Phenotypic Antibiotic Resistance in ZEUS: A Multi-center, Randomized, Double-Blind Phase 2/3 Study of ZTI-01 versus Piperacillin-Tazobactam (P-T) in the Treatment of Patients with Complicated Urinary Tract Infections (cUTI) including Acute Pyelonephritis (AP)

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Background: Phenotypic resistance profiles are frequently employed to target appropriate antibiotic treatments. With increasing rates of resistance, antibiotics with a new mechanisms of action are needed. ZTI-01 (fosfomycin for injection) is an injectable epoxide antibiotic with a broad spectrum of activity including multidrug-resistant (MDR) pathogens. ZTI-01 acts at an early step in cell wall synthesis inhibition by covalently binding to MurA, and is being developed for the treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP) in the US.

Methods: ZEUS study was a multicenter, randomized, double-blind Phase 2/3 trial designed to evaluate safety and efficacy of ZTI-01 in treatment of hospitalized adults with cUTI or acute pyelonephritis versus piperacillin/tazobactam (P-T). Patients received either 6 g ZTI-01 or 4.5 g P-T as 1-hour IV infusions q8h for a fixed 7 days (up to 14 days if concurrent bacteremia). Clinical cure and microbiologic eradication were assessed at the test-of-cure (TOC) visit (Day 19). Using minimum inhibitory concentrations (MICs), blood or urine isolates bearing phenotypic resistance for extended-spectrum beta-lactamases (ESBL: ≥2 µg/mL, aztreonam, ceftazidime or ceftriaxone), carbapenem-resistant *Enterobacteriaceae*(CRE: ≥4 µg/mL imipenem or meropenem), Amino-R (gentamicin or amikacin resistance), or MDR (nonsusceptibility ≥3 classes) were identified to assess patient and microbiologic outcome.

Results: In the m-MITT population, 123/362 patients (34%) were infected with a pathogen exhibiting phenotypic resistance: MDR (19%), ESBL (31%), Amino-R (17%), and CRE (6.1%). Clinical cure and microbiologic eradication are presented in Table 1.

Table 1. Phenotypic Resistance (TOC, m-MITT, % (n))

	ESBL		**Amino-R**		**CRE**		**MDR**	
	Cure	Erad.	Cure	Erad.	Cure	Erad.	Cure	Erad.
ZTI-01	93% (52/56)	55% (32/58)	97% (29/30)	67% (20/30)	100% (9/9)	56% (5/9)	92% (34/37)	54% (20/37)
P-T	93% (51/55)	47% (27/58)	94% (29/31)	38% (12/32)	85% (11/13)	31% (4/13)	90% (28/31)	36% (12/33)

Conclusion: Overall, treatment arms were balanced with number and type of isolates bearing phenotypic resistance and clinical cure rates were high. Eradication rates numerically favored ZTI-01.