

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

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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 (\pm SD) age 26 \pm 5 years, mean (\pm SD) weight 69.9 \pm 11.2 kg, mean (\pm SD) CrCl 139.3 \pm 23.9 mL/min. Mean (\pm 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-∞} 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 \pm 7.6	370 \pm 61.9	26.8 \pm 6.4
T _{max} (h)	1.1 \pm 0.05	1.08 \pm 0.01	2.25 \pm 0.4
V _d or V _d /F* (L)	29.7 \pm 5.7	31.5 \pm 10.4	204 \pm 70.7*
CL _T or CL _T /F* (L/h)	8.7 \pm 1.7	7.8 \pm 1.4	17.0 \pm 4.7*
CL _R (L/h)	6.6 \pm 1.9	6.3 \pm 1.6	6.5 \pm 1.8
AUC _{0-∞} (mg·h/L)	120 \pm 28.5	1060 \pm 192	191 \pm 57.6
$t_{1/2}$ (h)	2.4 \pm 0.4	2.8 \pm 0.6	9.04 \pm 4.5