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WCK 5222 (Cefepime-Zidebactam) Antimicrobial Activity Tested against Enterobacteriaceae Clinical Isolates Collected Worldwide (2015)

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Amended Abstract*

Background: Zidebactam (ZID), a bicyclo-acyl hydrazide, is a β-lactam-enhancer with a dual mechanism of action involving selective and high binding affinity to Gram-negative PBP2 and β-lactamase inhibition. We evaluated the *in vitro* activity of cefepime (FEP) combined with ZID against contemporary clinical isolates of Enterobacteriaceae (ENT).

Methods: 5,946 isolates from USA (2,172), Europe (2,485), Asia-Pacific (882) and Latin America (407) were collected in 2015 by the SENTRY Antimicrobial Surveillance Program and susceptibility (S) tested by a reference broth microdilution method against FEP-ZID (1:1 and 2:1 ratios) and comparator agents.

Results: FEP-ZID was the most active compound with $MIC_{50/90}$ of ≤0.03/0.12 and 0.06/0.25 µg/mL and >99.9% inhibited at ≤4 (1:1 ratio) and ≤8 µg/mL (2:1). Amikacin ($MIC_{50/90}$, 2/4 µg/mL; 98.0% S) and meropenem (MEM; $MIC_{50/90}$, 0.03/0.06 µg/mL; 97.2% S; Table) were also very active. FEP-ZID was active against individual ENT species ($MIC_{50/90}$, ≤0.03-0.06/≤0.03-0.5 µg/mL [1:1 ratio]) and retained potent activity against MEM-non-S *K. pneumoniae* (KPN; $MIC_{50/90}$, 1/4 µg/mL; 99.3% inhibited at ≤8/8 µg/mL [1:1]) and ceftazidime-non-S *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.5 µg/mL; highest MIC, 4/4 µg/mL [1:1]). FEP-ZID activity was consistent among geographic regions and only 1 isolate, a KPN from Turkey with a MIC of 64 µg/mL, showed MIC values of >8 µg/mL (1:1 ratio). S rates for MEM among KPN were lower in Latin America (70.9%) compared to the other regions (87.6-94.7%).

Conclusion: FEP-ZID (WCK 5222) was very active against this worldwide collection of ENT, including isolates resistant to broad-spectrum cephalosporins and/or carbapenems. These results support the further clinical development of WCK 5222.

Organism (n)	MIC_{50}/MIC_{90} (% susceptible[a])			
	FEP-ZID (1:1)	FEP	PIP-TAZ[b]	Meropenem
Enterobacteriaceae (5,946)	≤0.03/0.12 (99.6/>99.9)[c]	0.06/16 (84.3)	2/32 (88.7)	0.03/0.06 (97.2)
E. coli (2,494)	≤0.03/0.12 (100.0/100.0)[c]	0.06/16 (84.2)	2/8 (93.6)	≤0.015/0.03 (99.7)
Klebsiella spp. (1,517)	≤0.03/0.5 (98.7/99.9)[c]	0.06/>64 (74.6)	2/>64 (79.5)	0.03/0.5 (91.0)
MEM-NS KPN (134)	1/4 (85.1/99.3)[c]	>64/>64 (0.7)	>64/>64 (2.3)	32/>32 (0.0)
COL-NS KPN (54)	1/4 (87.0/100.0)[c]	>64/>64 (9.3)	>64/>64 (22.2)	16/>32 (31.5)
Enterobacter spp. (752)	≤0.03/0.25 (99.7/100.0)[c]	0.06/4 (87.2)	2/64 (79.1)	0.03/0.06 (97.9)
P. mirabilis (383)	0.06/0.12 (100.0/100.0)[c]	0.06/2 (91.4)	≤0.5/1 (99.7)	0.06/0.12 (99.7)
S. marcescens (282)	0.06/0.12 (100.0/100.0)[c]	0.06/0.25 (95.7)	2/8 (96.4)	0.06/0.06 (97.9)

a. According to CLSI breakpoints.
b. PIP-TAZ = piperacillin-tazobactam.
c. % inhibited at ≤2/≤8 µg/mL (for comparison purposes only).

* Abstract has been updated with results of additional isolates tested after its submission.

Introduction

Zidebactam, a bicyclo-acyl hydrazide ($C_{13}H_{21}N_5O_7S$ [**see poster 446; Figure 1**]), has a dual mechanism of action involving selective and high-affinity Gram-negative PBP2 binding and β-lactamase inhibition. Due to PBP2 binding, zidebactam demonstrates antibacterial activity against various Enterobacteriaceae and *Pseudomonas aeruginosa*. Cefepime is a parenteral fourth-generation oxyimino-cephalosporin that was initially approved by the United States Food and Drug Administration (US-FDA) in 1997. Cefepime has a broad-spectrum of activity against aerobic Gram-positive and Gram-negative bacteria, including *P. aeruginosa*. Clinical indications currently approved by the US-FDA for treatment with cefepime include moderate to severe pneumonia, complicated and uncomplicated urinary tract infections, complicated intra-abdominal infections, and uncomplicated skin and skin structure infections, as well as empiric therapy for febrile neutropenic patients.

Cefepime clinical breakpoints have recently (2014) been revised by the Clinical and Laboratory Standards Institute (CLSI) based on results from clinical and pharmacokinetic/pharmacodynamics (PK-PD) studies and contemporary MIC distributions. According to the current CLSI breakpoint criteria for Enterobacteriaceae published in the M100-S26 document, cefepime susceptible and resistant breakpoints are ≤2 and ≥16 µg/mL, respectively, and Enterobacteriaceae isolates with cefepime MIC of 4 and 8 µg/mL should be reported as "susceptible-dose dependent" (SDD). The SDD interpretative criteria essentially provides three susceptible breakpoints for cefepime according to the dosage, i.e. ≤2 µg/mL for 1g of cefepime q12 hours (low-dosage), ≤4 µg/mL for 1g q 8 hours or 2g q12 hours, and ≤8 µg/mL for 2g q8 hours (high-dosage).

Zidebactam combined with cefepime (WCK 5222) is under clinical development for treatment of Gram-negative infections (NCT02707107 and NCT02674347; www.clinicaltrials.gov). We evaluated the *in vitro* activity of cefepime combined with zidebactam against a large worldwide collection of contemporary clinical isolates of Enterobacteriaceae.

Methods

Susceptibility testing: MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology as described in CLSI document M07-A10 (2015). The combination of cefepime-zidebactam (WCK 5222; two ratio concentrations, 1:1 and 2:1), both compounds alone, and various comparator agents were tested in 96-well, frozen-form panels produced by JMI Laboratories (North Liberty, Iowa, USA). Quality control (QC) isolates were tested daily and the inoculum density was monitored by colony counts. QC ranges and interpretive criteria for the comparator compounds were as published in CLSI M100-S26 (2016). The sponsor provided available MIC information for cefepime-zidebactam and zidebactam alone tested against the listed QC strains. The tested QC strains included the following: *Escherichia coli* ATCC 25922, ATCC 35218 and NCTC 13353, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-1705 and *Pseudomonas aeruginosa* ATCC 27853.

Organism collection: A total of 5,946 Enterobacteriaceae isolates collected as part of a global surveillance program were tested. All isolates were collected in 2015, except those from China (194 isolates), which were collected in 2013. Isolates were consecutively collected from 134 medical institutions worldwide, including Europe (EU; 2,485 isolates from 38 medical centers), United States (USA; 2,172 isolates from 64 medical centers), Latin America (LA; 407 isolates from eight medical centers), Asia-West Pacific (APAC) region (excluding China, 688 isolates from 14 medical centers), and China (194 isolates from 10 medical centers).

Results

- Cefepime-zidebactam was the most active compound with $MIC_{50/90}$ of ≤0.03/0.12 (1:1) and 0.06/0.25 µg/mL (2:1), and ≥99.9% inhibited at ≤4/4 µg/mL (1:1 ratio) and ≤8/4 µg/mL (2:1 ratio; **Tables 1** and **2**). Only one isolate showed a cefepime-zidebactam (1:1) MIC >8 µg/mL, a *K. pneumoniae* isolated from a patient with a urinary tract infection in a hospital located in Ankara, Turkey.
- Cefepime-zidebactam 1:1 ratio was generally 2-fold more active than cefepime-zidebactam 2:1 ratio, and zidebactam alone exhibited variable activity ($MIC_{50/90}$, 0.12/>64 µg/mL) when tested against Enterobacteriaceae (**Table 2**).
- Overall, *E. coli* ($MIC_{50/90}$, 0.12/0.12 µg/mL) and *Citrobacter* spp. ($MIC_{50/90}$, 0.12/0.5 µg/mL) isolates exhibited low zidebactam MIC values, whereas *P. mirabilis*, indole-positive Proteeae and *S. marcescens* showed much higher zidebactam MIC results (MIC_{50}, >64 µg/mL). Among *Klebsiella* spp. ($MIC_{50/90}$, 0.5/>64 µg/mL) and *Enterobacter* spp. ($MIC_{50/90}$, 0.12/>64 µg/mL) isolates zidebactam MIC values ranged from ≤0.03 to >64 µg/mL, and 66.3 and 83.4% of isolates were inhibited at ≤8 µg/mL of zidebactam, respectively (**Table 2**).
- Amikacin ($MIC_{50/90}$, 2/4 µg/mL; 98.0% susceptible) and meropenem ($MIC_{50/90}$, 0.03/0.06 µg/mL; 97.2% susceptible) were also very active overall, whereas cefepime ($MIC_{50/90}$, 0.06/16 µg/mL) and gentamicin ($MIC_{50/90}$, ≤1/>8 µg/mL) where active against 84.3% and 85.8% of Enterobacteriaceae isolates at the respective susceptible breakpoints (**Table 3**).
- Cefepime-zidebactam was active against individual Enterobacteriaceae species ($MIC_{50/90}$, ≤0.03-0.06/≤0.03-0.5 µg/mL [1:1 ratio]) and retained potent activity against meropenem-non-susceptible *K. pneumoniae* ($MIC_{50/90}$, 1/4 µg/mL; 99 .3% inhibited at ≤8/8 µg/mL) and ceftazidime-non-susceptible *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.5 µg/mL; highest MIC, 4/4 µg/mL; **Table 1**).
- Cefepime-zidebactam (1:1 and 2:1 ratios) activity was consistent among geographic regions with >99.9 to 100.0% of isolates inhibited at ≤8/8 µg/mL and 99.0 to 100.0% inhibited at ≤2/2 µg/mL (1:1 ratio; **Tables 1** and **4**).

Table 1. Summary of cefepime-zidebactam (1:1) activity against Enterobacteriaceae isolates included in this study.

Organisms	N	MIC (µg/mL)			% inhibited at ≤8/8 µg/mL[a]
		Range	50%	90%	
Enterobacteriaceae	5,946	≤0.03 to 64	≤0.03	0.12	>99.9
E. coli	2,494	≤0.03 to 2	≤0.03	0.12	100.0
MEM-NS[a]	7	0.12 to 2	0.25	--	100.0
Klebsiella spp.	1,517	≤0.03 to 64	≤0.03	0.5	99.9
K. pneumoniae	1,275	≤0.03 to 64	≤0.03	0.5	99.9
MEM-NS[b]	134	0.12 to 64	1	4	99.3
Colistin-NS[c]	54	≤0.03 to 8	1	4	100.0
K. oxytoca	234	≤0.03 to 1	≤0.03	0.06	100.0
P. mirabilis	383	≤0.03 to 0.5	0.06	0.12	100.0
Enterobacter spp.	752	≤0.03 to 4	≤0.03	0.25	100.0
E. cloacae	569	≤0.03 to 4	0.06	0.25	100.0
CAZ-NS[d]	169	≤0.03 to 4	0.12	0.5	100.0
M. morganii	117	≤0.03 to 0.25	≤0.03	0.06	100.0
Citrobacter spp.	259	≤0.03 to 1	≤0.03	0.12	100.0
C. koseri	101	≤0.03 to 0.06	≤0.03	≤0.03	100.0
C. freundii	147	≤0.03 to 1	≤0.03	0.12	100.0
S. marcescens	282	≤0.03 to 1	0.06	0.12	100.0
P. vulgaris	34	≤0.03 to 0.12	0.06	0.06	100.0
Providencia spp.	56	≤0.03 to 0.5	≤0.03	0.12	100.0
Other species	52	≤0.03 to 0.25	≤0.03	0.12	100.0

a. For comparison purpose only.
b. Meropenem-non-susceptible (MEM-NS); MIC, ≥2 µg/mL.
c. Colistin-non-susceptible; MIC, ≥4 µg/mL (EUCAST).
d. Ceftazidime-non-susceptible (CAZ-NS); MIC, ≥8 µg/mL.

Table 2. Antimicrobial activity of cefepime-zidebactam (1:1 and 2:1), cefepime, and zidebactam tested against the main organisms and organism groups of isolates included in this study.

Organisms / antimicrobials	No. of isolates at MIC (µg/mL; cumulative %)													MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64		
Enterobacteriaceae (5,946)															
Cefepime-zidebactam 1:1	3338 (56.1%)	1347 (78.8%)	759 (91.6%)	275 (96.2%)	100 (97.9%)	67 (99.0%)	38 (99.6%)	17 (99.9%)	4 (>99.9%)	0 (>99.9%)	0 (>99.9%)	1 (100.0%)		≤0.03	0.12
Cefepime-zidebactam 2:1	2817 (47.4%)	1423 (71.3%)	684 (82.8%)	575 (92.5%)	244 (96.6%)	88 (98.1%)	58 (99.0%)	38 (99.7%)	16 (99.9%)	2 (>99.9%)	0 (>99.9%)	1 (100.0%)		0.06	0.25
Cefepime	2568 (43.2%)	1372 (66.3%)	510 (74.8%)	220 (78.5%)	125 (80.6%)	117 (82.6%)	102 (84.3%)	107 (86.1%)	109 (88.0%)	140 (90.3%)	135 (92.6%)	137 (94.9%)	304 (100.0%)	0.06	16
Zidebactam	8 (0.1%)	1082 (18.4%)	2311 (57.4%)	526 (66.2%)	222 (70.0%)	93 (71.5%)	49 (72.4%)	39 (73.0%)	34 (73.6%)	35 (74.2%)	78 (75.5%)	101 (77.2%)	1352 (100.0%)	0.12	>64
***Escherichia coli* (2,494)**															
Cefepime-zidebactam 1:1	1572 (63.0%)	539 (84.6%)	325 (97.7%)	48 (99.6%)	6 (99.8%)	1 (99.9%)	3 (100.0%)							≤0.03	0.12
Cefepime-zidebactam 2:1	1298 (52.0%)	579 (75.3%)	293 (87.0%)	267 (97.7%)	49 (99.7%)	4 (99.8%)	2 (99.9%)	2 (100.0%)						≤0.03	0.25
Cefepime	1147 (46.0%)	564 (68.6%)	184 (76.0%)	85 (79.4%)	50 (81.4%)	35 (82.8%)	36 (84.2%)	49 (86.2%)	52 (88.3%)	67 (91.0%)	57 (93.3%)	69 (96.0%)	99 (100.0%)	0.06	16
Zidebactam	5 (0.2%)	897 (36.2%)	1379 (91.5%)	109 (95.9%)	23 (96.8%)	4 (97.0%)	5 (97.2%)	4 (97.3%)	0 (97.3%)	1 (97.4%)	6 (97.6%)	6 (97.8%)	54 (100.0%)	0.12	0.12
meropenem-non-susceptible (MIC, ≥ 2 µg/mL) (7)															
Cefepime-zidebactam 1:1		0 (0.0%)	3 (42.9%)	2 (71.4%)	0 (71.4%)	0 (71.4%)	2 (100.0%)							0.25	--
Cefepime-zidebactam 2:1			0 (0.0%)	3 (42.9%)	2 (71.4%)	0 (71.4%)	0 (71.4%)	2 (100.0%)						0.5	--
Cefepime							0 (0.0%)	1 (14.3%)	1 (28.6%)	0 (28.6%)	0 (28.6%)	0 (28.6%)	5 (100.0%)	>64	--
Zidebactam		0 (0.0%)	3 (42.9%)	2 (71.4%)	0 (71.4%)	0 (71.4%)	1 (85.7%)	1 (100.0%)						0.25	--
***Klebsiella* spp. (1,517)**															
Cefepime-zidebactam 1:1	861 (56.8%)	216 (71.0%)	146 (80.6%)	124 (88.8%)	62 (92.9%)	56 (96.6%)	32 (98.7%)	15 (99.7%)	4 (99.9%)	0 (99.9%)	0 (99.9%)	1 (100.0%)		≤0.03	0.5
Cefepime-zidebactam 2:1	783 (51.6%)	207 (65.3%)	115 (72.8%)	137 (81.9%)	117 (89.6%)	60 (93.5%)	45 (96.5%)	36 (98.9%)	14 (99.8%)	2 (99.9%)	0 (99.9%)	1 (100.0%)		≤0.03	1
Cefepime	755 (49.8%)	179 (61.6%)	99 (68.1%)	37 (70.5%)	25 (72.2%)	19 (73.4%)	17 (74.6%)	20 (75.9%)	29 (77.8%)	47 (80.9%)	53 (84.4%)	55 (88.0%)	182 (100.0%)	0.06	>64
Zidebactam	0 (0.0%)	38 (2.5%)	466 (33.6%)	226 (48.6%)	109 (55.9%)	64 (60.1%)	37 (62.6%)	27 (64.4%)	29 (66.3%)	25 (68.0%)	51 (71.4%)	75 (76.4%)	355 (100.0%)	0.5	>64
meropenem-non-susceptible *K. pneumoniae* (MIC, ≥ 2 µg/mL) (134)															
Cefepime-zidebactam 1:1		0 (0.0%)	10 (7.5%)	18 (20.9%)	19 (35.1%)	37 (62.7%)	30 (85.1%)	15 (96.3%)	4 (99.3%)	0 (99.3%)	0 (99.3%)	1 (100.0%)		1	4
Cefepime-zidebactam 2:1			0 (0.0%)	13 (9.7%)	18 (23.1%)	20 (38.1%)	32 (61.9%)	34 (87.3%)	14 (97.8%)	2 (99.3%)	0 (99.3%)	1 (100.0%)		2	8
Cefepime						0 (0.0%)	1 (0.7%)	2 (2.2%)	3 (4.5%)	9 (11.2%)	10 (18.7%)	14 (29.1%)	95 (100.0%)	>64	>64
Zidebactam		0 (0.0%)	4 (3.0%)	13 (12.9%)	12 (22.0%)	18 (35.6%)	18 (49.2%)	12 (58.3%)	1 (59.1%)	2 (60.6%)	5 (64.4%)	5 (68.2%)	42 (100.0%)	4	>64
colistin-non-susceptible *K. pneumoniae* (MIC, ≥ 4 µg/mL) (54)															
Cefepime-zidebactam 1:1	2 (3.7%)	2 (7.4%)	4 (14.8%)	8 (29.6%)	10 (48.1%)	11 (68.5%)	10 (87.0%)	5 (96.3%)	2 (100.0%)					1	4
Cefepime-zidebactam 2:1	1 (1.9%)	4 (9.3%)	0 (9.3%)	2 (13.0%)	9 (29.6%)	13 (53.7%)	7 (66.7%)	12 (88.9%)	4 (96.3%)	2 (100.0%)				2	8
Cefepime	2 (3.7%)	2 (7.4%)	1 (9.3%)	0 (9.3%)	0 (9.3%)	0 (9.3%)	0 (9.3%)	0 (9.3%)	0 (9.3%)	0 (9.3%)	8 (24.1%)	6 (35.2%)	35 (100.0%)	>64	>64
Zidebactam	0 (0.0%)	1 (1.9%)	1 (3.8%)	4 (11.5%)	9 (28.8%)	4 (36.5%)	7 (50.0%)	2 (53.8%)	1 (55.8%)	0 (55.8%)	2 (59.6%)	1 (61.5%)	20 (100.0%)	4	>64
***Proteus mirabilis* (383)**															
Cefepime-zidebactam 1:1	144 (37.6%)	182 (85.1%)	42 (96.1%)	13 (99.5%)	2 (100.0%)									0.06	0.12
Cefepime-zidebactam 2:1	81 (21.1%)	218 (78.1%)	42 (89.0%)	26 (95.8%)	14 (99.5%)	2 (100.0%)								0.06	0.25
Cefepime	73 (19.1%)	211 (74.2%)	38 (84.1%)	6 (85.6%)	7 (87.5%)	8 (89.6%)	7 (91.4%)	8 (93.5%)	6 (95.0%)	7 (96.9%)	4 (97.9%)	1 (98.2%)	7 (100.0%)	0.06	2
Zidebactam		0 (0.0%)	7 (1.8%)	17 (6.3%)	4 (7.3%)	3 (8.1%)	2 (8.6%)	0 (8.6%)	1 (8.9%)	0 (8.9%)	4 (9.9%)	4 (11.0%)	341 (100.0%)	>64	>64
***Enterobacter* spp. (752)**															
Cefepime-zidebactam 1:1	376 (50.0%)	184 (74.5%)	103 (88.2%)	59 (96.0%)	20 (98.7%)	5 (99.3%)	3 (99.7%)	2 (100.0%)						≤0.03	0.25
Cefepime-zidebactam 2:1	300 (39.9%)	203 (66.9%)	87 (78.5%)	91 (90.6%)	47 (96.8%)	14 (98.7%)	8 (99.7%)	0 (99.7%)	2 (100.0%)					0.06	0.25
Cefepime	270 (35.9%)	185 (60.5%)	70 (69.8%)	45 (75.8%)	25 (79.1%)	34 (83.6%)	27 (87.2%)	26 (90.7%)	10 (92.0%)	16 (94.1%)	20 (96.8%)	12 (98.4%)	12 (100.0%)	0.06	4
Zidebactam	1 (0.1%)	71 (9.6%)	343 (55.2%)	121 (71.3%)	58 (79.0%)	18 (81.4%)	4 (81.9%)	8 (83.0%)	3 (83.4%)	7 (84.3%)	10 (85.6%)	11 (87.1%)	97 (100.0%)	0.12	>64
***Morganella morganii* (117)**															
Cefepime-zidebactam 1:1	90 (76.9%)	18 (92.3%)	6 (97.4%)	3 (100.0%)										≤0.03	0.06
Cefepime-zidebactam 2:1	84 (71.8%)	23 (91.5%)	5 (95.7%)	3 (98.3%)	2 (100.0%)									≤0.03	0.06
Cefepime	79 (67.5%)	23 (87.2%)	7 (93.2%)	1 (94.0%)	2 (95.7%)	2 (97.4%)	0 (97.4%)	0 (97.4%)	3 (100.0%)					≤0.03	0.12
Zidebactam		0 (0.0%)	2 (1.7%)	1 (2.6%)	1 (3.4%)	0 (3.4%)	0 (3.4%)	0 (3.4%)	0 (3.4%)	0 (3.4%)	1 (4.3%)	1 (5.1%)	111 (100.0%)	>64	>64
***Citrobacter* spp. (259)**															
Cefepime-zidebactam 1:1	200 (77.2%)	28 (88.0%)	19 (95.4%)	8 (98.5%)	3 (99.6%)	1 (100.0%)								≤0.03	0.12
Cefepime-zidebactam 2:1	184 (71.0%)	32 (83.4%)	23 (92.3%)	12 (96.9%)	7 (99.6%)	1 (100.0%)								≤0.03	0.12
Cefepime	159 (61.4%)	40 (76.8%)	14 (82.2%)	9 (85.7%)	7 (88.4%)	13 (93.4%)	11 (97.7%)	3 (98.8%)	2 (99.6%)	1 (100.0%)				≤0.03	1
Zidebactam	2 (0.8%)	74 (29.3%)	111 (72.2%)	39 (87.3%)	11 (91.5%)	0 (91.5%)	1 (91.9%)	0 (91.9%)	1 (92.3%)	2 (93.1%)	3 (94.2%)	1 (94.6%)	14 (100.0%)	0.12	0.5
***Serratia marcescens* (282)**															
Cefepime-zidebactam 1:1	16 (5.7%)	134 (53.2%)	105 (90.4%)	17 (96.5%)	6 (98.6%)	4 (100.0%)								0.06	0.12
Cefepime-zidebactam 2:1	14 (5.0%)	115 (45.7%)	104 (82.6%)	33 (94.3%)	6 (96.5%)	7 (98.9%)	3 (100.0%)							0.12	0.25
Cefepime	14 (5.0%)	132 (51.8%)	83 (81.2%)	30 (91.8%)	7 (94.3%)	2 (95.0%)	2 (95.7%)	1 (96.1%)	4 (97.5%)	2 (98.2%)	1 (98.6%)	0 (98.6%)	4 (100.0%)	0.06	0.25
Zidebactam			0 (0.0%)	4 (1.4%)	3 (2.5%)	1 (2.8%)	0 (2.8%)	0 (2.8%)	0 (2.8%)	0 (2.8%)	2 (3.5%)	1 (3.9%)	271 (100.0%)	>64	>64

Table 3. Activity of cefepime-zidebactam (1:1) and comparator antimicrobial agents when tested against 5,946 Enterobacteriaceae isolates.

Organisms/ antimicrobials	MIC_{50}	MIC_{90}	CLSI[a]	
			%S	%R
Enterobacteriaceae (5,946)				
Cefepime-zidebactam 1:1	≤0.03	0.12	-	-
Cefepime	0.06	16	84.3	12.0
Ceftazidime	0.25	32	82.2	16.4
Ceftriaxone	≤0.06	>8	77.6	21.6
Piperacillin-tazobactam	2	32	88.7	6.4
Meropenem	0.03	0.06	97.2	2.5
Levofloxacin	≤0.12	>4	78.4	18.9
Gentamicin	≤1	>8	85.8	13.1
Amikacin	2	4	98.0	1.3
Colistin	0.12	>8	81.9	18.1
***E. coli* (2,494)**				
Cefepime-zidebactam 1:1	≤0.03	0.12	-	-
Cefepime	0.06	16	84.2	11.7
Ceftazidime	0.25	16	85.7	12.4
Ceftriaxone	≤0.06	>8	81.0	18.8
Piperacillin-tazobactam	2	8	93.6	3.3
Meropenem	≤0.015	0.03	99.7	0.3
Levofloxacin	≤0.12	>4	69.6	27.2
Gentamicin	≤1	>8	84.4	15.2
Amikacin	2	4	99.4	0.2
Colistin	0.12	0.25	99.5	0.5
***Klebsiella* spp. (1,517)**				
Cefepime-zidebactam 1:1	≤0.03	0.5	-	-
Cefepime	0.06	>64	74.6	22.2
Ceftazidime	0.25	>32	73.7	25.0
Ceftriaxone	≤0.06	>8	71.8	27.7
Piperacillin-tazobactam	2	>64	79.5	14.8
Meropenem	0.03	0.5	91.0	7.9
Levofloxacin	≤0.12	>4	79.2	18.9
Gentamicin	≤1	>8	81.7	17.2
Amikacin	1	4	94.7	3.6
Colistin	0.12	0.5	96.2	3.8
***K. pneumoniae* meropenem-non-susceptible (134)**				
Cefepime-zidebactam 1:1	1	4	-	-
Cefepime	>64	>64	0.7	95.5
Ceftazidime	>32	>32	0.8	98.5
Ceftriaxone	>8	>8	0.0	100.0
Piperacillin-tazobactam	>64	>64	2.3	94.0
Meropenem	32	>32	0.0	88.1
Levofloxacin	>4	>4	7.5	89.5
Gentamicin	>8	>8	39.8	54.1
Amikacin	16	>32	54.1	28.6
Colistin	0.25	>8	71.4	28.6
***Proteus mirabilis* (383)**				
Cefepime-zidebactam 1:1	0.06	0.12	-	-
Cefepime	0.06	2	91.4	5.0
Ceftazidime	0.06	0.5	96.3	3.4
Ceftriaxone	≤0.06	>8	87.5	11.5
Piperacillin-tazobactam	≤0.5	1	99.7	0.0
Meropenem	0.06	0.12	99.7	0.0
Levofloxacin	≤0.12	>4	75.2	20.4
Gentamicin	≤1	>8	83.6	12.8
Amikacin	2	4	98.2	1.3
Colistin	>8	>8	0.3	99.7
***Enterobacter* spp. (752)**				
Cefepime-zidebactam 1:1	≤0.03	0.25	-	-
Cefepime	0.06	4	87.2	8.0
Ceftazidime	0.25	>32	70.4	28.1
Ceftriaxone	0.25	>8	66.7	32.6
Piperacillin-tazobactam	2	64	79.1	6.4
Meropenem	0.03	0.06	97.9	1.7
Levofloxacin	≤0.12	1	93.1	4.8
Gentamicin	≤1	≤1	92.5	6.1
Amikacin	1	2	99.1	0.5
Colistin	0.12	>8	84.6	15.4
***Serratia marcescens* (282)**				
Cefepime-zidebactam 1:1	0.06	0.12	-	-
Cefepime	0.06	0.25	95.7	2.5
Ceftazidime	0.12	0.5	95.4	4.6
Ceftriaxone	0.25	2	88.3	8.2
Piperacillin-tazobactam	2	8	96.4	2.8
Meropenem	0.06	0.06	97.9	2.1
Levofloxacin	≤0.12	1	96.1	1.8
Gentamicin	≤1	≤1	96.8	1.4
Amikacin	2	4	98.9	1.1
Colistin	>8	>8	5.3	94.7

a. Criteria as published by CLSI [2016], except for colistin, for which EUCAST [2016] criteria were applied.

- Overall susceptibility rate for meropenem was lower in Latin America (89.9%) compared to other geographic regions (97.1-98.3%), and susceptibility to ceftriaxone ranged from 52.9% (China), 59.7% (Latin America), 75.7% (Europe), 81.5% (APAC, excluding China) to 84.0% in the USA (**Table 4**).
- Susceptibility rates for meropenem among *K. pneumoniae* were lower in Latin America (70.9%; data not shown) compared to the other regions (87.6-94.7%), and the most active compounds tested against meropenem-non-susceptible *K. pneumoniae* were cefepime-zidebactam ($MIC_{50/90}$, 1/4 µg/mL; 99.3% inhibited at ≤8 µg/mL), colistin ($MIC_{50/90}$, 0.25/>8 µg/mL; 71.4% susceptible), and amikacin ($MIC_{50/90}$, 16/>32 µg/mL; 54.1% susceptible; **Table 3**).

Table 4. Activity of cefepime-zidebactam (1:1) and comparator antimicrobial agents when tested against 5,946 isolates of Enterobacteriaceae and stratified by geographic region.

Antimicrobial agent	% Susceptible[a] (no.)					
	USA (2,172)	EU (2,485)	APAC[b] (688)	China (194)	LA (407)	All regions (5,946)
Cefepime-zidebactam 1:1	(100.0/100.0)[c]	(>99.9/99.4)[c]	(100.0/99.4)[c]	(100.0/100.0)[c]	(100.0/99.0)[c]	(>99.9/99.6)[c]
Cefepime	91.6	82.1	87.8	61.3	64.1	84.3
Ceftazidime	88.0	79.7	84.9	70.3	66.8	82.2
Ceftriaxone	84.0	75.7	81.5	52.9	59.7	77.6
Piperacillin-tazobactam	93.0	85.8	91.3	87.2	79.9	88.7
Meropenem	98.3	97.1	98.1	97.4	89.9	97.2
Levofloxacin	81.8	76.2	84.6	65.1	68.7	78.4
Gentamicin	90.1	85.8	88.8	64.3	67.5	85.8
Amikacin	99.2	97.2	99.3	96.5	95.3	98.0
Colistin	80.7	82.0	87.6	84.1	76.7	81.9

a. Criteria as published by CLSI [2016], except for colistin, for which EUCAST [2016] criteria was applied.
b. Excluding China.
c. % inhibited at ≤8/≤2 µg/mL for comparison purpose only.

Conclusions

- **Cefepime-zidebactam (WCK 5222) was very active against this worldwide collection of Enterobacteriaceae, including isolates resistant to broad-spectrum cephalosporins and/or carbapenems and/or colistin.**
- **Zidebactam demonstrated potent *in vitro* activity against many Enterobacteriaceae species, independent of β-lactamase production. Organisms with elevated zidebactam MIC values were susceptible to cefepime.**
- **The results of this investigation support the further clinical development of WCK 5222.**

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