Per Pathogen Outcomes from the ZEUS study, a Multi-center, Randomized, Double-Blind Phase 2/3 Study of ZTI-01 (fosfomycin for injection) versus Piperacillin-Tazobactam (P-T) in the Treatment of Patients with Complicated Urinary Tract Infections (cUTI) including Acute Pyelonephritis (AP)

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Background: ZTI-01 (fosfomycin for injection) is a novel injectable epoxide antibiotic with a unique mechanism of action by inhibiting MurA at an early step in cell wall synthesis. ZTI-01 as a broad spectrum of activity, including multidrug-resistant pathogens, and 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 designed to evaluate the safety and efficacy of ZTI-01 in treatment of hospitalized adults with cUTI or AP versus piperacillin/tazobactam (P-T). The primary endpoint of overall success was defined as clinical cure plus microbiologic eradication in the microbiologic modified intent-to-treat (m-MITT) population at test-of-cure (TOC) visit (Day 19). Patients were randomized to receive 6 g ZTI-01 as 1-hour IV infusion q8h or 4.5 g IV P-T as 1-hour IV infusion q8h for 7 days (up to 14 days if concurrent bacteremia). Clinical cure was defined as complete resolution or significant improvement of signs/symptoms of cUTI or AP present at baseline and no new symptoms, and microbiologic eradication as baseline bacterial pathogen(s) reduced to $<10^4$CFU/mL on urine culture and negative on repeat blood culture.

Results: Of the patients enrolled (N=465), 77.8% had >1 baseline pathogen (m-MITT); the most common baseline pathogens were *E. coli* (266) and *K. pneumoniae*(52). Clinical cure and microbial eradication are presented by pathogen with a frequency of >10 patients with pathogen at baseline (Table 1).

Table 1. Clinical Cure/Microbial Eradication by Pathogen (TOC, m-MITT)

Baseline Pathogen	**Clinical Cure n/N1 (%)**		**Micro Eradication n/N1 (%)**	
	ZTI-01 (N=184)	**P-T (N=178)**	**ZTI-01 (N=184)**	**P-T (N=178)**
E. coli	120/133 (90.2)	120/133 (90.2)	91/133 (68.4)	79/133 (59.4)
K. pneumoniae	25/27 (92.6)	25/25 (100)	18/27 (66.7)	12/25 (48.0)
P. mirabilis	8/9 (88.9)	3/5 (60.0)	7/9 (77.8)	1/5 (20.0)
E. cloacae spp	8/9 (88.9)	3/3 (100)	5/9 (55.6)	3/3 (100)
P. aeruginosa	8/8 (100)	9/9 (100)	2/8 (25.0)	3/9 (33.3)
E. faecalis	2/3 (66.7)	6/7 (85.7)	1/3 (33.3)	4/7 (57.1)

Conclusion: Clinical outcome rates by pathogen at the TOC visit were high and similar for both ZTI-01 and P-T. ZTI-01 is effective in the treatment of cUTI and AP due to Gram-negative uropathogens.