720. Efficacy of Fosfomycin for Injection (FOS) vs. Piperacillin–Tazobactam (PIP-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. Safety and efficacy of FOS vs. PIP-TAZ were demonstrated in the noninferiority 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 PIP-TAZ) after enrollment in ZEUS.

Methods. Patients received IV FOS 6g q8h or PIP-TAZ 4.5g q8h 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 19–21). Reduced susceptibility to FOS or PIP-TAZ was defined as a ≥4-fold increase from baseline in minimum inhibitory concentration (MIC) at Day 5, end of treatment (EOT; Day 7–8), TOC, or late follow-up (LFU; 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 69.0/90.8/70.7% (FOS) and 57.3/91.6/60.1% (PIP-TAZ). Reduced study drug susceptibility was identified in 7/184 (3.8%) FOS and 8/178 (4.5%) PIP-TAZ patients; all had monomicrobial infections (Table 1). Of these patients, almost all were aged ≥50 years (93%), male (73%), white (100%), and had a screening diagnosis of cUTI (93%). At TOC, 7/7 FOS patients and 7/8 PIP-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 PIP-TAZ. No trend was observed in isolate species associated with decreased susceptibility to FOS or PIP-TAZ, including various *Enterobacteriaceae* species and *Pseudomonas aeruginosa*. Despite microbiologic persistence at TOC in a small number of patients, all of these patients were clinical cures at TOC and sustained cures at LFU.

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

Treatment Group Patient	Visit	Pathogen	Uropathogen Identity Based on Molecular Typing (With PFGE Analysis)			Responses at TOC/LFU (With PFGE Analysis)		
			Baseline MIC (µg/mL)	Post-Baseline MIC (µg/mL)	Fold Change†	Clinical	Microbiologic	Overall
FOS (n=7)								
1	LFU	*Pseudomonas aeruginosa*	64	>512	>8	C/SC	P/CP	F/F
2	LFU	*Escherichia coli*	0.5	64	128	C/SC	P/CP	F/F
3	Day 5	*Klebsiella pneumoniae*	4	32	8	C/SC	P/CP	F/F
4	Day 5, EOT, TOC, LFU	*Enterobacter cloacae* species complex	64	≥512	>8	C/SC	P/CP	F/F
5	EOT, TOC	*Pseudomonas aeruginosa*	64	>512	>8	C/SC	P/CP	F/F
6	TOC	*Pseudomonas aeruginosa*	64	>512	>8	C/SC	P/CP	F/F
7	EOT, TOC	*Klebsiella pneumoniae*	16	>512	>32	C/SC	P/CP	F/F
PIP-TAZ (n=8)								
8	TOC	*Escherichia coli*	1	4	4	C/SC	P/CP	F/F
9	TOC	*Klebsiella pneumoniae*	4	64	16	C/SC	P/CP	F/F
10	LFU	*Klebsiella pneumoniae*	1	4	4	C/SC	P/CP	F/F
11	TOC	*Escherichia coli*	16	>64	>4	C/SC	P/CP	F/F
12	LFU	*Klebsiella pneumoniae*	2	>64	>32	C/SC	E/R	S/F
13	LFU	*Klebsiella pneumoniae*	2	64	32	C/SC	P/CP	F/F
14	LFU	*Klebsiella pneumoniae*	8	32	4	C/SC	P/CP	F/F
15	TOC	*Escherichia coli*	2	8	4	C/SC	P/CP	F/F

C=cure; CP=continued persistence; E=eradication; EOT=end of treatment; F=failure; FOS=fosfomycin for injection; LFU=late follow-up; MIC=minimum inhibitory concentration; m-MITT=microbiologic modified intent to treat; P=persistence; PFGE=pulsed-field gel electrophoresis; PIP-TAZ=piperacillin-tazobactam; R=recurrence; S=success; SC=sustained cure; TOC=test-of-cure
*All randomized patients who received study drug and had ≥1 baseline Gram-negative pathogen from an appropriately collected pretreatment baseline urine or blood sample.
†Ratio of post-baseline MIC value to baseline MIC value.

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

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Background. Multidrug-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 carbapenemase- 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* gathered 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 also done on a collection of carbapenem-resistant isolates from a similar surveillance study conducted in 2013–2014. MICs were performed with iron-depleted cation-adjusted Mueller–Hinton broth for CFDC and agar dilution for other antibiotics according to CLSI methodology. The provisional CLSI breakpoint (≤4 µg/mL susceptible) was used for CFDC. Cephalosporin-resistant isolates were tested for common carbapenemases by PCR.

Results. The susceptibility results for CFDC and meropenem for the isolates gathered in 2017 are listed in the Table. All of the Enterobacteriacae were susceptible to CFDC including KPC-possessing *E. coli* (n = 4), *K. pneumoniae* (n = 20), and *Enterobacter* spp (n = 3). 99.6% of *P. aeruginosa* and 100% of *A. baumannii* (including 8 with bla_{OXA-23}, 2 with bla_{OXA-24}, and 1 with bla_{KPC}) were susceptible to CFDC. For the collection of carbapenem-resistant isolates gathered in 2013–14, 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*.

	MIC_{50}	MIC_{90}	Range	Percent susceptible
	µg/ml			
E. coli (n=1869)				
Meropenem	≤0.125	≤0.125	≤0.125 - 4	99.9%
Cefiderocol	0.125	0.5	≤0.03 - 2	100%
K. pneumoniae (n=518)				
Meropenem	≤0.125	≤0.125	≤0.125 - >8	96.5%
Cefiderocol	0.125	0.5	≤0.03 - 2	100%
Enterobacter spp. (n=172)				
Meropenem	≤0.125	≤0.125	≤0.125 - >8	97.6%
Cefiderocol	0.125	0.5	≤0.03 - 1	100%
P. aeruginosa (n=269)				
Meropenem	1	8	≤0.125 - >8	76%
Cefiderocol	0.25	0.5	≤0.03 - 8	99.6%
A. baumannii (n=46)				
Meropenem	8	>8	≤0.125 - >8	48%
Cefiderocol	0.25	1	0.06 - 4	100%

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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. LEF, a novel pleuromutilin antibiotic (IV/oral) with primary liver elimination, was generally well tolerated and noninferior to moxifloxacin in two phase 3 studies of adults with CABP. We investigated the PK and safety of LEF and its main metabolite, BC-8041, in subjects with hepatic impairment.

Methods. In this open-label study, subjects were allocated to 1 of 3 groups based on hepatic function level; Moderate (Child-Pugh score 7–9) or Severe subjects (Child-Pugh score ≥10) were matched (gender, age, and weight) to subjects in the Normal group (normal hepatic function, no liver cirrhosis). 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 similar across all hepatic function groups (table), and the majority of LEF and BC-8041 were excreted nonrenally. TEAEs were reported in 2 (18.2%) subjects in the Normal group, 2 (25%) in the Moderate group, and 1 (12.5%) in the Severe group. None of the TEAEs were serious or led to study drug discontinuation. No subject met Hy's law criteria. Within 4 hours postdose, the maximum mean change from baseline in the QTcF interval was 12.4, 19.2, and 14.1 msec in the Normal, Moderate, and Severe groups, respectively.

Conclusion. No dosage adjustment for LEF appears to be required when treating subjects with hepatic impairment. LEF was generally well tolerated in all subjects regardless of hepatic functional status.

Table. Mean (SD) Lefamulin and BC-8041 PK Parameters by Hepatic Functional Status Group

PK Parameter	Normal (n=11)	Moderate (n=8)	Severe (n=8)
Lefamulin			
C_{max}, ng/mL	2463 (403)	1746 (524)	1468 (328)
t_{max}, h	1.0 (0.2)	1.1 (0.2)	1.0 (0.0)
AUC, h•ng/mL	7615 (1554)	8233 (2286)	8938 (1640)
CL, L/h	20.5 (4.5)	19.6 (6.0)	17.4 (3.8)
$t_{1/2}$, h	11.5 (1.8)	13.6 (3.1)	17.5 (3.4)
BC-8041			
C_{max}, ng/mL	33.3 (9.7)	37.9 (41.2)	20.4 (12.3)
t_{max}, h	1.3 (0.1)	1.5 (0.3)	1.4 (0.1)
AUC, h•ng/mL	303 (116)	499 (463)	647 (441)
$t_{1/2}$, h	14.4 (4.5)	24.4 (20.0)	33.8 (14.8)

AUC=area under the plasma concentration-time curve extrapolated through infinity; CL=systemic clearance (observed) estimated using AUC; C_{max}=maximum observed concentration; PK=pharmacokinetic; SD=standard deviation; $t_{1/2}$=terminal elimination half-life; t_{max}=time of maximum observed concentration.

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723. Synergistic Effect of Cefiderocol Combined With Other Antibiotics Against Cefiderocol High MIC Isolates From the Multi-National SIDERO-WT Studies

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Background. Cefiderocol (CFDC) is a novel siderophore cephalosporin, which demonstrated potent activity at MICs of ≤4 µg/mL against ≥99% of the Gram-negative clinical isolates, including carbapenem-resistant Enterobacteriaceae spp. and nonfermenters in a multi-national SIDERO-WT study. In this study, we evaluated the synergistic effects of CFDC combined with other antibiotics against isolates with high CFDC MIC (i.e., ≥8 µg/mL).

Methods. The combination effects of CFDC and other antibiotics were evaluated by several ***Methods.*** (1) broth microdilution method in the presence of β-lactamase inhibitors avibactam and/or picolinic acid, (2) checkerboard method or time-kill assays in the presence of amikacin, meropenem, colistin, ceftazidime/avibactam or ceftolozane/tazobactam, (3) chemostat model reproducing humanized antibiotic exposures. Iron-depleted cation-adjusted Mueller–Hinton broth was used as the standard medium for CFDC as recommended by the Clinical Laboratory and Standard Institute (CLSI).

Results. A total of 39 CFDC nonsusceptible (NS) isolates were found among 9,205 isolates in the SIDERO-WT-2014 study. Among 28 CFDC-NS *A. baumannii*, 25 isolates were PER producers mainly from Russia and Turkey. Among 9 CFDC-NS Enterobacteriaceae, 5 isolates were NDM-producers from Turkey. Against all 34 non-NDM-producing isolates, the addition of avibactam significantly reduced CFDC MIC. The combination of CFDC with ceftazidime/avibactam and ceftolozane/tazobactam also showed strong synergy against these isolates, presumably due to the effect of β-lactamase inhibition. In addition, CFDC had synergistic effects with meropenem against 42.9% (9 of 21) of carbapenem NS isolates. Against the CFDC-NS isolates, including PER-producing *A. baumannii*, the combination of CFDC and meropenem under humanized drug exposures (chemostat model) showed synergistic effect leading to sustained eradication of bacteria over 24 hours.

Conclusion. Even against the non-NDM-producing CFDC-NS isolates, including PER-producing *A. baumannii*, the combinations of CFDC with ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem were effective due to synergistic effects. The mechanism of CFDC-meropenem synergy against *A. baumannii* is not known.

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724. The *In Vitro* Activity of Gepotidacin and Comparator Agents Against Anaerobic Bacterial Isolates

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Background. Gepotidacin (GSK2140944) is a first in class novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in clinical development for the treatment of gonorrhea and uncomplicated UTI (acute cystitis). Gepotidacin selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism not utilized by any currently approved therapeutic agent and demonstrates *in vitro* activity against most target pathogens resistant to established antibacterials, including fluoroquinolones. This study assessed the *in vitro* activity of gepotidacin and comparators against a collection of 649 Gram-positive and Gram-negative anaerobic bacterial clinical isolates.

Methods. A total of 649 clinically significant Gram-negative (333) and Gram-positive (316) anaerobic clinical isolates previously collected and frozen at –70°C were tested. Isolates came from North America (315/48.5%) and Europe (334/51.5%) and were collected between 2000 and 2017. Minimum inhibitory concentrations (MICs) for gepotidacin and 6 comparators were determined by agar dilution (AD) for all isolates, and by both AD and broth microdilution (BMD) for *Bacteroides* spp. according to CLSI guidelines (CLSI M11-A8). Most *Lactobacillus* spp. tested in this study require anaerobic conditions for growth and were tested by anaerobic AD.

Results. The *in vitro* activity results of gepotidacin and comparators are shown in the table below. The gepotidacin MIC_{90} for all Gram-negative anaerobic isolates tested in this study was 4 µg/mL and for the comparators tested was as follows: ceftriaxone 512 µg/mL, clindamycin >8 µg/mL, imipenem 0.5 µg/mL, metronidazole 2 µg/mL, moxifloxacin 8 µg/mL and piperacillin–tazobactam 16 µg/mL. Gepotidacin had the lowest MIC_{90} (2 µg/mL) for the Gram-positive anaerobic isolates compared with the other antibiotics tested, with the exception of metronidazole (MIC_{90} = 0.5 µg/mL).

Conclusion. Gepotidacin showed *in vitro* activity against a collection of 649 anaerobic Gram-negative and Gram-positive clinical isolates, with an MIC_{90} value against all Gram-negative anaerobic isolates of 4 µg/mL, and against all Gram-positive anaerobic isolates of 2 µg/mL.

Organism (n)	MIC_{90}(% susceptible)						
	GEP	CRO	CLI	IMI	MET	MOX	PTZ
All Gram-negative anaerobes (333)	4 (na)	512 (58.6)	> 8 (73.3)	0.5 (99.1)	2 (98.5)	8 (78.1)	16 (97.6)
Bacteroides fragilis group (191)	4 (na)	>512 (34.0)	>8 (64.4)	1 (99.0)	1 (100)	8 (71.7)	8 (99.0)
All Gram-positive anaerobes (225)	2 (na)	256 (46.2)	> 8 (66.2)	8 (87.6)	0.5 (98.7)	> 8 (68)	16 (100)
Lactobacillus spp. (91)	1 (na)	64 (na)	4 (na)	2 (na)	> 16 (na)	4 (na)	4 (na)
Clostridioides difficile (100)	2 (na)	128 (1.0)	>8 (37.0)	8 (72.0)	1 (100)	>8 (56.0)	8 (100)
Peptostreptococcus anaerobius (26)	0.03 (na)	≤8 (100)	>8 (88.0)	2 (100)	0.5 (100)	8 (72.0)	16 (100)

MIC_{90} in µg/mL; GEP, gepotidacin; CRO, ceftriaxone; CLI, clindamycin; IMI, imipenem; MET, metronidazole; MOX, moxifloxacin; PTZ, piperacillin-tazobactam (tazobactam tested as a fixed 4 µg/mL); na, no breakpoints available

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725. WCK 5222 (Cefepime/Zidebactam): An *In Vitro* Assessment of Activity Compared with Current Dual-Antibiotic Options Against Multidrug-Resistant *Pseudomonas aeruginosa*

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Background. *Pseudomonas aeruginosa* (PSA) is an opportunistic pathogen known to cause complications in critically ill patients worldwide. In those at risk of infection with multidrug-resistant strains (MDR-PSA), dual antibiotic therapy is often considered. However, this practice may contribute to rising resistance rates and poor outcomes if empirical selection is suboptimal. WCK 5222 (cefepime/zidebactam), a novel β-lactam/β-lactam enhancer, may offer a solution.

Methods. Minimum inhibitory concentrations (MICs) were determined for WCK 5222, amikacin (AMK), fosfomycin (FOF), cefepime (FEP), ceftolozane/tazobactam (C/T), and meropenem (MEM) against 18 clinical PSA isolates using gradient diffusion strip (GDS) methods. Activities of FEP, C/T, and MEM in combination with AMK and FOF were assessed using GDS for isolates nonsusceptible to the β-lactam (MICs >8 mg/L, >4/4 mg/L, and >2 mg/L, respectively). Synergy was defined as a fractional inhibitory concentration index ≤ 0.5. Instances of restored β-lactam susceptibility when tested in combination were compared with the proportion of WCK 5222 MICs ≤ 8 mg/L.

Results. WCK 5222 MICs ranged from 2 to 32 mg/L (MIC_{50}, 8 mg/L). Rates of susceptibility were: AMK (67%), FOF (44%, MIC ≤ 64 mg/L), FEP (6%), C/T (33%), MEM (0%). Combinations with C/T most frequently demonstrated synergy (C/T-FOF, 42%; C/T-AMK, 33%) and restored C/T susceptibility was observed in 42% of assessments with FOF and in 50% with AMK. For FEP combinations, synergy was observed in 29% and 18% of assessments with FOF and AMK, respectively, with restored susceptibility in 6% for both combinations. Synergy occurred in 11% and 6% of assessments of MEM with FOF and AMK, respectively, with zero instances of restored susceptibility. In total, β-lactam susceptibility was restored in 14% (13/94) of combinations compared with 78% (14/18) of WCK 5222 MICs ≤ 8 mg/L.

Conclusion. In a selection of MDR-PSA isolates that included carbapenem- and C/T-resistant strains, WCK 5222 MICs ≤ 8 mg/L (cefepime susceptible) were observed more frequently than restoration of susceptibility in select β-lactams in combination with FOF or AMK. WCK 5222 monotherapy may offer enhanced coverage of MDR-PSA over empirically selected combination therapies.

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726. APX001 (Fosmanogepix) Is Effective in an Immunosuppressed Mouse Model of *Rhizopus oryzae* Infection

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