Activity of Cefepime in Combination with Taniborbactam (formerly VNRX-5133) Against *Pseudomonas aeruginosa* from a Global 2018-2020 Surveillance Collection

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Background: Taniborbactam is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor (BLI) with potent and selective inhibitory activity against both serine- and metallo-β-lactamases (MBLs). Taniborbactam restores the activity of cefepime (FEP) against many multidrug resistant organisms, including cephalosporin- and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa* (PA). We evaluated the *in vitro* activity of the investigational combination cefepime-taniborbactam and comparators against clinical isolates of PA collected during a 2018-2020 surveillance.

Methods: MICs of FEP with taniborbactam fixed at 4 µg/mL (FTB) and comparators were determined against 3,219 PA collected from 221 sites in 52 countries in 2018-2020. Resistant phenotypes were based on 2021 CLSI breakpoints. Acquired β-lactamase (BL) genes were identified via PCR/Sanger sequencing or whole-genome sequencing (WGS) for 516 isolates with meropenem (MEM) MIC ≥8 µg/mL, and for 94 randomly selected isolates with FEP or ceftazidime MIC ≥16 µg/mL. 186 isolates with FTB MIC ≥16 µg/mL, 16 with FTB MIC=8 µg/mL and one with FTB MIC=4 µg/mL were subjected to WGS.

Results: Overall, 28.7%, 26.2% and 20.3% of PA isolates were nonsusceptible (NS) to piperacillin-tazobactam (TZP), MEM or FEP, respectively (Table). FTB demonstrated potent activity ($MIC_{50/90}$, 2/8 µg/mL; 94.2% inhibited at ≤8 µg/mL) against PA overall and inhibited between 63.4% (ceftazidime-avibactam [CZA] NS) and 82.1% (TZP NS) of isolates in the NS subsets compared to 0% to 69.1% S for comparators. Against the 111 strains carrying VIM or NDM MBL genes, 67.6% had FTB MICs ≤8 µg/mL, with 11.7% having FTB MICs of 16 µg/mL. Plausible explanations for elevated FTB MICs included IMP MBL genes, penicillin binding protein 3 variations, and/or possible efflux pump up-regulation.

Resistance Phenotype/Genotype	N (%)	Percent susceptible					
		FTB[a]	FEP	CZA	CT	MEV[b]	TZP
P. aeruginosa, all	3219 (100%)	94.2	79.7	90.7	89.1	87.2	71.3
FEP NS	654 (20.3%)	71.6	0	56.1	50.5	53.1	5.8
MEM NS	842 (26.2%)	81.0	44.2	67.0	63.9	51.1	30.5
CZA NS	298 (9.3%)	63.4	3.7	0	16.1	24.5	4.0
CT NS	350 (10.9%)	68.0	7.4	28.6	0	35.4	6.3
MEV NS[b]	412 (12.8%)	70.2	25.5	45.4	45.2	0	9.7
TZP NS	925 (28.7%)	82.1	33.4	69.1	64.5	59.8	0
MBL-positive (VIM or NDM)	111 (13.7%)[c]	67.6	3.6	2.7	0.9	8.1	2.7

FTB, cefepime-taniborbactam; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MBL, metallo-β-lactamase; NS, nonsusceptible based on 2021 CLSI breakpoints

[a] corresponds to a provisional susceptible breakpoint of ≤8 µg/mL

[b] as there is no CLSI breakpoint, susceptibility is based on EUCAST susceptible breakpoint of ≤8 µg/mL

[c] percent based on total of 813 molecularly characterized isolates

Conclusions: FTB demonstrated potent *in vitro* activity against PA with different resistance profiles, including NS to FEP, MEM, and TZP, and to the BL/BLI combinations CZA, ceftolozane-tazobactam, and meropenem-vaborbactam. FTB was the most active agent tested against PA harboring VIM and NDM MBLs. These findings support the continued development of FTB as a potential new treatment option for challenging infections due to MDR PA.