29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

P1180 *In vitro* activity of the orally available ceftibuten/VNRX-7145 combination against a challenge set of *Enterobacteriaceae* pathogens carrying molecularly characterised beta-lactamase genes

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Background: The increasing trends of Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs) and carbapenemases in hospital and community settings have challenged treatment options for infections caused by such pathogens, including oral drugs. Ceftibuten/VNRX-7145 is an orally bioavailable β-lactam-β-lactamase inhibitor combination under clinical development. In vivo, VNRX-7145 undergoes biotransformation to the active inhibitor, VNRX-5236. This study assessed the activity of ceftibuten with VNRX-5236 and comparators against a challenge set of multidrug-resistant (MDR) pathogens.

Materials/methods: A total of 205 non-duplicate single-patient Enterobacteriaceae (11 species) isolates were collected from patients from European and US medical centres in 2015–2016. Isolates were selected by the presence of plasmid AmpC (pAmpC)-, ESBL-, KPC-, and OXA-48-like-encoding genes, which were detected by genome sequencing and *in silico* analysis (Table). Susceptibility (S) testing followed CLSI/EUCAST methods and interpretation. VNRX-5236 and avibactam were tested at fixed 4 mg/L.

Results: Overall, ceftibuten/VNRX-5236 ($MIC_{50/90}$, 0.12/1 mg/L) MICs were 256-fold lower than those of ceftibuten alone ($MIC_{50/90}$, 32/256 mg/L) against all Enterobacteriaceae, and 2- to 4-fold lower than those of ceftazidime-avibactam ($MIC_{50/90}$, 0.5/2 mg/L; 98.5%S). Meropenem ($MIC_{50/90}$, 0.25/32 mg/L; 58.5-64.9%S) and piperacillin-tazobactam ($MIC_{50/90}$, >64/>64 mg/L; 34.1–38.0%S) had limited activity against this set, as did oral options (≤45.1%S). VNRX-5236 decreased the ceftibuten MICs ($MIC_{50/90}$, 0.12/1 mg/L) at least 512-fold compared to ceftibuten alone ($MIC_{50/90}$, 128/>256 mg/L) against pAmpC producers. Ceftibuten/VNRX-5236 ($MIC_{50/90}$, 0.06/0.12 mg/L) and meropenem ($MIC_{50/90}$, ≤0.03/0.06 mg/L; 100%S) MICs were similar against ESBL isolates, and these agents had MIC_{90} values 4- to 8-fold lower than ceftazidime-avibactam ($MIC_{50/90}$, 0.25/0.5 mg/L; 100%S) and imipenem ($MIC_{50/90}$, ≤0.12/0.5 mg/L; 94.0–100%S). Ceftibuten/VNRX-5236 inhibited all but 2 carbapenemase producers (98.0%) at ≤4 mg/L. While ceftibuten/VNRX-5236 had an MIC_{90} value 16-fold lower than ceftazidime-avibactam against KPC producers, these 2 combinations had similar MIC_{90} results against OXA-48-like organisms. Other agents were less active against carbapenemase producers.

Conclusions: VNRX-5236 significantly increased ceftibuten potency against this challenge set of pathogens. These *in vitro* data suggest that dosing of ceftibuten/VNRX-7145 may be a potent and convenient oral option for treating infections caused by MDR Enterobacteriaceae producing β-lactamase enzymes, including Ambler class A and D carbapenemases. Further clinical development of ceftibuten/VNRX-7145 is warranted.

Genotype (no. isolates)	MIC_{50}/MIC_{90} in mg/L (% susceptible by CLSI/EUCAST criteria)[a]				
	Ceftibuten	Ceftibuten/VNRX-5236[b]	Meropenem	CAZ-AVI	Levofloxacin
All (205)	32/256 (40.5/7.3)	0.12/1 (98.5/94.6)	0.25/32 (58.5/64.9)	0.5/2 (98.5/98.5)	16/>16 (31.7/22.4)
AmpC (53)	128/>256 (3.8/0.0)	0.12/1 (96.2/94.3)	≤0.03/0.06 (98.1/100)	0.25/2 (96.2/96.2)	0.5/>16 (64.2/50.9)
ESBL (50)	4/16 (84.0/24.0)	0.06/0.12 (100.0/98.0)	≤0.03/0.06 (100/100)	0.25/0.5 (100/100)	16/>16 (28.0/22.0
KPC (50)[c]	16/64 (48.0/0.0)	0.12/0.25 (100/92.0)	16/>64 (6.0/16.0)	2/4 (98.0/98.0)	16/>16 (18.0/4.0)
OXA-48-like (52)[d]	32/128 (28.8/5.8)	0.25/1 (98.1/94.2)	8/64 (28.8/42.3)	1/1 (100/100)	16/>16 (15.4/11.5)

CAZ-AVI, ceftazidime-avibactam

[a]VNRX-5236 and avibactam were tested at fixed 4 mg/L; MIC results were interpreted by CLSI and EUCAST criteria; ceftibuten/VNRX-5236 used the ceftibuten susceptible breakpoints.

[b]VNRX-5236 is the active β-lactamase inhibitor of the orally available VNRX-7145 product

[c] Includes KPC-2-, KPC-3-, KPC-4-, and KPC-6-encoding gene variants.

[d] Includes OXA-48- and OXA-232-encoding gene variants.