Pharmacokinetics, Safety, and Tolerability of Single Dose Intravenous and Oral Fosfomycin in Healthy Volunteers

E. Wenzler[1], E. Ellis-Grosse[2], K. Rodvold[1]

[1]Univ. of Illinois at Chicago, Chicago, IL

[2]Zavante Therapeutics, San Diego, CA

Background: The purpose of this study was to determine the safety, tolerability, and PK of a single dose of intravenous (IV) fosfomycin (FOS) disodium and oral (PO) fosfomycin tromethamine in healthy subjects.

Methods: Phase I, open-label study evaluating IV (ZTI-01) and PO (Monurol®) FOS in healthy adult subjects. Subjects received a single dose of 1 g IV, 8 g IV, and 3 g PO FOS in a randomized, crossover fashion with a washout period in between. Blood and urine samples were collected serially before and through 48 hours post-dose and analyzed via LC/MS-MS. Noncompartmental analyses were performed via WinNonlin. Safety was monitored throughout the course of the study.

Results: Subject demographics: 39% male, 75% white, mean (±SD) age 26±5 years, mean (±SD) weight 69.9±11.2 kg, mean (±SD) CrCl 139.3±23.9 mL/min. Mean (±SD) plasma PK parameters after IV and PO administration are shown in Table 1. The % relative bioavailability of PO FOS in relation to the 1 g IV dose was 52.8%. The fraction of the dose excreted in urine after 48 hours for 1 g, 8 g IV, and 3 g PO were: 74%, 80%, and 37%, respectively. 80% of subjects reported a treatment-emergent adverse event (TEAE), the majority (67.9%) of which occurred after the 8 g IV dose. All TEAE were mild-moderate and resolved without sequelae. The most common TEAE after 8 g IV was bradycardia (28.6%), and hypocalcemia (17.9%) after 1 g IV. Headache was the most common (10.7%) FOS-related TEAE. Events were comparable between groups and no new safety concerns were identified.

Conclusions: The plasma PK of ZTI-01 were approximately linear and proportional between the 1 g and 8 g IV doses. The administration of 3 g of PO FOS resulted in a 1.5-fold higher plasma exposure in terms of $AUC_{0-\infty}$ compared to the 1 g IV dose, but a 5.5-fold lower AUC_{0-inf} than the 8 g dose. The plasma elimination $t_{1/2}$ of PO FOS was longer than that after IV administration, potentially due to “flip-flop kinetics”; i.e. slow absorption into the central compartment. The PK exposure and comparable safety profile of ZTI-01 support further investigation in the target patient population, and is currently under U.S. development to treat complicated UTIs at a dosage of 6 g q8h.

	FOS regimen		
PK parameters	**1 g IV (*n*=28)**	**8 g IV (*n*=28)**	**3 g PO (*n*=27)**
C_{max} (mg/L)	44.3±7.6	370±61.9	26.8±6.4
T_{max} (h)	1.1±0.05	1.08±0.01	2.25±0.4
V_d or V_d/F^* (L)	29.7±5.7	31.5±10.4	204±70.7*
CL_T or CL_T/F^* (L/h)	8.7±1.7	7.8±1.4	17.0±4.7*
CL_R (L/h)	6.6±1.9	6.3±1.6	6.5±1.8
$AUC_{0-\infty}$ (mg·h/L)	120±28.5	1060±192	191±57.6
$t_{1/2}$ (h)	2.4±0.4	2.8±0.6	9.04±4.5