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P1172 Cefepime-zidebactam (WCK-5222) activity when tested against Gram-negative organisms isolated from patients hospitalised in Europe and the Asia-Pacific region in 2018

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Background: Zidebactam, a bicyclo-acyl hydrazide, is a β-lactam-enhancer with a dual mechanism of action involving selective and high binding affinity to gram-negative penicillin-binding protein (PBP) 2 and β-lactamase inhibition. Cefepime-zidebactam is in clinical development at 2g/1g q8 hours dosage. We evaluated the *in vitro* activity of cefepime-zidebactam against contemporary clinical isolates from Europe and the Asia-Pacific region (APAC).

Materials/methods: A total of 4,996 isolates were collected by the 2018 SENTRY Antimicrobial Surveillance Program from medical centres in Europe (n=4,080; 29 centres in 14 nations) and APAC (n=916; 10 centres in 6 nations). The collection included 3,939 Enterobacteriaceae and 1,057 non-fermentative gram-negative bacilli (NF-GNB). Susceptibility testing was performed in a central laboratory by a reference broth microdilution method against cefepime-zidebactam (1:1 ratio) and comparators. Cefepime susceptible breakpoint of ≤8mg/L (CLSI, high dose) was applied for cefepime-zidebactam for comparison purposes only. Moreover, a cefepime-zidebactam susceptible breakpoint of ≤64mg/L has been proposed based on pharmacokinetic/pharmacodynamic target attainment and was applied for NF-GNB. When available, EUCAST breakpoints were applied for comparators.

Results: Cefepime-zidebactam was very active against Enterobacteriaceae with $MIC_{50/90}$ values of 0.03/0.12 mg/L in Europe and APAC, and the highest MIC values of 8 mg/L in Europe and 2mg/L in APAC (Table), and retained good activity against multidrug-resistant (n=632; $MIC_{50/90}$, 0.12/1 mg/L), extensively drug-resistant (n=88; $MIC_{50/90}$, 1/2mg/L), and carbapenem-resistant (CRE; n=92; $MIC_{50/90}$, 1/2mg/L) Enterobacteriaceae. The most active comparators against Enterobacteriaceae were ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5mg/L; 99.2% susceptible [S]), the carbapenems (meropenem $MIC_{50/90}$, 0.03/0.06mg/L; 97.6%S), and amikacin ($MIC_{50/90}$, 2/4mg/L; 97.0%S). Only 69.6% of CRE isolates were ceftazidime-avibactam-susceptible. Cefepime-zidebactam was also very active against *Pseudomonas aeruginosa* (n=849, $MIC_{50/90}$, 1/4mg/L overall), and retained activity against meropenem-nonsusceptible isolates (n=223; $MIC_{50/90}$, 4/8mg/L; 97.3% inhibited at ≤8mg/L). Cefepime-zidebactam inhibited 38.5/99.3% of *Acinetobacter* spp. ($MIC_{50/90}$, 16/32mg/L) and 82.2/100.0% of *Stenotrophomonas maltophilia* ($MIC_{50/90}$, 4/16mg/L) at ≤8/≤64 mg/L.

Conclusions: Cefepime-zidebactam demonstrated potent *in vitro* activity against gram-negative bacilli isolates collected in European and APAC medical centres in 2018, including multidrug-resistant Enterobacteriaceae, meropenem-nonsusceptible *P. aeruginosa*, and *S. maltophilia*. These *in vitro* results support further development of cefepime-zidebactam for treatment of systemic gram-negative infections.

Organism / Geographic region (no. tested)	Cumulative % inhibited at cefepime-zidebactam MIC (mg/L) of:												
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Enterobacteriaceae													
Europe (3,234)	8.5	54.5	77.7	90.2	96.1	97.8	98.8	99.8	99.9	100.0			
APAC (705)	4.8	54.2	77.0	91.9	96.9	99.4	99.9	100.0					
P. aeruginosa													
Europe (684)	0.3	0.6	0.6	1.2	3.2	11.8	49.0	71.5	90.9	99.3	99.9	100.0	
APAC (165)			1.2	1.8	4.8	16.4	64.2	83.0	96.4	98.8	100.0		
Acinetobacter spp. (135)			1.5	3.0	5.2	5.9	8.9	16.3	32.6	38.5	70.4	93.3	99.3
S. maltophilia (73)							1.4	12.3	57.5	82.2	94.5	98.6	100.0