720. Activity of Cefiderocol Against Gram-Negative Clinical Isolates (P1P-TAZ) in Adults With Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP): ZEUS Study Outcomes in Patients With Reduced Study Drug Susceptibility

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Background. FOS is being pursued for US registration in cUTI/AP and efficacy of P1P-TAZ was demonstrated in the nonderestricted ZEUS trial in hospitalized patients with cUTI/AP. Although FOS resistance has been observed in several in vitro studies, resistance rates in clinical settings have remained relatively stable despite >40 years of clinical use of FOS outside of the United States. Here we report outcomes in patients who developed reduced susceptibility to study drug (FOS or P1P-TAZ) after enrollment in ZEUS.

Methods. Patients received IV FOS 6 g q8h or P1P-TAZ 4.5 g q7d for 7 days (no oral switch allowed). The primary endpoint was overall success (clinical cure + microbiologic eradication) in microbiologic modified intent-to-treat (m-MITT) population at test-of-cure (TOC; Day 10–21). Reduced susceptibility to FOS or P1P-TAZ was defined as a ≥4-fold increase in baseline in minimum inhibitory concentration (MIC) at Day 5, end of treatment (EOT; Day 7–8), or late follow-up (L FU; Day 26 ± 2). Microbiologic eradication/persistence of baseline and postbaseline pathogens was confirmed post hoc by pulsed-field gel electrophoresis (PFGE).

Results. In all m-MITT patients, overall success clinical cure/microbiologic eradication rates (with PFGE) at TOC were 68.0/90.8/70.7% (FOS) and 57.3/96/60.1% (P1P-TAZ). Reduced study drug susceptibility was identified in 7/184 (3.8%) patients on FOS and 8/178 (4.5%) P1P-TAZ patients; all had monomicrobial infections (Table 1). Of these, almost all were aged ≥250 years (93%), male (73%), white (100%), and had a screening diagnosis of UTI (93%). At TOC, 77% FOS patients and 78% P1P-TAZ patients had microbiologic persistence but all patients were clinical cures; these responses were all sustained through LFU (Table 1).

Conclusion. In the ZEUS study, few patients had urine isolates with reduced postbaseline susceptibility to either FOS or P1P-TAZ. No trend was observed in isolate species associated with decreased susceptibility to FOS or P1P-TAZ, including Enterobacteriaceae species and Pseudomonas aeruginosa. Despite microbiologic persistence at TOC in a small number of patients, all of these patients were clinical cures and sustained cures at L FU.

Table 1. Summary of Outcomes in Patients With Reduced Study Drug Susceptibility (m-MITT population)

| Treatment Group | Patient | Pathogen | Baseline MIC (µg/mL) | Fold Change | Clinical | Microbiologic | Overall |
|-----------------|---------|----------|---------------------|-------------|----------|---------------|---------|
| FOS             | 1       | Pseudomonas aeruginosa | 0.5 | 0.5 | Clinical | Microbiologic | Overall |
| P1P-TAZ         | 2       | Escherichia coli | 0.5 | 0.5 | Clinical | Microbiologic | Overall |
| P1P-TAZ         | 3       | K. pneumoniae | 0.5 | 0.5 | Clinical | Microbiologic | Overall |

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721. In Vivo Activity of Cefiderocol Against Gram-Negative Clinical Isolates From New York City

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Background. Multi-drug-resistant Gram-negative bacteria have become a serious problem in hospitals worldwide. Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against a wide range of carbapenem- and ESBL-producing bacteria. We tested the activity of CFDC against (1) a recent collection of clinical isolates and (2) a separate collection of carbapenem-resistant isolates gathered from NYC hospitals.

Methods. Susceptibility testing was performed on isolates of E. coli, K. pneumoniae, Enterobacter spp., P. aeruginosa, and A. baumannii collected in 2017 from 7 hospitals in Brooklyn, NY. Consecutive unique patient clinical isolates from all sources were collected for a three-month period. Testing was done on a collection of carbapenem-resistant isolates from a similar surveillance study conducted in 2013–2014. MICs were determined via broth microdilution. 100% of A. baumannii (including 8 with blaoxa-23, 2 with blaOXA-31, and 1 with blaOXA-24) were susceptible to CFDC. For the collection of carbapenem-resistant isolates gathered in 2014–2015, 100% of K. pneumoniae (n = 111), 100% of P. aeruginosa (n = 130), and 90% of A. baumannii (n = 78) were susceptible to CFDC.

Conclusion. CFDC has excellent in vitro activity against Gram-negative clinical isolates from NYC, including a large collection of carbapenem-resistant Enterobacteriaceae, P. aeruginosa, and A. baumannii.

722. Pharmacokinetics (PK) and Safety of Lefamulin (LEF) After Single Intravenous Dose Administration in Subjects With Impaired Hepatic Function

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Background. Patients with chronic liver disease (CLD) have impaired immune function, are prone to community-acquired bacterial pneumonia (CABP), and experience greater morbidity/mortality and healthcare costs than CABP patients without CLD. Lefamulin pleuromutilin antibiotic (IV/oral) with primary liver elimination, was generally well tolerated and noninferior to moxifloxacin in two phase 3 studies of CABP patients.

Methods. In this open-label study, subjects were allocated to 1 of 3 groups based on hepatic impairment with a continuous Pugh score (A = 6; B = 7–9; C = ≥10). Subjects received a single 1-hour 150 mg LEF infusion. Blood and urine samples were collected predose and over a 48-hour period postdose for PK analysis. Plasma and urine were assayed for LEF and BC-8041 using validated assays. Safety assessments included treatment-emergent adverse events (TEAEs), labs, vital signs, and electrocardiograms.

Results. 27 subjects enrolled in and completed the study (n = 11, Normal; n = 8, Moderate; n = 8, Severe). Mean LEF and BC-8041 plasma concentration profiles were comparable across all hepatic function groups through the first 12 hours following the start of infusion. Subjects with hepatic impairment had slightly slower rates of elimination in the later elimination phases. LEF and BC-8041 exposures were not across all hepatic function groups (table). the majority of LEF and BC-8041 were excreted nonrenally. TEAEs were reported in 2 (18.2%) subjects in the Moderate group. Subjects received a single 1-hour 150 mg LEF infusion. Blood and urine samples were collected predose and over a 48-hour period postdose for PK analysis. Plasma and urine were assayed for LEF and BC-8041 using validated assays. Safety assessments included treatment-emergent adverse events (TEAEs), labs, vital signs, and electrocardiograms.

Disclosures. All authors: No reported disclosures.