Friday – CIV-148

Fosfomycin for Injection (FOS) Versus (vs) Piperacillin-Tazobactam (PIP-TAZ) for Treating Complicated Urinary Tract Infections (cUTI) and Acute Pyelonephritis (AP): Further Analyses of the ZEUS Study

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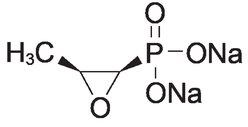
INTRODUCTION

- The emergence of multidrug-resistant (MDR) gram-negative pathogens has left clinicians with few effective therapeutic options and led to the use of toxic alternative therapies (eg, polymyxins, aminoglycosides),[1,2] resulting in the need for safe and effective antibiotics with differentiated mechanisms of action
- Fosfomycin for injection (FOS; **Figure 1**) is a first-in-class injectable epoxide antibiotic under evaluation by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infection (cUTI), including acute pyelonephritis (AP)
  - FOS inhibits an early step in bacterial cell wall synthesis by covalently binding to UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) to prevent the first step in peptidoglycan biosynthesis[3]
  - FOS displays a broad spectrum of in vitro activity against MDR gram-negative pathogens, including extended-spectrum β-lactamase producers and carbapenem-resistant Enterobacteriaceae[4,5]
  - The efficacy and safety of intravenous (IV) fosfomycin is supported by over 40 years of use outside of the United States in a number of serious infections, including cUTI[3,6]
- The ZEUS trial evaluated the efficacy and safety of FOS vs piperacillin-tazobactam (PIP-TAZ) in patients hospitalized with cUTI/AP based on 2015 FDA cUTI Guidance[7]
  - New FDA Guidance was issued in 2018 that reduced the microbial eradication threshold from $<10^4$ CFU/mL to $<10^3$ CFU/mL[8]
- The objectives of this investigation were to reanalyze ZEUS efficacy by the 2018 FDA Guidance and by baseline PIP-TAZ susceptibility

Figure 1. Structure of Fosfomycin for Injection



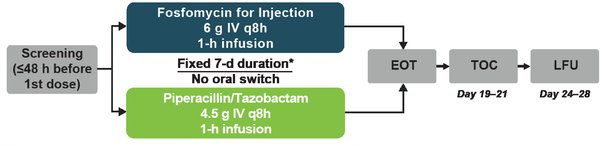
METHODS

- The ZEUS study was a phase 2/3, multicenter, randomized, double-blind, noninferiority trial conducted at 92 sites in 16 countries from June 2016 to January 2017 **(Figure 2)**
  - A sample size of 230 patients per group (*N*=460), based on 70% predicted evaluability rate and 70% overall success rates in both treatment groups, provided 80% power to demonstrate noninferiority using a 15% noninferiority margin and a 1-sided alpha of 0.025
- Hospitalized adults with suspected or microbiologically confirmed cUTI/AP were randomized 1:1 to receive FOS 6 g as a 1-hour IV infusion every 8 hours (q8h) (total daily dose of 18 g) or 4.5 g IV PIP-TAZ as a 1-hour infusion q8h (total daily dose of 13.5 g) for 7 days
  - Patients with concurrent bacteremia received up to 14 days of treatment
  - Oral step-down and outpatient parenteral therapies were prohibited

METHODS (continued)

- The primary endpoint of overall success was defined as clinical cure and microbiologic eradication in the microbiologic modified intent-to-treat (m-MITT) population at the test-of-cure (TOC) visit (Day 19–21)
  - The m-MITT population included patients who received any amount of study drug and had ≥1 baseline gram-negative pathogen from an appropriately collected pretreatment baseline urine or blood sample

Figure 2. ZEUS Study Design



EOT=end of treatment; IV=intravenous; LFU=late follow-up; q8h=every 8 hours; TOC=test of cure.
*Treatment extended up to 14 days for patients with baseline bacteremia.

RESULTS

Efficacy by 2018 FDA Guidance Reanalysis

- In the original primary analysis based on the 2015 FDA cUTI Guidance, FOS was noninferior to PIP-TAZ based on the prespecified noninferiority margin of 15% **(Table 1)**
  - Use of the more stringent 2018 Guidance criteria for this analysis resulted in a slightly greater treatment difference that further favored FOS and had a 95% confidence interval (CI) with a lower bound above zero
  - While success rates among FOS and PIP-TAZ were lower with the more stringent 2018 criteria vs the 2015 criteria, overall success rates remained generally comparable between the 2 treatment groups

Table 1. Comparison of Overall Response at TOC Using 2015 vs 2018 FDA Guidance (m-MITT Population)

FDA Guidance	Overall Success*			
	Eradication Threshold	FOS *n*=184 *n* (%)	PIP-TAZ *n*=178 *n* (%)	Treatment Difference (95% CI)†
2015 (primary analysis)	$<10^4$ CFU/mL	119 (64.7)	97 (54.5)	10.2 (–0.4, 20.8)
2018 (post hoc reanalysis)	$<10^3$ CFU/mL	115 (62.5)	89 (50.0)	12.5 (1.8, 23.2)
Responses lost‡	–	4 (2.2)	8 (4.5)	–

CFU=colony forming units; CI=confidence interval; FDA=US Food and Drug Administration; FOS=fosfomycin for injection; m-MITT=microbiologic modified intent to treat; PIP-TAZ=piperacillin-tazobactam; TOC=test of cure.
*Overall success was defined as clinical cure and microbiologic eradication. Within each treatment group, percentages were calculated using the number of patients in the m-MITT population as the denominator.
†Treatment difference was the difference in the overall success rate between the 2 treatment groups (FOS – PIP-TAZ). The 95% CIs (2-sided) were computed using a continuity-corrected Z-statistic.
‡Responses lost = (Overall success using 2015 Guidance) – (Overall success using 2018 Guidance).

RESULTS (continued)

Efficacy by Baseline PIP-TAZ Susceptibility

- Baseline cUTI/AP caused by a PIP-TAZ–resistant pathogen was uncommon (*n*=14 FOS, *n*=9 PIP-TAZ) **(Table 2)**
  - Among these patients, overall success rates at TOC were 78.6% (11/14) in the FOS group and 33.3% (3/9) in the PIP-TAZ group
- In patients infected with a PIP-TAZ–intermediate pathogen at baseline, overall success rates at TOC were 58.3% (7/12) and 62.5% (5/8) for the FOS and PIP-TAZ groups, respectively **(Table 2)**
- In patients infected with a PIP-TAZ–susceptible pathogen at baseline, overall success rates at TOC (64.7% [99/153] for FOS vs 56.7% [85/150] for PIP-TAZ) were similar to those observed in the primary endpoint analysis (64.7% [119/184] for FOS vs 54.5% [97/178] for PIP-TAZ; **Table 2**)
- Upon exclusion of those patients with a baseline pathogen resistant to PIP-TAZ, overall success rates were 63.5% (108/170) in the FOS group and 55.6% (94/169) in the PIP-TAZ group (treatment difference 7.9%; 95% CI, –3.1 to 18.9)

Table 2. Overall Response at TOC in Patients With Baseline Pathogens Resistant, Intermediate, or Susceptible to PIP-TAZ (m-MITT Population)

	FOS *n*=184 *n* (%)	PIP-TAZ *n*=178 *n* (%)	Treatment Difference (95% CI)*
Patients With Baseline Pathogen per PIP-TAZ Susceptibility‡			
Resistant, N_1	14	9	
Success†	11 (78.6)	3 (33.3)	45.2 (–1.4, 91.9)
Failure	3 (21.4)	6 (66.7)	–
Intermediate, N_1	12	8	
Success†	7 (58.3)	5 (62.5)	–4.2 (–58.2, 49.9)
Failure	5 (41.7)	3 (37.5)	–
Susceptible, N_1	153	150	
Success†	99 (64.7)	85 (56.7)	8.0 (–3.6, 19.7)
Failure	44 (28.8)	58 (38.7)	–
Indeterminate	10 (6.5)	7 (4.7)	–

CI=confidence interval; CLSI=Clinical and Laboratory Standards Institute; FOS=fosfomycin for injection; MIC=minimum inhibitory concentration; m-MITT=microbiologic modified intent to treat; PIP-TAZ=piperacillin-tazobactam; TOC=test of cure.
*Treatment difference was the difference in the overall success rate between the 2 treatment groups (FOS – PIP-TAZ). The 95% CIs (2-sided) were computed using a continuity-corrected Z-statistic.
†Overall success was defined as clinical cure and microbiologic eradication. Percentages were calculated using N_1, the number of patients in the subgroup, as the denominator. Resistant (MIC ≥128 µg/mL), intermediate (MIC 32–64 µg/mL), and susceptible (MIC ≤16 µg/mL) isolates were determined using CLSI breakpoints for Enterobacteriaceae for PIP-TAZ.
‡Five patients receiving FOS and 11 receiving PIP-TAZ were excluded from the analysis because of noninterpretable (eg, gram-positive) or missing MIC values.

CONCLUSIONS

- Reanalysis of the ZEUS primary endpoint using either a stricter definition for microbial eradication or excluding patients with cUTI/AP caused by PIP-TAZ–resistant pathogens further supports the robustness of FOS noninferiority to PIP-TAZ
- FOS was associated with higher overall success rates in both post hoc analyses compared with PIP-TAZ
- FOS may provide a useful treatment option for cUTI/AP, including for cases caused by PIP-TAZ–resistant and MDR pathogens

REFERENCES

(1) Alemayehu D, et al. *Clin Infect Dis.* 2012;55(4):562-567.

(2) Shields RK, et al. *Clin Infect Dis.* 2016;63(12):1615-1618.

(3) Falagas ME, et al. *Clin Microbiol Rev.* 2016;29(2):321-347.

(4) Falagas ME, et al. *Int J Antimicrob Agents.* 2010;35(3):240-243.

(5) Flamm RK, et al. *Diagn Microbiol Infect Dis.* 2019;93(2):143-146.

(6) Grabein B, et al. *Clin Microbiol Infect.* 2017;23(6):363-372.

(7) Kaye KS, et al. *Clin Infect Dis.* 2019; doi: 10.1093/cid/ciz181.

(8) US Food and Drug Administration. Complicated Urinary Tract Infections: Developing Drugs for Treatment. Guidance for Industry. Center for Drug Evaluation and Research, Division of Drug Information. Available at: https://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf. Accessed April 17, 2019.

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Disclosures

Evelyn J. Ellis-Grosse served as CSO during the design, execution, and analysis of the study and is currently a consultant with shares in Nabriva Therapeutics plc. David Skarinsky and Kristina Manvelian were employees of Nabriva Therapeutics and held stock options in Nabriva Therapeutics plc at the time of analysis and currently serve as consultants for Nabriva Therapeutics. Paul B. Eckburg served as a consultant for Nabriva Therapeutics during the design and execution of the study and has also served as a consultant for Paratek, Geom, Spero, and UTILITY. Anita F. Das served as a consultant for Nabriva Therapeutics during the design and execution of the study and has also served as a consultant for ContraFect, Tetraphase, Paratek, Cempra, Achaogen, Zavante, UTILITY, Iterum, AntibioTx, and Wockhardt. Keith S. Kaye has served as a consultant for Nabriva Therapeutics, Melinta Therapeutics, Allergan, and Merck & Co., and has received research grant funding from Merck & Co.

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