Intravenous Fosfomycin (ZTI) 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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**Abstract**

**Introduction**

- Drug resistance has increased steadily during the past several decades resulting in the need for safe and effective treatment strategies, particularly for multidrug-resistant (MDR) and nosocomial infections, including those that are often Gram-negative, such as Enterobacteriaceae (ESBL and/or carbapenem-resistant [CRE]).

- Intravenous fosfomycin (ZTI [IV-FOS]) offers a new IV therapeutic option with a unique MOA for patients with difficult to treat Gram-negative infections (ABSSSI), complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI) and a variety of other, often severe, infections. ZTI is indicated for the treatment of uncomplicated urinary tract infections (UTIs) including acute pyelonephritis (AP) and cUTI. ZTI is contraindicated for patients with a known allergy to ZTI and for patients concurrently receiving IV calcium. ZTI has been shown to be well tolerated in clinical trials.

**Purpose**

- The ZEUS study was a randomized, double-blind, placebo-controlled, multicenter study of ZTI compared with piperacillin-tazobactam (P-T) for the treatment of cUTI including AP and for the treatment of complicated intra-abdominal infections (cIAI). The primary objective was to compare ZTI and P-T for non-inferiority in microbiologic eradication plus clinical cure among patients with cUTI including AP.

**Methods**

- Patients with cUTI were randomized to receive 6 g ZTI or P-T for treatment of 12 days. Patients with cIAI were randomized to receive 16 g ZTI or P-T for treatment of 14 days. To be eligible for the IV-FOS study, patients were required to have 1 or more baseline pathogens identified as unique, unrelated strains compared to baseline pathogens. Patients with chronic diffusing alveolar disease were prohibited (Figure 2).

- The IV-FOS study was a multicenter, randomized, double-blind, placebo-controlled, phase II/III study that enrolled 464 participants with complicated urinary tract infections (cUTI) including acute pyelonephritis (AP) or complicated intra-abdominal infections (cIAI) at 102 study centers in 22 countries. The trial was conducted between May 2015 and November 2016. The primary endpoint of non-inferiority compared with P-T to achieve microbiologic eradication plus clinical cure in patients with cUTI at the 100% level was met at the 0.001 level of significance (95% CI = 1.3, 22.1) for all pathogens identified as baseline pathogens. The authors thank the ZEUS study group and participating investigators and employees who contributed to the ZEUS study.

**Results**

- Overall, clinical and microbiological responses were similar in both treatment arms for patients with cUTI including AP and for patients with cIAI. Overall success rates for ZTI and P-T were 92.7% and 86.9%, respectively. ZTI treatment was associated with clinical cure and microbiological eradication/persistence in a higher percentage of patients than P-T treatment at the time of follow-up. Treatment difference was in favor of ZTI at the 95% level of significance (1.7%, 11.7% CI = 1.3, 22.1). The authors thank the ZEUS study group and participating investigators and employees who contributed to the ZEUS study.

**Safety**

- Most TEAEs were mild in severity (Table 5). There were no serious TEAEs leading to study drug discontinuation. TEAEs were uncommon (Table 5). 98 (42.1%) of the 231 patients in the ZTI group and 100 (56.2%) of the 184 patients in the P-T group experienced any TEAEs. One SAE was related to study drug in the P-T group. The authors thank the ZEUS study group and participating investigators and employees who contributed to the ZEUS study.

**Conclusion**

- ZTI would provide a new IV therapeutic option with a unique MOA for patients with difficult to treat Gram-negative infections. ZTI is a well tolerated drug in clinical trials. ZTI is contraindicated for patients with a known allergy to ZTI and for patients concurrently receiving IV calcium. ZTI is indicated for the treatment of uncomplicated urinary tract infections (UTIs) including acute pyelonephritis (AP) and cUTI. ZTI has been shown to be well tolerated in clinical trials.

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**Poster #1845**

**Poster Session**

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