ECCMID 2019 | Poster #P1180

In vitro Activity of the Orally Bioavailable Ceftibuten/VNRX-7145 Combination against a Challenge Set of Enterobacteriaceae Pathogens Carrying Molecularly Characterized β-Lactamase Genes

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Introduction

- β-lactam agents are important therapeutic options for treating infections caused by gram-negative organisms, and carbapenems are potent agents in the armamentarium against multidrug-resistant bacteria
- The emergence and dissemination of Enterobacteriaceae-producing extended-spectrum β-lactamases (ESBLs) and consequent increased use of carbapenems in clinical practice has promoted the emergence of carbapenem-resistant Enterobacteriaceae (CRE)
- ESBL- and carbapenemase-producing gram-negative isolates are now commonplace in hospital and community settings, limiting mainstay treatment options to injectable drugs like polymyxins, tigecycline, fosfomycin, and aminoglycosides
- This scenario demands new and effective gram-negative therapies, including oral options
  - 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 alone, ceftibuten/VNRX-5236, and comparator agents against a challenge set of multidrug-resistant (MDR) gram-negative pathogens

Materials and Methods

Bacterial isolates

- A total of 198 non-duplicate single-patient Enterobacteriaceae (11 species) isolates were collected from patients from European and US medical centres in 2015–2016 through the SENTRY Antimicrobial Surveillance Program
  - Seven isolates were collected from Latin American and Asia-Pacific hospitals for a total of 205 isolates
- Enterobacteriaceae isolates had their identification confirmed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- The challenge set was composed of the following species
  - *Citrobacter freundii* (4 isolates), *Enterobacter cloacae* (8), *Escherichia coli* (71), *Hafnia alvei* (1), *Klebsiella oxytoca* (3), *Klebsiella pneumoniae* (106), *Pluralibacter gergoviae* (1), *Proteus mirabilis* (6), *Providencia stuartii* (1), *Raoultella ornithinolytica* (2), and *Serratia marcescens* (2)
- Isolates were selected by the presence of plasmid AmpC (53 isolates)-, ESBL- (50), *Klebsiella pneumoniae* carbapenemase (KPC)- (50), and OXA-48-like (52)-encoding genes, which were detected by genome sequencing and *in silico* analysis

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution in cation-adjusted Mueller-Hinton broth following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) document
- VNRX-5236 and avibactam were tested at a fixed concentration of 4 mg/L
- Testing used reference 96-well panels manufactured by JMI Laboratories
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains
- Breakpoint criteria for comparator agents were from the M100 CLSI (2018) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2018) documents

Figure 1 Cumulative MIC distributions of ceftibuten and ceftibuten/VNRX-5236 tested against a challenge set of 205 Enterobacteriaceae clinical isolates

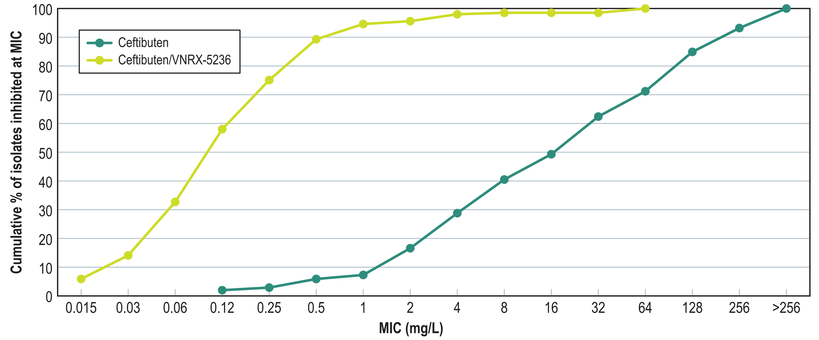

Table 1 Antimicrobial activity of ceftibuten and ceftibuten/VNRX-5236 tested against a challenge set of 205 Enterobacteriaceae clinical isolates

Organism / organism group (no. of isolates)	No. of isolates and cumulative % inhibited at MIC (mg/L) of:																	MIC$_{50}$	MIC$_{90}$
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	>[a]	
Enterobacteriaceae (205)																			
Ceftibuten					4 2.0	2 2.9	6 5.9	3 7.3	19 16.6	25 28.8	24 40.5	18 49.3	27 62.4	18 71.2	28 84.9	17 93.2		14 100.0	32	256
Ceftibuten/ VNRX-5236 [b]		12 5.9	17 14.1	38 32.7	52 58.0	35 75.1	29 89.3	11 94.6	2 95.6	5 98.0	1 98.5	0 98.5	0 98.5					3 100.0	0.12	1
AmpC (53)																			
Ceftibuten										1 1.9	1 3.8	2 7.5	4 15.1	4 22.6	18 56.6	12 79.2		11 100.0	128	>256
Ceftibuten/ VNRX-5236 [b]	1 1.9	1 3.8	8 18.9	19 54.7	12 77.4	5 86.8	4 94.3	0 94.3	1 96.2	0 96.2	0 96.2	0 96.2						2 100.0	0.12	1
Extended-spectrum β-lactamase (50)																			
Ceftibuten					4 8.0	2 12.0	5 22.0	1 24.0	8 40.0	11 62.0	11 84.0	3 90.0	4 98.0	1 100.0					4	16
Ceftibuten/ VNRX-5236 [b]	9 18.0	8 34.0	18 70.0	11 92.0	2 96.0	1 98.0	0 98.0	1 100.0											0.06	0.12
Klebsiella pneumoniae carbapenemase [c] (50)																			
Ceftibuten									7 14.0	7 28.0	10 48.0	5 58.0	13 84.0	3 90.0	2 94.0	2 98.0		1 100.0	16	64
Ceftibuten/ VNRX-5236 [b]	1 2.0	4 10.0	5 20.0	16 52.0	10 72.0	9 90.0	1 92.0	0 92.0	3 98.0	1 100.0									0.12	0.5
OXA-48-like [d] (52)																			
Ceftibuten							1 1.9	2 5.8	4 13.5	6 25.0	2 28.8	8 44.2	6 55.8	10 75.0	8 90.4	3 96.2		2 100.0	32	128
Ceftibuten/ VNRX-5236 [b]	1 1.9	4 9.6	7 23.1	6 34.6	11 55.8	14 82.7	6 94.2	1 96.2	1 98.1	0 98.1	0 98.1	0 98.1						1 100.0	0.25	1

[a] Represents an MIC result of >512 mg/L for ceftibuten alone or >64 mg/L for ceftibuten/VNRX-5236.
[b] VNRX-5236 was tested at fixed 4 mg/L. 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.

Table 2 Antimicrobial activity of ceftibuten and ceftibuten/VNRX-5236 tested against a challenge set of 205 Enterobacteriaceae clinical isolates

Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	Range	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
Enterobacteriaceae (205)									
Ceftibuten	32	256	≤0.12 – >256	40.5	8.8	50.7	7.3		92.7 [b]
Ceftibuten/VNRX-5236	0.12	1	≤0.015 – >32	98.5	0.0	1.5	94.6		5.4 [b]
Ceftazidime-avibactam	0.5	2	0.06 – 32	98.5		1.5	98.5		1.5
Piperacillin-tazobactam	>64	>64	0.5 – >64	38.0	10.7	51.2	34.1	3.9	62.0
Ceftazidime	64	>256	0.25 – >256	7.8	7.3	84.9	4.9	2.9	92.2
Cefepime	16	>256	≤0.12 – >256	27.8	10.2 [e]	62.0	22.9	9.3	67.8
Meropenem	0.25	32	≤0.03 – >64	58.5	6.3	35.1	64.9	8.3	26.8
Imipenem	2	>8	≤0.12 – >8	49.8	11.2	39.0	61.0	16.6	22.4
Levofloxacin	16	>16	0.03 – >16	31.7	4.4	63.9	22.4	5.9	71.7
Trimethoprim-sulfamethoxazole	>4	>4	≤0.5 – >4	29.9		70.1	29.9	4.4	65.7
AmpC (53)									
Ceftibuten	128	>256	4 – >256	3.8	3.8	92.5	0.0		100.0 [b]
Ceftibuten/VNRX-5236	0.12	1	≤0.015 – >32	96.2	0.0	3.8	94.3		5.7 [b]
Ceftazidime-avibactam	0.25	2	0.06 – 32	96.2		3.8	96.2		3.8
Piperacillin-tazobactam	8	>64	1 to >64	73.6	15.1	11.3	67.9	5.7	26.4
Ceftazidime	32	256	4 – >256	1.9	5.7	92.5	0.0	1.9	98.1
Cefepime	0.5	4	≤0.12 – 32	83.0	11.3 [e]	5.7	79.2	11.3	9.4
Meropenem	≤0.03	0.06	≤0.03 – 2	98.1	1.9	0.0	100.0	0.0	0.0
Imipenem	0.25	0.5	≤0.12 to 2	96.2	3.8	0.0	100.0	0.0	0.0
Levofloxacin	0.5	>16	0.03 – >16	64.2	0.0	35.8	50.9	9.4	39.6
Trimethoprim-sulfamethoxazole	1	>4	≤0.5 – >4	52.8		47.2	52.8	0.0	47.2
Extended-spectrum β-lactamase (50)									
Ceftibuten	4	16	≤0.12 – 64	84.0	6.0	10.0	24.0		76.0 [b]
Ceftibuten/VNRX-5236	0.06	0.12	≤0.015 – 2	100.0	0.0	0.0	98.0		2.0 [b]
Ceftazidime-avibactam	0.25	0.5	0.06 – 2	100.0		0.0	100.0		0.0
Piperacillin-tazobactam	4	64	0.5 to >64	76.0	18.0	6.0	68.0	8.0	24.0
Ceftazidime	16	128	0.25 – >256	20.0	18.0	62.0	12.0	8.0	80.0
Cefepime	16	128	1 – >256	14.0	20.0 [e]	66.0	2.0	20.0	78.0
Meropenem	≤0.03	0.06	≤0.03 – 0.25	100.0	0.0	0.0	100.0	0.0	0.0
Imipenem	≤0.12	0.5	≤0.12 to 2	94.0	6.0	0.0	100.0	0.0	0.0
Levofloxacin	16	>16	0.03 – >16	28.0	4.0	68.0	22.0	4.0	74.0
Trimethoprim-sulfamethoxazole	>4	>4	≤0.5 – >4	32.0		68.0	32.0	2.0	66.0
Klebsiella pneumoniae carbapenemase [c] (50)									
Ceftibuten	16	64	2 – >256	48.0	10.0	42.0	0.0		100.0 [b]
Ceftibuten/VNRX-5236	0.12	0.5	≤0.015 – 8	100.0	0.0	0.0	92.0		8.0 [b]
Ceftazidime-avibactam	2	4	0.25 – 16	98.0		2.0	98.0		2.0
Piperacillin-tazobactam	>64	>64	16 to >64	2.0	4.0	94.0	0.0	2.0	98.0
Ceftazidime	256	>256	8 – >256	0.0	2.0	98.0	0.0	0.0	100.0
Cefepime	64	>256	1 – >256	2.0	4.0 [e]	94.0	2.0	0.0	98.0
Meropenem	16	>64	0.06 – >64	6.0	10.0	84.0	16.0	26.0	58.0
Imipenem	>8	>8	1 to >8	2.0	4.0	94.0	6.0	30.0	64.0
Levofloxacin	16	>16	0.25 – >16	18.0	6.0	76.0	4.0	8.0	88.0
Trimethoprim-sulfamethoxazole	>4	>4	≤0.5 – >4	18.4		81.6	18.4	10.2	71.4
OXA-48-like [d] (52)									
Ceftibuten	32	128	0.5 – >256	28.8	15.4	55.8	5.8		94.2 [b]
Ceftibuten/VNRX-5236	0.25	1	≤0.015 – >32	98.1	0.0	1.9	94.2		5.8 [b]
Ceftazidime-avibactam	1	1	0.12 – 4	100.0		0.0	100.0		0.0
Piperacillin-tazobactam	>64	>64	64 to >64	0.0	5.8	94.2	0.0	0.0	100.0
Ceftazidime	128	256	0.5 – >256	9.6	3.8	86.5	7.7	1.9	90.4
Cefepime	128	>256	0.5 – >256	9.6	5.8 [e]	84.6	5.8	5.8	88.5
Meropenem	8	64	0.12 – >64	28.8	13.5	57.7	42.3	7.7	50.0
Imipenem	4	>8	≤0.12 to >8	5.8	30.8	63.5	36.5	36.5	26.9
Levofloxacin	16	>16	0.03 – >16	15.4	7.7	76.9	11.5	1.9	86.5
Trimethoprim-sulfamethoxazole	>4	>4	≤0.5 – >4	15.4		84.6	15.4	5.8	78.8

[a] MIC results were interpreted by CLSI and EUCAST criteria (2018).
[b] VNRX-5236 was tested at fixed 4 mg/L; ceftibuten/VNRX-5236 used the ceftibuten susceptible breakpoints; 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.
[e] Intermediate interpreted as susceptible-dose dependent.

Results

- Overall, ceftibuten/VNRX-5236 (MIC$_{50/90}$, 0.12/1 mg/L) MIC results 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) (Tables 1 and 2; Figure 1)
- Meropenem (MIC$_{50/90}$, 0.25/32 mg/L; 58.5-64.9% susceptible) and piperacillin-tazobactam (MIC$_{50/90}$, >64/>64 mg/L; 34.1–38.0% susceptible) had limited activity against this set, as did other options, including oral agents (≤45.1% susceptible) (Table 2)
- VNRX-5236 in combination with ceftibuten (MIC$_{50/90}$, 0.12/1 mg/L) decreased the MIC values by at least 512-fold compared to ceftibuten alone (MIC$_{50/90}$, 128/>256 mg/L) against isolates producing plasmid-encoded AmpC (Tables 1 and 2)
- Ceftibuten/VNRX-5236 (MIC$_{50/90}$, 0.06/0.12 mg/L) and meropenem (MIC$_{50/90}$, ≤0.03/0.06 mg/L; 100% susceptible) MIC values 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% susceptible) and imipenem (MIC$_{50/90}$, ≤0.12/0.5 mg/L; 94.0–100% susceptible) (Table 2)
- While ceftibuten/VNRX-5236 had an MIC$_{90}$ value 8-fold lower than ceftazidime-avibactam against KPC producers, these 2 combinations had similar MIC$_{90}$ results against OXA-48-like organisms
- Ceftibuten/VNRX-5236 inhibited all but 1 carbapenemase producer (98.0%) at ≤4 mg/L (Table 1)
  - Other agents were less active against carbapenemase producers (Table 2)

Conclusions

- VNRX-5236 significantly increased ceftibuten *in vitro* potency against this challenge set of clinical pathogens, and the ceftibuten/VNRX-5236 combination inhibited 94.6% of isolates at the EUCAST breakpoint of ≤1 mg/L for Enterobacteriaceae (UTI only)
- These *in vitro* data suggest that ceftibuten/VNRX-7145 may provide a potent oral option for treating infections caused by MDR Enterobacteriaceae producing β-lactamase enzymes, including Ambler class A and D carbapenemases
- These results warrant further clinical development of this β-lactam-β-lactamase combination

Acknowledgements

This study was supported by VenatoRx Pharmaceuticals, Inc. JMI Laboratories received compensation for services related to preparing this poster. Discovery and development of VNRX-7145 are supported by NIH R01 grant 1R01AI111539 and by NIAID contract HHSN272201600029C.

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