linked with efficacy. PD target AUC/MIC and T>MIC targets were similar between organism groups. Maximal survival was noted at exposures similar to stasis endpoints. This data should prove useful for dosing regimen design and optimization for clinical studies including current development for cUTI.