Poster #1830

Phenotypic Antibiotic Resistance in ZEUS: 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) Poster

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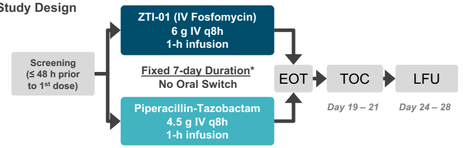
Abstract (Amended)

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 P-T (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 (CR: ≥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, 117/362 patients (32%) were infected with a pathogen exhibiting phenotypic resistance: MDR (21%), ESBL (30%), Amino-R (18%), and CR (4%). Clinical cure and microbiologic eradication are presented in Table.
Conclusions: 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.

Table. Clinical Cure and Microbiologic Eradication Rates for Patients from ZEUS Trial with Antimicrobial Resistant Phenotypes (TOC, m-MITT, % [n])

	ESBL		Amino-R		CR		MDR	
	Cure	Erad.	Cure	Erad.	Cure	Erad.	Cure	Erad.
ZTI-01	92% (49/53)	57% (32/56)	97% (29/30)	67% (20/30)	100% (7/7)	57% (4/7)	92% (36/39)	59% (23/39)
P-T	93% (51/55)	47% (27/57)	88% (30/34)	40 (14/35)	89% (8/9)	33% (3/9)	86% (31/36)	37% (14/38)

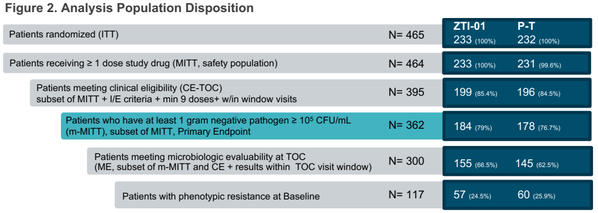
Figure 1. Study Design



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

Treatment extension up to 14 days if baseline bacteremia

Figure 2. Analysis Population Disposition



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; P-T: piperacillin/tazobactam; TOC: test-of-cure

Introduction

- Antimicrobial resistance has increased steadily during the past several decades resulting in a crisis and necessitating more antibiotic treatment options, particularly among Gram-negative bacteria, including those that produce extended spectrum beta-lactamases (ESBLs) and carbapenemases (e.g., carbapenemase-resistant *Enterobacteriaceae* [CRE])
- The development of antibiotic resistance is usually associated with genetic changes (e.g. mutations relevant to an antibiotic's activity or the acquisition of resistance genes) and may be screened by reviewing minimum inhibitory concentrations (MICs) for category and classes of antimicrobial agents
- The Center for Disease Control and Prevention (CDC) has implemented Guidelines and Phenotype definitions to assist clinical laboratories for surveillance of institutional antimicrobial resistance (www.cdc.gov/nhsn/pdfs/ps-analysis-resources/phenotype_definitions.pdf)

- ZTI-01 (ZOLYD™, fosfomycin for injection) is a first-in-class injectable epoxide antibiotic with a unique mechanism of action (MOA) inhibiting an early step in bacterial cell wall synthesis compared to other antibacterial agents
- ZTI-01 is being developed in the US for the treatment of cUTI, including acute pyelonephritis
- ZTI-01 has a broad *in vitro* spectrum of activity, including multidrug-resistant (MDR) Gram-negative pathogens
- Outside of the US, IV fosfomycin has been extensively used and provided safe and effective means for treating patients with cUTI and a variety of other, often very severe, infections
- Despite decades of use ex-US, fosfomycin has retained excellent *in vitro* antimicrobial activity, including activity against the increasingly problematic ESBL-positive Gram-negative pathogens and carbapenemase producing organisms
- A tromethamine salt of fosfomycin is available in US as an oral sachet, and indicated for the treatment of uncomplicated UTIs (eg, cystitis), however, the oral form has poor bioavailability (~37%) and gastrointestinal intolerance following multiple doses that limits utility for complicated infections. An IV form may provide improved tolerability, as well as the ability to reliably achieve higher blood concentrations necessary to treat serious infections

Methods

ZEUS (ZTI-01 Efficacy and Safety) Study
- ZEUS study was a multicenter, randomized, double-blind Phase 2/3 trial designed to evaluate safety and efficacy of ZTI-01 in the treatment of hospitalized adults with cUTI or AP versus P-T
- Primary endpoint of overall success was defined as clinical cure (resolution of signs and symptoms) plus microbiologic eradication (isolated organism <10^4 colony forming units [CFU]/mL) in the microbiologic modified intent-to-treat (m MITT) population at the test-of-cure (TOC) visit (Day 19). A late follow-up (LFU) visit was performed on Day 28
- Patients enrolled (n=465) were randomized to receive 6 g ZTI-01 as a one-hour IV infusion q8h (18 g total daily dose) or 4.5 g IV P-T as a one-hour infusion q8h (13.5 g total daily dose) for a fixed 7 days, except patients with concurrent bacteremia received up to 14 days. Oral step-down therapy was prohibited
- While failure or relapse was infrequent, clinical and microbiologic data were assessed for trends by review of patient baseline diagnosis, instrumentation removal/replacement, bacterial species and MIC parameters

Phenotypic Resistance
- Phenotypic resistance profiles are frequently employed by clinical laboratories to target appropriate antibiotic treatments and aid in surveillance. The CDC has provided Guidelines for Antimicrobial Resistant Phenotype Definitions that were employed from the ZEUS results to identify concerning pathogens
- Using MICs from an accompanying antibiotic panel or agar dilution supplemented with glucose 6-phosphate for fosfomycin, blood or urine isolates were identified to assess patient and microbiologic outcome. The following definitions were used for this assessment:
  - ESBL: ≥2 µg/mL MIC for aztreonam, ceftazidime or ceftriaxone,
  - CR: ≥4 µg/mL imipenem or meropenem,
  - Amino-R: gentamicin ≥ 8 µg/mL or amikacin ≥32 µg/mL
  - MDR: nonsusceptibility ≥3 classes, using definitions above plus levofloxacin ≥4 µg/mL and trimethoprim/sulfamethoxazole ≥32 µg/mL
- Patients could have more than 1 isolate from blood and/or urine sources and all organisms are presented for completeness. Patients with multiple organisms were counted only once per resistance grouping. If the same species was identified from a different source, the isolate was counted once for microbiological outcome

Results

Phenotypic Resistance
- In the m-MITT population, 117 of 362 patients (32%) had at least 1 pathogen exhibiting ≥1 resistance phenotype. A total of 130 unique isolates were identified from the clinical study that met antimicrobial resistant phenotype definitions for ESBL, Amino-R, CR or MDR (Table 1)
- Clinical cure and microbiologic eradication rates for each phenotype are presented (Table 2)
- The percentage of phenotypes by bacterial species from either the ZTI-01 or P-T treatment are presented in Tables 3-6
- The most frequently observed phenotypes were ESBL (30%) followed by MDR (21%). Phenotypic categories were balanced among treatment groups
- A range of bacterial species common to cUTI were identified in each phenotypic category.
- Of the P-T treated patients, n=16 had P-T MICs at or above the susceptibility breakpoint (≥64 µg/mL). Notably, 15 of these patients were considered clinically cured (warranting no other treatment), including 7 patients with confirmed microbiological eradication. One patient relapsed with signs and symptoms of infection at LFU
- At TOC, while patient numbers were small, no distinct relationship of explored parameters was associated with failure in either treatment arm:
  - ZTI-01 group: 7 patients were identified having both clinical failure and microbiological persistence (n=5) or a response of indeterminant (n=2), which comprised of patients with AP (n=3) and cUTI (n=4). Of these patients, baseline pathogens and ZTI-01 MIC included: *Klebsiella pneumoniae* (n=1, MIC 32), *Enterobacter cloacae* (n=1, MIC >512), *Proteus mirabilis* (n=1, MIC 64) and *E. coli* (n=4, MICs 0.5, 1 and 32 µg/mL)
  - P-T group: 9 patients were identified having both clinical failure and microbiological persistence (n=8) or a response of indeterminant (n=1), which comprised of patients with AP (n=5) and cUTI (n=4). Of these patients, baseline pathogens and P-T MICs included: *Enterococcus faecalis* (n=1, MIC 4), *Proteus mirabilis* (n=2, MICs ≤=0.5 and 1) and *E. coli* (n=9, MICs of 1, 2, 8 and >64 µg/mL

Table 1. Phenotypic Resistance in the m-MITT Population (by patient), % (n/N)

	Phenotypic Resistance		
Bacteria	**Total**	**ZTI-01**	**P-T**
ESBL	30% (108/362)	29% (53/184)	31% (55/178)
Amino-R	18% (64/362)	16% (30/184)	19% (34/178)
CR	4% (16/362)	4% (7/184)	5% (9/178)
MDR	2% (75/362)	21% (39/184)	20% (36/178)

Table 2. Clinical Cure and Microbiologic Eradication Rates for Patients from ZEUS Trial with Antimicrobial Resistant Phenotypes (TOC, m-MITT), % (n/N)

	ESBL		Amino-R		CR		MDR	
	Cure	Erad.	Cure	Erad.	Cure	Erad.	Cure	Erad.
ZTI-01	92% (49/53)	57% (32/56)	97% (29/30)	67% (20/30)	100% (7/7)	57% (4/7)	92% (36/39)	59% (23/39)
P-T	93% (51/55)	47% (27/57)	88% (30/34)	40 (14/35)	89% (8/9)	33% (3/9)	86% (31/36)	37% (14/38)

CR: Carbapenem-resistant; ESBL: extended spectrum beta-lactamase; MDR: multidrug-resistant; m-MITT: microbiologic modified intent-to-treat

Table 3. ESBL Phenotype by Treatment Group, n/N (%)

	ESBL Phenotype		
Bacteria	Total	ZTI-01	P-T
Acinetobacter baumannii-calcoaceticus species complex	2/2 (100%)	2/2 (100%)	0/0 (0)
Enterobacter cloacae species complex	8/12 (67%)	6/9 (66.7%)	2/3 (67%)
Escherichia coli	51/292 (18%)	22/149 (18%)	29/143 (7%)
Klebsiella oxytoca	2/4 (50%)	1/2 (50%)	1/2 (50%)
Klebsiella pneumoniae	30/54 (56%)	18/28 (64%)	12/26 (46%)
Proteus mirabilis	3/13 (23%)	1/9 (11%)	2/4 (50%)
Pseudomonas aeruginosa	17/17 (100%)	8/8 (100%)	9/9 (100%)
Morganella morganii	1/1 (100%)	0/0 (0)	1/1 (100%)
Serratia marcescens	1/2 (50%)	0/1 (50%)	1/1 (100%)

Table 4. CR Phenotype by Treatment Group, n/N (%)

	CR Phenotype		
Bacteria	**Total**	**ZTI-01**	**P-T**
Acinetobacter baumannii-calcoaceticus species complex	1/2 (50%)	1/2 (50%)	0/0 (0)
Klebsiella oxytoca	1/4 (25%)	0/2 (0)	1/2 (50%)
Klebsiella pneumoniae	3/54 (6%)	2/28 (7%)	1/26 (4%)
Proteus mirabilis	4/13 (31%)	2/9 (56%)	2/4 (50%)
Pseudomonas aeruginosa	7/17 (41%)	2/8 (25%)	5/9 (56%)

Table 5. Aminoglycoside-R Phenotype by Treatment Group, n/N (%)

	Animoglycoside-R Phenotype		
Bacteria	**Total**	**ZTI-01**	**P-T**
Acinetobacter baumannii-calcoaceticus species complex	1/2 (50%)	1/2 (50%)	0/0 (0)
Enterobacter cloacae species complex	6/12 (50%)	5/9 (56%)	1/3 (33%)
Escherichia coli	19/292 (7%)	7/149 (5%)	12/143 (8%)
Klebsiella oxytoca	1/4 (25%)	0/2 (0)	1/2 (50%)
Klebsiella pneumoniae	12/54 (22%)	9/28 (32%)	10/26 (38%)
Proteus mirabilis	6/13 (46%)	2/9 (22%)	4/4 (100%)
Pseudomonas aeruginosa	12/17 (71%)	6/8 (75%)	6/9 (67%)
Morganella morganii	1/1 (100%)	0/0 (0)	1/1 (100%)

Table 6. MDR3+ Phenotype by Treatment Group, n/N (%)

	MDR Phenotype		
Bacteria	**Total**	**ZTI-01**	**P-T**
Acinetobacter baumannii-calcoaceticus species complex	1/2 (50%)	1/2 (50%)	0/0 (0)
Enterobacter cloacae species complex	7/12 (58%)	6/9 (67%)	1/3 (33%)
Escherichia coli	30/292 (10%)	13/149 (9%)	17/143 (12%)
Klebsiella oxytoca	1/4 (25%)	0/2 (0)	1/2 (50%)
Klebsiella pneumoniae	19/54 (35%)	11/28 (39%)	8/26 (331%)
Proteus mirabilis	5/13 (38%)	1/9 (11%)	4/4 (100%)
Pseudomonas aeruginosa	13/17 (76%)	7/8 (88%)	6/9 (67%)
Morganella morganii	1/1 (100%)	0/0 (0)	1/1 (100%)

CR: Carbapenem-resistant; ESBL: extended spectrum beta-lactamase; MDR: multidrug-resistant; m-MITT: microbiologic modified intent-to-treat

Conclusion

- A high incidence of ZEUS cUTI/AP patients were infected with various resistant phenotypes. ESBL phenotypes were most common, followed by MDR
- The treatment arms were balanced with respect to number and type of isolates bearing phenotypic resistance
- Clinical cure rates were high across treatment groups and the eradication rates numerically favored ZTI-01
- While overall failures were uncommon among patients infected with these resistant pathogens, they were more common in the P-T group and driven by higher rates of microbiological persistence in this group; the high rates of MDR, including ESBL and CR phenotypes, may in part explain this observation
- If approved in the US, ZTI-01 may provide a new IV therapeutic option with a unique MOA for treating cUTI patients, including those with resistant Gram-negative infections

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ZEUS
ZTI-01 Efficacy and Safety