Safety Results from the ZEUS Study: Multi-center, Randomized, Double-Blind Phase 2/3 Study in Hospitalized Adults with Complicated Urinary Tract Infections (cUTI) Including Acute Pyelonephritis (AP) who Received Intravenous Fosfomycin (ZTI-01)

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Background: Intravenous (IV) fosfomycin has been extensively used over four decades outside the US. ZTI-01 (fosfomycin for injection) is an injectable epoxide antibiotic with a unique mechanism of action and broad in vitro spectrum of activity, including multidrug-resistant pathogens. ZTI-01 is being developed for the treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP) in the US.

Methods: ZEUS was a multicenter, randomized, double-blind Phase 2/3 trial that evaluated safety and efficacy of ZTI-01 in treating hospitalized adults with cUTI or AP vs piperacillin/tazobactam (P-T). Patients enrolled (N=465) were randomized to receive 6 g ZTI-01 as 1-hour IV infusion q8h (18 g total daily dose) or 4.5 g IV P-T as 1-hour IV infusion q8h (13.5 g total daily dose) for a fixed 7 days (up to 14 days if concurrent bacteremia); oral step-down therapy was prohibited. Safety parameters were analyzed, including adverse events (AEs), vital signs, laboratory assessments and electrocardiograms.

Results: Most treatment emergent AEs (TEAEs) were mild, transient and did not lead to discontinuation of study drug. Serious adverse events (SAEs) and severe AEs were uncommon; no deaths were reported during the study (Table 1). The most common TEAEs were gastrointestinal (GI) in nature.

Table 1. Adverse Events

n (%)	**ZTI-01 (n=233)**	**P-T (n=231)**
Any AEs	99 (42.5)	74 (32.0)
Any TEAEs	98 (42.1)	74 (32.0)
Mild	84 (36.1)	49 (21.2)
Moderate	35 (15.0)	38 (16.5)
Severe	5 (2.1)	4 (1.7)
Drug-related TEAEs	48 (20.6)	32 (13.9)
SAEs	5 (2.1)	6 (2.6)
Drug-related SAE	1 (0.4)	1 (0.4)
TEAEs leading to study drug discontinuation	7 (3.0)	6 (2.6)
Serious TEAEs leading to study drug discontinuation	0	1 (0.4%)
TEAEs ≥5%		
GI Disorders	25 (10.7)	17 (17.4)
Investigations (Lab Abnormalities)	20 (8.6)	8 (3.5)
Infections/Infestations	17 (7.3)	20 (8.7)
Metabolism/Nutrition Disorders	17 (7.3)	4 (1.7)
General Disorders/Administration Site	14 (6.0)	14 (6.1)

Conclusion: ZTI-01 was well tolerated in patients with cUTI and AP. ZTI-01, if approved in the US, would provide a new therapeutic option with a unique MOA for patients with serious Gram-negative infections.