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

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Background: ZTI-01 (fosfomycin for injection) is a novel injectable epoxide antibiotic with a unique mechanism of action (MOA) inhibiting an early step in bacterial cell wall synthesis. ZTI-01 has a broad in vitro spectrum of activity, including multidrug-resistant (MDR) Gram-negative pathogens, and is being developed for the treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP) in the United States.

Methods: The ZEUS study was a multicenter, randomized, double-blind Phase 2/3 trial designed to evaluate safety and efficacy of ZTI-01 in the 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 the test-of-cure (TOC) visit (Day 19). Patients enrolled (n=465) were randomized to receive 6 g ZTI-01 as a one-hour IV infusion q8h (18 g total daily dose) or 4.5 g IV P-T as a one-hour infusion q8h (13.5 g total daily dose) for a fixed 7 days, except patients with concurrent bacteremia received up to 14 days. Oral step-down therapy was prohibited.

Results: In the m-MITT population, ZTI-01 met the primary objective of non-inferiority compared with P-T with an overall success rate of 64.7% (119/184 patients) vs 54.5% (97/178 patients), respectively; treatment difference was 10.2% (95% CI: -0.4, 20.8). Clinical cure rates at TOC were high and similar between treatment groups (90.8% vs 91.6%, respectively). ZTI-01 was generally well tolerated. In the safety population (n=464), treatment-emergent adverse events (TEAEs) were observed in 42.1% and 32.0% of patients in the ZTI-01 and P-T groups, respectively. Most TEAEs were mild and transient; premature discontinuation of study drug was uncommon. The most frequent clinical TEAEs were gastrointestinal in nature. Serious adverse events were uncommon (5 ZTI-01, 6 P-T), with no deaths reported during the study.

Conclusion: These results demonstrate efficacy and tolerability of ZTI-01 in patients with cUTI and AP. If approved in the US, ZTI-01 would provide a new IV therapeutic option with a unique MOA for patients with difficult to treat Gram-negative infections.