Population Pharmacokinetic (PPK) Analysis of ZTI-01 (Fosfomycin for Injection) Using Data from Healthy Subjects and Patients with Complicated Urinary Tract Infections (cUTI)

Michael Trang, Pharm.D.[1], Evelyn J. Ellis-Grosse, Ph.D.[2], Paul B. Eckburg, M.D.[2], David Skarinsky, B.S.[2], Sujata M. Bhavnani, Pharm.D., M.S.[1] and Christopher M. Rubino, Pharm.D.[1], (1)ICPD, Schenectady, NY, (2)Zavante Therapeutics, Inc., San Diego, CA

Background: ZTI-01 (fosfomycin [FOS] for injection) has *in vitro* activity against Gram-positive and -negative organisms, including carbapenem-resistant Enterobacteriaceae. This activity, coupled with a primarily renal route of elimination, makes ZTI-01 a potentially favorable treatment for patients with cUTI. A PPK model, originally developed using Phase 1 data and an empirical relationship between FOS clearance (CLt) and creatinine clearance (CLcr) [Microbe 2017 Abstr. P1134], was refined using pooled data from healthy subjects and patients with cUTI, including acute pyelonephritis.

Methods: The PPK model was developed in NONMEN 7.2. In the Phase 1 study, 28 healthy subjects who received ZTI-01 as single (1 and 8 g infused over 1 hour) IV doses in crossover fashion provided plasma and urine samples for FOS concentration determination over 24 hours. Patients from the Phase 2/3 study (ZEUS, NCT02753946.) received ZTI-01 at 6 g every 8 hours, with dosage adjustment for patients with renal impairment. Blood samples for PK (n = 4 per patient) were collected on Day 1 and on either Days 3, 4, or 5. Model development involved refinement of the previous CLt:CLcr relationship using the pooled data and a full covariate analysis to identify other patient descriptors associated with the interindividual variability (IIV) in FOS PK. Model qualification included standard goodness-of-fit metrics and visual predictive check plots.

Results: A 3-compartment model with zero-order input and linear elimination best described FOS plasma and urine PK. A sigmoidal equation best described the relationship between renal clearance (~83% of CLt when CLcr ~ 100) and CLcr. The PPK model provided an excellent fit to the plasma data while showing acceptable precision when fit to the urine data. The visual predictive check revealed that the model adequately described the central tendency and IIV in FOS PK concentration-time profiles.

Conclusion: A PPK model was successfully developed to describe FOS PK in healthy subjects and infected patients. This model will facilitate additional analyses, including generation of individual PK exposures for pharmacokinetic-pharmacodynamic analyses (PK-PD) for safety and efficacy and Monte Carlo simulations to evaluate PK-PD target attainment.