IDWeek 2017
Poster #1226

Cefepime-Zidebactam (WCK 5222) Activity Tested against Gram-Negative Organisms Causing Bloodstream Infections Worldwide

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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 (GN) PBP2 and β-lactamase inhibition. We evaluated the *in vitro* activity of cefepime (FEP) combined with ZID against GN organisms causing bloodstream infections (BSI) in hospitals worldwide.

Methods: A total of 2,094 isolates from 105 medical centers were evaluated. Isolates were collected from Europe (1,050), the US (331), Latin America (LA; 200), and the Asia-Pacific region (AP; 393) in 2015, and China (120) in 2013 by the SENTRY Program. Susceptibility (S) testing was performed by reference broth microdilution method against FEP-ZID (1:1 ratio) and comparators. The collection included 1,809 *Enterobacteriaceae* (ENT), 170 *P. aeruginosa* (PSA), and 115 *Acinetobacter* spp. (ASP).

Results: FEP-ZID was very active against ENT ($MIC_{50/90}$ of ≤0.03/0.12 μg/mL) with 99.9 and 100.0% of isolates inhibited at ≤4/4 and ≤8/8 μg/mL, respectively, and retained potent activity against carbapenem-resistant (CRE; n=44; $MIC_{50/90}$, 1/4 μg/mL), multidrug-resistant (MDR), and extensively drug-resistant (XDR) isolates (Table). Amikacin (AMK; $MIC_{50/90}$, 2/4 μg/mL; 97.7% S) was also very active against ENT, and colistin (COL; $MIC_{50/90}$, 0.12/>8 μg/mL) inhibited only 87.3% of isolates at ≤2 μg/mL. FEP-ZID was highly active against PSA, including isolates resistant to other antipseudomonal β-lactams, MDR ($MIC_{50/90}$, 4/8 μg/mL), and XDR ($MIC_{50/90}$, 4/8 μg/mL) isolates. Among the comparators, COL ($MIC_{50/90}$ of ≤0.5/1 μg/mL; 100.0% S) and AMK ($MIC_{50/90}$, 4/16 μg/mL; 91.2% S) were the most active agents against PSA. FEP-ZID ($MIC_{50/90}$, 16/32 μg/mL) was 4-fold more active than FEP against ASP.

Conclusions: FEP-ZID (WCK 5222) exhibited potent *in vitro* activity against a large worldwide collection of GN isolates from BSI, including MDR and XDR isolates. These results support further clinical development of WCK 5222 for treating BSI.

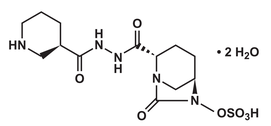
	$MIC_{50/90}$ (% at ≤8 μg/mL)	$MIC_{50/90}$ in μg/mL (%S)		
Organism	**FEP-ZID**	**FEP**	**CAZ**	**P/T**	**MEM**
ENT (1,809)	≤0.03/0.12 (100.0)	0.06/32 (82.4)	0.25/32 (81.1)	2/32 (89.0)	0.03/0.06 (97.3)
MDR (216)	0.12/1 (100.0)	32/>64 (17.6)	>32/>32 (19.0)	32/>64 (39.8)	0.06/>32 (77.8)
XDR (37)	1/4 (100.0)	>64/>64 (5.4)	>32/>32 (0.0)	>64/>64 (0.0)	32/>32 (5.4)
PSA (170)	2/4 (98.8)	4/32 (80.6)	2/32 (78.2)	4/64 (79.4)	1/16 (69.4)
CAZ-NS (37)	4/8 (94.6)	16/>64 (18.9)	32/>32 (0.0)	64/>64 (16.2)	16/>32 (18.9)
P/T-NS (35)	4/8 (94.3)	16/>64 (25.7)	32/>32 (11.4)	64/>64 (0.0)	16/>32 (20.0)
MEM-NS (52)	4/8 (96.2)	8/>64 (50.0)	16/>32 (42.3)	32/>64 (46.2)	16/>32 (0.0)
ASP (115)	16/32 (49.6)	64/>64 (34.8)	>32/>32 (33.0)	>64/>64 (33.3)	32/>32 (42.6)

CAZ, ceftazidime; P/T, piperacillin/tazobactam; MEM, meropenem; NS, non susceptible

Introduction

- Zidebactam, a bicyclo-acyl hydrazide ($C_{13}H_{21}N_5O_7S$ [Figure 1]), is a non-β-lactam agent with a dual mechanism of action involving selective and high-affinity gram-negative penicillin-binding protein 2 (PBP2) binding and β-lactamase inhibition
- Due to PBP2 binding, zidebactam demonstrates antibacterial activity against various *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates
- Cefepime is a parenteral fourth-generation oxyimino-cephalosporin with broad-spectrum activity against aerobic gram-positive and gram-negative bacteria, including *P. aeruginosa*, that was initially approved by the United States Food and Drug Administration (US FDA) in 1977

Figure 1 Chemical structure of zidebactam



- 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
- Zidebactam combined with cefepime (WCK 5222) displays potent activity against several multidrug-resistant (MDR) pathogens, including *P. aeruginosa* and *Acinetobacter baumannii*
- It has been demonstrated that zidebactam driven "enhancer" action leads to rapid cidality due to binding to multiple PBPs
- WCK 5222 is under clinical development for treating 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 gram-negative organisms isolated from patients hospitalized with bloodstream infections

Materials and Methods

Organism collection

- 2,094 isolates were collected as part of a global surveillance program, mostly in 2015 (except those from China collected in 2013)
- The organism collection included 1,809 *Enterobacteriaceae*, 170 *P. aeruginosa,* and 115 *Acinetobacter* spp. isolates
- Isolates were consecutively collected from 105 medical institutions worldwide, including the United States (US; 331 isolates from 36 medical centers), Europe (1,050 isolates from 37 medical centers), Latin America (200 isolates from 8 medical centers), the Asia-Pacific (APAC) region (excluding China, 393 isolates from 14 medical centers), and China (120 isolates from 10 medical centers)
- Each participating center was requested to collect consecutive bacterial isolates from bloodstream infections (1/patient) determined to be clinically significant by local criteria

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; tested at ratio concentrations of 1:1), both compounds alone, and various comparator agents were tested in 96-well frozen-form panels produced by JMI Laboratories (North Liberty, Iowa, USA)
  - Cefepime breakpoint for high dose (2g q8hs; CLSI), ie, ≤8 μg/mL, was applied for cefepime-zidebactam for comparison purposes only. However, a pharmacokinetic/pharmacodynamic (PK/PD) susceptible breakpoint of ≤64 μg/mL has been proposed based on the results of phase 1 studies where 2g of cefepime plus 1g of zidebactam q8 hours provided >99% PK/PD target attainment for *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* isolates with cefepime-zidebactam MICs up to 64 μg/mL (Wockhardt data on file)
- Tested QC strains included *Escherichia coli* ATCC 25922, ATCC 35218, and NCTC 13353; *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA 1705; and *Pseudomonas aeruginosa* ATCC 27853

Results

- Cefepime-zidebactam was the most active combination tested against *Enterobacteriaceae* with $MIC_{50/90}$ results of ≤0.03/0.12 μg/mL and 100.0% inhibited at ≤8/8 μg/mL (Tables 1–3 and Figure 2)
- Amikacin ($MIC_{50/90}$, 2/4 μg/mL; 97.7% susceptible), doripenem ($MIC_{50/90}$, ≤0.06/0.12 μg/mL; 97.4% susceptible), meropenem ($MIC_{50/90}$, 0.03/0.06 μg/mL; 97.3% susceptible), and imipenem ($MIC_{50/90}$, ≤0.12/0.5 μg/mL; 94.5% susceptible) were also very active against *Enterobacteriaceae* (Table 3), but these compounds exhibited limited activity against carbapenem-resistant *Enterobacteriaceae* (CRE; only 54.5% susceptible to amikacin; data not shown)
- Cefepime-zidebactam was active against individual *Enterobacteriaceae* species (MIC_{50}, ≤0.03 to 0.12 μg/mL and MIC_{90}, 0.12 to 0.5 μg/mL) and retained potent activity against CRE (n=44; $MIC_{50/90}$, 1/4 μg/mL), colistin-nonsusceptible *K. pneumoniae* ($MIC_{50/90}$, 2/4 μg/mL), and ceftazidime-nonsusceptible *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.5 μg/mL; Table 1)
- Cefepime-zidebactam was very active against *P. aeruginosa* with $MIC_{50/90}$ results of 2/4 μg/mL and 98.8% of isolates inhibited at ≤8/8 μg/mL; highest MIC, 16/16 μg/mL (Tables 1–3 and Figure 2)
- Among the comparators, colistin ($MIC_{50/90}$ of ≤0.5/1 μg/mL; 100.0% susceptible) and amikacin ($MIC_{50/90}$, 4/16 μg/mL; 91.2% susceptible) were the most active compounds against *P. aeruginosa* (Table 3)
- Cefepime-zidebactam exhibited consistent activity against *P. aeruginosa* from all regions (from 96.0% [US] to 100.0% [Latin America, APAC, and China] inhibited at ≤8/8 μg/mL) and retained potent activity against multidrug-resistant isolates (MDR; $MIC_{50/90}$, 4/8 μg/mL; 95.6% inhibited at ≤8/8 μg/mL) and extensively drug-resistant isolates (XDR; $MIC_{50/90}$, 4/8 μg/mL; 93.3% inhibited at ≤8/8 μg/mL; Table 1)

Table 1 Summary of cefepime-zidebactam 1:1 activity against isolates collected from patients hospitalized with bloodstream infections

Organisms	No.	MIC (μg/mL)			% inhibited at ≤8/8 μg/mL[a]
		Range	50%	90%	
Enterobacteriaceae	1,809	≤0.03 to 8	≤0.03	0.12	100.0%
CRE	44	0.06 to 8	1	4	100.0%
Escherichia coli	951	≤0.03 to 0.5	≤0.03	0.12	100.0%
ESBL-phenotype *Escherichia coli*	200	≤0.03 to 0.5	0.12	0.12	100.0%
Klebsiella pneumoniae	408	≤0.03 to 8	≤0.03	0.5	100.0%
ESBL-phenotype	127	≤0.03 to 8	0.25	2	100.0%
Meropenem-nonsusceptible (MIC, ≥2 μg/mL)	39	0.12 to 8	1	4	100.0%
Colistin-nonsusceptible (MIC, ≥4 μg/mL)	13	0.25 to 8	2	4	100.0%
Klebsiella oxytoca	63	≤0.03 to 0.25	≤0.03	0.12	100.0%
Proteus mirabilis	82	≤0.03 to 0.25	0.06	0.12	100.0%
Enterobacter spp.	162	≤0.03 to 2	0.06	0.25	100.0%
Ceftazidime-nonsusceptible (MIC, ≥8 μg/mL)	55	≤0.03 to 2	0.12	0.5	100.0%
Enterobacter cloacae	136	≤0.03 to 0.5	0.06	0.25	100.0%
Morganella morganii	24	≤0.03 to 0.25	≤0.03	0.12	100.0%
Citrobacter spp.	40	≤0.03 to 0.5	≤0.03	0.06	100.0%
Serratia marcescens	51	≤0.03 to 1	0.06	0.25	100.0%
Proteus vulgaris	3	0.06 to 0.12	0.12	—	100.0%
Providencia spp.	9	≤0.03 to 0.12	≤0.03	—	100.0%
Pseudomonas aeruginosa	170	0.5 to 16	2	4	98.8%
Ceftazidime-nonsusceptible (MIC, ≥16 μg/mL)	37	2 to 16	4	8	94.6%
Meropenem-nonsusceptible (MIC, ≥4 μg/mL)	52	0.5 to 16	4	8	96.2%
Piperacillin-nonsusceptible (MIC, ≥16 μg/mL)	35	2 to 16	4	8	94.3%
MDR	45	0.5 to 16	4	8	95.6%
XDR	30	2 to 16	4	8	93.3%
Acinetobacter spp.	115	0.5 to 64	16	32	49.6%

[a] Cefepime breakpoint for high dose (2g q8hs; CLSI), ie, ≤8 μg/mL, was applied for cefepime-zidebactam for comparison purposes only.

Table 2 Antimicrobial activity of cefepime-zidebactam 1:1, cefepime, and zidebactam tested against the organisms isolated from patients with bloodstream infections in US medical centers

Organisms / organism groups	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* (1,809)**															
Cefepime-zidebactam 1:1 (1,809)	1,052 (58.2%)	373 (78.8%)	242 (92.2%)	79 (96.5%)	29 (98.1%)	14 (98.9%)	14 (99.7%)	4 (99.9%)	2 (100.0%)					≤0.03	0.12
Cefepime (1,809)		812 (44.9%)	370 (65.3%)	148 (73.5%)	63 (77.0%)	30 (78.7%)	34 (80.5%)	34 (82.4%)	42 (84.7%)	34 (86.6%)	49 (89.3%)	41 (91.6%)	54 (94.6%)	98 (100.0%)	0.06	32
Zidebactam (1,799)		2 (0.1%)	409 (22.8%)	760 (65.1%)	159 (73.9%)	57 (77.1%)	20 (78.2%)	11 (78.8%)	11 (79.4%)	10 (80.0%)	11 (80.6%)	16 (81.5%)	31 (83.2%)	302 (100.0%)	0.12	>64
CRE (44)															
Cefepime-zidebactam 1:1 (44)			1 (2.3%)	5 (13.6%)	9 (34.1%)	6 (47.7%)	8 (65.9%)	9 (86.4%)	4 (95.5%)	2 (100.0%)					1	4
Cefepime (44)			1 (2.3%)	0 (2.3%)	0 (2.3%)	1 (4.5%)	0 (4.5%)	1 (6.8%)	2 (11.4%)	1 (13.6%)	2 (18.2%)	5 (29.5%)	5 (40.9%)	26 (100.0%)	>64	>64
Zidebactam (44)			4 (9.1%)	6 (22.7%)	3 (29.5%)	4 (38.6%)	6 (52.3%)	2 (56.8%)	0 (56.8%)	1 (59.1%)	2 (63.6%)	1 (65.9%)	15 (100.0%)		2	>64
***Pseudomonas aeruginosa* (170)**															
Cefepime-zidebactam 1:1 (170)					22 (12.9%)	61 (48.8%)	45 (75.3%)	29 (92.4%)	11 (98.8%)	2 (100.0%)					2	4
Cefepime (170)					2 (1.2%)	33 (20.6%)	49 (49.4%)	25 (64.1%)	28 (80.6%)	15 (89.4%)	6 (92.9%)	4 (95.3%)	8 (100.0%)		4	32
Zidebactam (170)					2 (1.2%)	15 (10.0%)	58 (44.1%)	65 (82.4%)	23 (95.9%)	3 (97.6%)	1 (98.2%)	1 (98.8%)	2 (100.0%)		4	8
***Acinetobacter* spp. (115)**															
Cefepime-zidebactam 1:1 (115)					3 (2.6%)	5 (7.0%)	14 (19.1%)	16 (33.0%)	19 (49.6%)	31 (76.5%)	25 (98.3%)	2 (100.0%)			16	32
Cefepime (115)					2 (1.7%)	5 (6.1%)	16 (20.0%)	8 (27.0%)	9 (34.8%)	5 (44.3%)	6 (49.6%)	24 (70.4%)	34 (100.0%)		64	>64
Zidebactam (115)													115 (100.0%)		>64	>64

- Cefepime-zidebactam ($MIC_{50/90}$, 16/32 μg/mL) was 4-fold more active than cefepime against *Acinetobacter* spp., and the most active compounds tested against *Acinetobacter* spp. were colistin ($MIC_{50/90}$, ≤0.5/1 μg/mL; 95.7%S) and amikacin ($MIC_{50/90}$, 32/>32 μg/mL; 47.8%S; Table 3)

Conclusions

- **Cefepime-zidebactam (WCK 5222) was very active against this worldwide collection of gram-negative bacteria from hospitalized patients with bloodstream infection, including MDR isolates**
- **Importantly, cefepime-zidebactam showed potent activity against CRE, colistin-nonsusceptible *K. pneumoniae*, and meropenem-nonsusceptible *P. aeruginosa***
- **Cefepime-zidebactam MIC_{90} value for *Acinetobacter* spp. (32 μg/mL) was 2-fold lower than the proposed PK/PD-based susceptible breakpoint of ≤ 64 μg/mL**

Figure 2 Cefepime-zidebactam MIC distributions for *Enterobacteriaceae* (n=1,809) and *P. aeruginosa* (n=170) from patients hospitalized worldwide with bloodstream infections

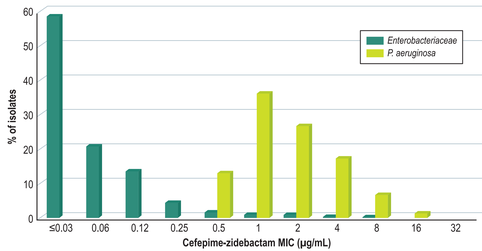


Table 3 Activity of cefepime-zidebactam 1:1 and comparator antimicrobial agents

Organism (no. of isolates)/ antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]	
			%S	%R
Enterobacteriaceae (1,809)				
Cefepime-zidebactam 1:1	≤0.03	0.12	—	—
Cefepime	0.06	32	82.4	13.4 [b]
Ceftazidime	0.25	32	81.1	17.4
Ceftriaxone	≤0.06	>8	76.2	23.3
Piperacillin-tazobactam	2	32	89.0	5.8
Imipenem	≤0.12	0.5	94.5	2.8
Meropenem	0.03	0.06	97.3	2.3
Doripenem	≤0.06	0.12	97.4	2.2
Levofloxacin	≤0.12	>4	77.2	20.7
Gentamicin	≤1	>8	85.5	13.6
Amikacin	2	4	97.7	1.6
Colistin	0.12	>8	—	—
Pseudomonas aeruginosa (170)				
Cefepime-zidebactam 1:1	2	4	—	—
Cefepime	4	32	80.6	10.6
Ceftazidime	2	32	78.2	14.7
Piperacillin-tazobactam	4	64	79.4	5.9
Imipenem	1	>8	68.2	28.2
Meropenem	1	16	69.4	24.7
Levofloxacin	0.5	>4	70.0	23.5
Gentamicin	2	>8	82.9	14.7
Amikacin	4	16	91.2	7.1
Colistin	≤0.5	1	100.0	0.0
Acinetobacter spp. (115)				
Cefepime-zidebactam 1:1	16	32	—	—
Cefepime	64	>64	34.8	55.7
Ceftazidime	>32	>32	33.0	62.6
Ampicillin-sulbactam	32	>32	38.3	50.4
Piperacillin-tazobactam	>64	>64	33.3	63.2
Imipenem	>8	>8	46.1	53.9
Meropenem	32	>32	42.6	56.5
Levofloxacin	>4	>4	36.5	53.9
Gentamicin	>8	>8	41.7	55.7
Amikacin	32	>32	47.8	47.8
Colistin	≤0.5	1	95.7	4.3

[a] Criteria as published by CLSI M100-S27 document [2017]

Acknowledgments

This study was supported by Wockhardt Bio AG.

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