Clinical Cure in Secondary Efficacy Populations in Patients With Complicated Urinary Tract Infection Treated With ZTI-01 (Fosfomycin for Injection): Findings From the ZEUS Trial

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ABSTRACT

Background: ZTI-01 (fosfomycin for injection) is an investigational epoxide antibiotic with a differentiated mechanism of action (MOA) and is being developed for the treatment of patients with complicated urinary tract infection (cUTI) or complicated intra-abdominal infection (cIAI). A phase 2 study demonstrated the feasibility of a 7-day regimen in hospitalized patients with severe Gram-negative infections.

Methods: In ZEUS (ClinicalTrials.gov: NCT02632074), eligible patients were randomized (1:1) to receive 4.5 g IV ZTI-01 as a 1-hour IV infusion over 7 days, with baseline demographic and microbiologic data collected. ZTI-01 met the primary endpoint of non-inferiority to PIP-TAZ. Secondary objectives included comparing clinical cure (mitigated intent to treat [MITT]) and microbiologic eradication (microbiology MITT [m-MITT]) rates for patients with cUTI versus cIAI.

Results: Patients randomized to ZTI-01 (n=231) were similar to those randomized to PIP-TAZ (n=233). A joint analysis using pulsed field gel electrophoresis (PFGE) was performed to identify prevalent, unrelated pathogens. Overall success rates were higher in the ZTI-01 arm vs the PIP-TAZ arm, which drove the microbiologic eradication results. The most common TEAEs were asymptomatic, reversible laboratory abnormalities (e.g., elevated ALT).

Conclusions: ZTI-01 (IV fosfomycin) was evaluated in hospitalized adults with cUTI or AP for 7 days. ZTI-01 met the primary endpoint of non-inferiority to PIP-TAZ. Secondary objectives included comparing clinical cure and microbiologic eradication rates in patients with cUTI versus cIAI. ZTI-01 was well tolerated and appeared safe. ZTI-01 is being developed for the treatment of cUTI, hospital-acquired pneumonia, ventilator-associated pneumonia, and complicated intra-abdominal infection.

RESULTS (continued)

• Clinical cure rates of TOC were high and similar between treatment groups (>90%). Figure 3
• Microbiologic response rates were higher in the ZTI-01 arm than in the PIP-TAZ arm, which drove the treatment group difference in overall response in each analysis (Figure 3). Treatment group differences in overall success rates were accompanied by similar microbiologic eradication rates (Figure 4). For PIP-TAZ, there was a high prevalence of multidrug-resistant organisms. These results demonstrated efficacy in secondary efficacy populations for patients with cUTI and AP who were treated with ZTI-01.

• Only 1 SAE in each treatment group was deemed related to study drug (ZTI-01: hypokalemia; PIP-TAZ: mortality due to sepsis).

• Safety: ZTI-01 was generally well tolerated. The majority of adverse events were mild to moderate in severity. In the safety population (n=464), treatment-emergent adverse events (TEAEs) were observed in 42% and 32% of patients in the ZTI-01 and PIP-TAZ groups, respectively. Most TEAEs were mild to moderate in severity, severe TEAEs, serious TEAEs, and prematurity discontinuation rates were similar in the two treatment groups.

• The most common TEAEs were asymptomatic, reversible laboratory abnormalities (e.g., elevated ALT). Most TEAEs were mild to moderate in severity, severe TEAEs, serious TEAEs, and prematurity discontinuation rates were similar in the two treatment groups.

• The most frequent clinical TEAEs were transfusion reactions (n=2; nausea, vomiting).

• In each treatment group, TOC was deemed related to study drug (ZTI-01: asymptomatic, PIP-TAZ: renal insufficiency). There were no deaths in the study.

METHODS

ZTI-01 (IV fosfomycin) was noninferior to PIP-TAZ in overall success among patients with cUTI and AP.

Cure rates were high (90%) and similar between treatment groups in all study analysis populations.

The treatment differences in overall success rates were driven by the higher microbiologic eradication rates in the ZTI-01 group, especially among patients with cUTI.

Most common types of AEs (asymptomatic laboratory abnormalities) were mild or moderate in severity and consistent with class effects described over the past 40 years of use outside the United States. Clinical TEAEs, such as GI events, were uncommon and not treatment limiting.

• If approved in the US, ZTI-01 would provide a new IV therapeutic option with a differentiated MOA for patients with difficult-to-treat Gram-negative infections.

REFERENCES


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Disclosures

Keith S. Kaye, MD, MPH, Kristina Manveelen, and Evelyn J. Ellis-Grose are employees of Nabriva Therapeutics US, Inc.

Figure 1. Study Design

Table 1. Patient Demographics: Primary Analysis Populations (n-MITT)

Figure 2. Analysis Population Disposition

Figure 3. Overall Clinical, Efficacy, and Microbiologic Response to TOC by Analysis Populations

Figure 4. Overall Response to TOC by Analysis Populations With PFGE Post Hoc Analysis

Efficacy

ZTI-01 met the primary endpoint of noninferiority to PIP-TAZ in overall success as TOC in the m-MITT population; overall success rates were 64.7% vs 54.5%, respectively (difference 10.2%, 95% CI: –0.8%, 8.6%; p=0.353).

Microbiologic Eradication (m-MITT)

Microbiologic eradication rates were higher in the ZTI-01 group vs the PIP-TAZ group, especially in patients with cUTI. Figure 4

In the ZTI-01 group, 72% of patients achieved microbiologic eradication vs 56% in the PIP-TAZ group. Treatment group difference was 16.6%, 95% CI: 4.7%, 28.6%, p=0.005. The most common TEAEs were asymptomatic, reversible laboratory abnormalities.

Safety

ZTI-01 was generally well tolerated. The majority of adverse events were mild to moderate in severity. In the safety population (n=464), treatment-emergent adverse events (TEAEs) were observed in 42% and 32% of patients in the ZTI-01 and PIP-TAZ groups, respectively. Most TEAEs were mild to moderate in severity, severe TEAEs, serious TEAEs, and prematurity discontinuation rates were similar in the two treatment groups.

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