Population Pharmacokinetic (PK) Analysis of ZTI-01 (Fosfomycin for Injection) Using Phase 1 Data for ZTI-01 and Evaluation of a Phase 2/3 Sparse PK Sampling Strategy

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Background: ZTI-01, fosfomycin for injection, has *in vitro* activity against Gram-positive and -negative organisms, including carbapenem-resistant Enterobacteriaceae. This activity, with a primarily renal route of elimination, makes ZTI-01 a potentially favorable treatment for patients with complicated urinary tract infections (cUTI). Phase 1 data were used to develop a population PK (PPK) model to describe the time-course of fosfomycin and to evaluate potential Phase 2/3 sparse PK sampling strategies.

Methods: The PPK model was developed in NONMEN 7.1.2 using Phase 1 plasma and urine PK data from 28 healthy subjects who received ZTI-01 as single (1 and 8 g infused over 1 hour) IV doses in a crossover fashion. PPK parameters were allometrically scaled to body weight *a priori*. Published data describing the relationship between fosfomycin PK and creatinine clearance (CLcr) [Fillastre JP *et al*. Pathologie Biologie 1988; 36: 728-30] were considered. An optimal sampling scheme (OSS) was derived based on the final PPK model and optimal sampling theory (OST) in ADAPT 5. The OSS was evaluated using Monte Carlo simulation. Plasma concentration-time data based on the OSS were generated for simulated patients who received ZTI-01 dosing regimens assigned by CLcr group. Maximum a-posteriori Bayesian estimation based on the OSS was performed in NONMEM to estimate individual PK parameters. Bias, the prediction error percent (PE%) for the Bayesian PK estimates relative to the true values for clearance and steady-state volume of distribution, and precision, the root mean squared error (RMSE) of the true and estimated PK parameters, were calculated.

Results: A 3-compartment model with zero-order input and first-order elimination best described fosfomycin plasma and urine PK. A sigmoidal equation best described the relationship between renal clearance and CLcr. The PPK model provided an excellent fit to the plasma data (r^2=0.99) while showing acceptable precision when fitting to the urine data (r^2=0.87). Based on the PPK model and OST, the optimal times to obtain PK samples identified were 1, 2, 4, and 8 hours after the start of the infusion. All PK parameters were estimated with minimal bias and relatively high precision as evidenced by median PE% values < 15% and RMSE estimates < 10 across all CLcr groups, respectively.

Conclusions: A PPK model describing fosfomycin PK after administration of ZTI-01 was successfully developed. This model was used to identify an OSS for an ongoing Phase 2/3 study evaluating ZTI-01 for the treatment of hospitalized patients with cUTI.

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