## 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)

Keith S. Kaye, MD, MPH[1], Louis B. Rice, MD, FIDSA[2], Aaron Dane, PhD[3], Viktor Stus, MD, PhD[4], Olexsiy Sagan, MD[5], Elena Fedosiuk, MD[6], Anita Das, PhD[7], David Skarinsky, BS[8], **Paul B Eckburg, MD**[8] and Evelyn J Ellis-Grosse, PhD[9], (1)University of Michigan Medical School, Ann Arbor, MI, (2)Brown University, Providence, RI, (3)DaneStat Consulting, Alderley Edge, United Kingdom, (4)Municipal Institution Dnipropetrovsk Medical Academy of MOH of Ukraine, Dnipropetrovsk, Ukraine, (5)Department of Urology, Communal Institution Zaporizhzhia Regional Clinical Hospital, Zaporizhzhia, Ukraine, (6)Brest Regional Hospital, Brest, Belarus, (7)Das Statistical Consulting, Guerneville, CA, (8)Zavante Therapeutics, Inc., San Diego, CA, (9)Zavante Therapeutics, Inc, San Diego, CA

**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.