

Pharmacokinetics-Pharmacodynamics (PK-PD) Target Attainment Analyses to Support ZTI-01 (Fosfomycin for Injection) Dose Selection for Patients with Complicated Urinary Tract Infections (cUTI)

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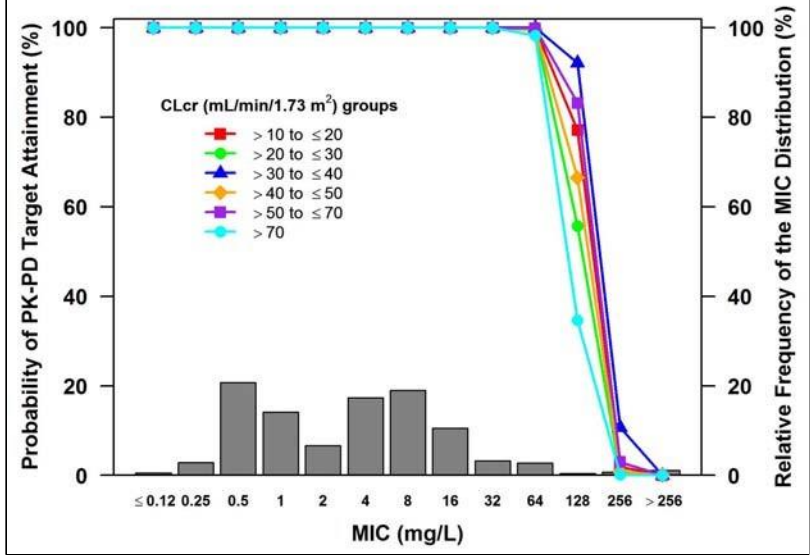
Background: ZTI-01, fosfomycin for injection, has *in vitro* activity against Gram -positive and -negative organisms, including carbapenem-resistant Enterobacteriaceae. ZTI-01 is currently in Phase 2/3 development for the treatment of patients with cUTI. PK-PD target attainment analyses were undertaken to provide support for the ZTI-01 dosing regimen to treat patients with cUTI.

Methods: Using parameter estimates from a population PK model (3-compartment model with zero-order input and 1st-order elimination), total-drug plasma concentration-time profiles were generated for 6000 simulated patients with varying creatinine clearance (CL_{cr}, mL/min/1.73m²). Simulated patients received ZTI-01 according to CL_{cr}: 6 g IV q8h for > 50 mL/min/1.73 m², 4 g IV q8h for >40 to 50 mL/min/1.73 m², 6 g IV loading followed 3 g IV q8h for >30 to 40 mL/min/1.73 m², and 6 g IV load followed by 5 g IV q24h for >10 to 30 mL/min/1.73 m². Day 1 AUC₀₋₂₄ was calculated. Percent probabilities of PK-PD target attainment by MIC and overall (i.e., weighted over the MIC distribution for 1091 Enterobacteriaceae isolates from the USA) were determined using median total-drug plasma AUC:MIC ratio targets associated with net bacterial stasis and a 1- log₁₀ CFU reduction from baseline at 24 h from a neutropenic murine- thigh infection model for Enterobacteriaceae (19.1 and 41.6, respectively).

Results: Percent probabilities of attaining PK-PD targets associated with net bacterial stasis (Figure 1) and a 1 log₁₀ CFU reduction were ≥98.3% at a MIC=64 mg/L and ≥97.3% at a MIC=32 mg/L, respectively, across renal function groups. These MIC values were 1 to 2 dilutions higher than the MIC₉₀ of 16 mg/L for Enterobacteriaceae. Overall percent probabilities of PK-PD target attainment for each target were 97.8 and 95.5%, respectively.

Conclusions: Together with clinical outcome data, these data will provide support for ZTI-01 dosing recommendations and fosfomycin susceptibility breakpoints for Enterobacteriaceae.

Figure 1. Percent probabilities of PK-PD target attainment by MIC based on the AUC:MIC ratio target associated with net bacterial stasis among simulated patients by renal function group after administration of ZTI-01 6 g q8h-based dosing regimens, overlaid on the fosfomycin MIC distribution for Enterobacteriaceae



Keywords: fosfomycin, pharmacokinetics/pharmacodynamics, ZTI-01

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