1367

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) inhibiting an early step in bacterial cell wall synthesis. *In vitro* studies suggest ZTI-01 has a broad spectrum of activity, including against multidrug-resistant Gram-negative pathogens, and is being developed for the treatment of patients with complicated urinary tract infection (cUTI) and acute pyelonephritis (AP) in the United States.

Methods: ZEUS was a multicenter, double-blind Phase 2/3 trial in hospitalized adults with cUTI and AP to evaluate safety and efficacy. Randomized patients received 6 g ZTI-01 q8h or 4.5 g IV piperacillin/tazobactam (PIP-TAZ) q8h for 7 days; patients with baseline bacteremia could receive up to 14 days; study continued to late follow-up (LFU, 26 ± 2 days). Oral step-down therapy was prohibited. ZTI-01 met the primary endpoint of non-inferiority to PIP-TAZ. Secondary objectives included comparing clinical cure rates (assessed by investigator) in the modified intent-to-treat (MITT), microbiologic MITT (m-MITT), clinical evaluable (CE), and microbiologic evaluable (ME) populations at test-of-cure (TOC, Day 19 ± 2 days).

Results: There were 464 patients who were randomized and received study drug. In all populations, clinical cure rates at TOC were high and similar between treatment groups (>90%).

Conclusion: These results demonstrated efficacy in secondary efficacy populations for patients with cUTI and AP who were treated with either ZTI-01 or PIP-TAZ. If approved by FDA, ZTI-01 may provide a new IV option with a differentiated MOA for patients in the US with serious Gram-negative infections.

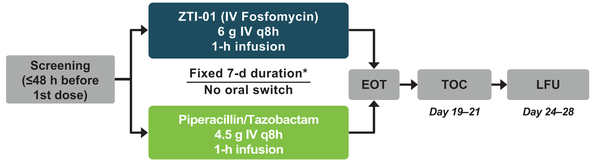
INTRODUCTION

- As rates of serious Gram-negative infections caused by multidrug-resistant (MDR) or pan-resistant pathogens are increasing, clinicians are often forced to use agents of last resort (e.g., carbapenems) or agents associated with toxicity (e.g., colistin, aminoglycosides)[1]
- New therapeutic options with different mechanisms of action and established safety are desperately needed[2]
- ZTI-01 (CONTEPO™, fosfomycin for injection) is a first-in-class injectable epoxide antibiotic with a differentiated MOA, inhibiting an early step in bacterial cell wall synthesis (covalently binds MurA, preventing the first step in peptidoglycan biosynthesis)[3]
- Efficacy and safety of IV fosfomycin is supported by over 40 years of use in more than 60 clinical studies outside of the US in a number of serious infections (including cUTI)[3,4]
- *In vitro* studies suggest ZTI-01 has a broad spectrum of activity, including against MDR Gram-negative pathogens (e.g., extended-spectrum beta-lactamase [ESBL] producers and carbapenem-resistant Enterobacteriaceae [CRE])[5]
- ZTI-01 is being developed for the treatment of cUTI, including AP in the US
- The FDA granted Fast Track and Qualified Infectious Disease Product (QIDP) designations for the investigation of ZTI-01 for cUTI, hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), acute bacterial skin and skin structure infection (ABSSSI), and complicated intra-abdominal infection (cIAI)

METHODS

- ZEUS study was a multicenter, randomized, double-blind, Phase 2/3, noninferiority trial designed to evaluate safety and efficacy of ZTI-01 in hospitalized adults with cUTI or AP versus PIP-TAZ (https://clinicaltrials.gov/ct2/show/NCT02753946; **Figure 1**)
- Sample size of 230 patients per arm (N=460) was based on a 15% noninferiority margin, 70% predicted evaluability rate, 70% overall success rate in both treatment groups, 80% power, 1-sided α=0.025

Figure 1. Study Design



EOT: end of treatment; LFU: late follow-up visit; TOC: test of cure.

METHODS (continued)

- Primary endpoint of overall success was defined as clinical cure plus microbiologic eradication in the microbiologic m-MITT population at TOC visit (Day 19–21; **Figure 1**)
- Patients were randomized (n=465) and treated (n=464) to receive 6 g ZTI-01 as a 1-hour IV infusion q8h (18 g total daily dose) or 4.5 g IV PIP-TAZ as a 1-hour infusion q8h (13.5 g total daily dose) for a fixed 7 days, except patients with concurrent bacteremia with option to receive up to 14 days. Oral step-down therapy was prohibited **(Figure 2)**

Figure 2. Analysis Population Disposition

		ZTI-01 n (%)	PIP-TAZ n (%)
Patients randomized (ITT)	N=465	233 (100)	232 (100)
Patients receiving ≥1 dose study drug (MITT, safety population)	N=464	233 (100)	231 (99.6)
Patients meeting clinical eligibility (CE-TOC) subset of MITT + I/E criteria + min 9 doses + within window visits	N=395	199 (85.4)	196 (84.5)
Patients who have ≥1 Gram-negative pathogen ≥10^5 CFU/mL (m-MITT), subset of MITT, primary endpoint	N=362	184 (79.0)	178 (76.7)
Patients meeting microbiologic evaluability at TOC (ME, subset of m-MITT and CE + results within TOC visit window)	N=300	155 (66.5)	145 (62.5)

CE: clinical evaluable; CFU: colony-forming unit; I/E: inclusion/exclusion; ITT: intent to treat; ME: microbiologic evaluable; MITT: modified ITT; m-MITT: microbiologic MITT; PIP-TAZ: piperacillin/tazobactam; TOC: test of cure.

- A post hoc analysis using pulsed-field gel electrophoresis (PFGE) was performed to molecularly type all baseline and TOC pathogens (both treatment arms), in order to confirm microbiological eradication/ persistence; a total of 20 postbaseline pathogens were identified as unique, unrelated to baseline strains

RESULTS

Demographics & Baseline Characteristics

- Patients were well matched in the ZTI-01 and PIP-TAZ populations **(Table 1, Figure 2)**
- Slightly more patients were diagnosed with AP than cUTI

Efficacy

- ZTI-01 met the primary endpoint of noninferiority to PIP-TAZ in overall success at TOC in the m-MITT population; overall success rates were 64.7% vs 54.5%, respectively (difference 10.2%, 95% CI: –0.4, 20.8) **(Figure 3)**

Table 1. Patient Demographics: Primary Analysis Population (m-MITT)

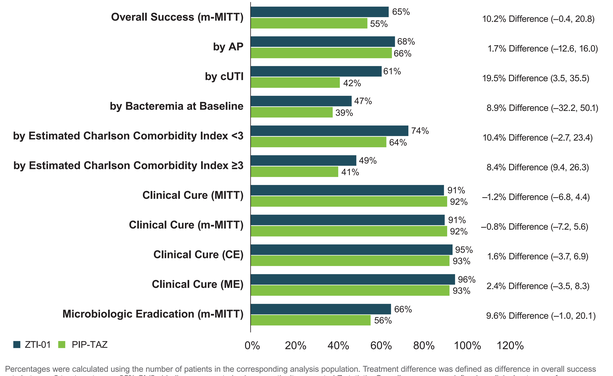
	ZTI-01 N=184	PIP-TAZ N=178	TOTAL N=362
Primary diagnosis, n (%)			
AP	100 (54.3)	96 (53.9)	196 (54.1)
cUTI	84 (45.7)	82 (46.1)	166 (45.9)
Age >65 y, n (%)	62 (33.7)	63 (35.4)	125 (34.5)
Female, n (%)	119 (64.7)	111 (62.4)	230 (63.5)
White, n (%)	184 (100)	178 (100)	362 (100)
Mean BMI, kg/m² (SD)	25.75 (5.26)	26.64 (5.84)	26.18 (5.56)
[range, min–max]	[17.1–48.9]	[15.6–44.6]	[15.6–48.9]
CrCl ≥20–50 mL/min, n (%)	26 (14.1)	20 (11.2)	46 (12.7)
SIRS at baseline, n (%)	62 (33.7)	52 (29.2)	114 (31.5)
Bacteremia at baseline, n (%)	19 (10.3)	13 (7.3)	32 (8.8)
No prior antibiotics, n (%)	168 (91.3)	166 (93.3)	334 (92.3)

AP: acute pyelonephritis; BMI: body mass index; CrCl: creatinine clearance; cUTI: complicated urinary tract infection; m-MITT: microbiologic modified intent to treat; PIP-TAZ: piperacillin/tazobactam; SIRS: systemic inflammatory response syndrome.

RESULTS (continued)

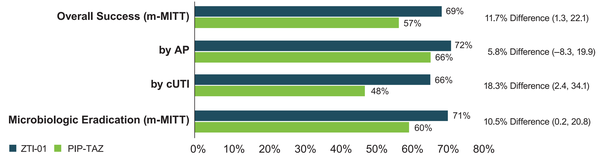
- Clinical cure rates at TOC were high and similar between treatment groups (>90%; **Figure 3**)
- Microbiological response rates were higher in the ZTI-01 arm vs the PIP-TAZ arm, which drove the treatment group difference in overall response in each analysis **(Figure 3)**
- Treatment group differences in overall success rates by infection type were more pronounced in patients with cUTI (19.5%) than AP (1.7%; **Figure 3**)
- Microbiological response rates at TOC varied among patients with severe disease (i.e., bacteremia); however, clinical cure rates in these subgroups were similar between treatment groups **(Figure 3)**
- Using unique pathogen strains typed by PFGE, overall success rates were 69.0% for ZTI-01 vs 57.3% for PIP-TAZ (difference 11.7%, 95% CI: 1.3, 22.1) **(Figure 4)**

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



Percentages were calculated using the number of patients in the corresponding analysis population. Treatment difference was defined as difference in overall success rate between 2 treatment arms. 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. Overall success was defined as clinical outcome of cure or improvement and microbiologic outcome of eradication (defined as the baseline bacterial pathogen being reduced to <10^5 CFU/mL).
AP: acute pyelonephritis; CE: clinical evaluable; CFU: colony-forming unit; cUTI: complicated urinary tract infection; ME: microbiologic evaluable; MITT: modified intent to treat; m-MITT: microbiologic MITT; PIP-TAZ: piperacillin/tazobactam; TOC: test of cure.

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



Percentages were calculated using the number of patients in the corresponding analysis population. Treatment difference was the difference in overall success rate between 2 treatment arms. 95% CI (2-sided) was computed using a continuity-corrected Z-statistic. Overall success was defined as clinical outcome of cure or improvement and microbiologic outcome of eradication (defined as the baseline bacterial pathogen being reduced to <10^5 CFU/mL). PFGE was a post hoc analysis performed to molecularly type all baseline and TOC pathogens (both treatment arms), in order to confirm microbiological eradication/persistence; a total of 20 postbaseline pathogens were identified as unique, unrelated strains compared with baseline.
AP: acute pyelonephritis; CFU: colony-forming unit; cUTI: complicated urinary tract infection; m-MITT: microbiologic modified intent to treat; PIP-TAZ: piperacillin/tazobactam; PFGE: pulse-field gel electrophoresis; TOC: test of cure.

RESULTS (continued)

Safety

- ZTI-01 was generally well tolerated; the majority of adverse events were mild to moderate. 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 PIP-TAZ groups, respectively
- Most TEAEs were mild to moderate in severity; severe TEAEs, serious TEAEs, and premature discontinuation of study drug were uncommon in both treatment groups
  - The most common TEAEs were asymptomatic, reversible laboratory abnormalities (e.g., elevated ALT/AST and hypokalemia)
  - The most frequent clinical TEAEs were transient GI events (e.g., nausea, vomiting)
  - Only 1 SAE in each treatment group was deemed related to study drug (ZTI-01: hypokalemia; PIP-TAZ: renal insufficiency); there were no deaths in the study

CONCLUSIONS

- ZTI-01 (fosfomycin for injection) 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 US. 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

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Disclosures

David Skarinsky, Paul B. Eckburg, Kristina Manevelian, and Evelyn J. Ellis-Grosse are employees of Nabriva Therapeutics US, Inc.

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