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 extendedspectrum 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) gramnegative pathogens

Materials and Methods

Bacterial isolates

- 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)
- 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
- 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



- 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
- The challenge set was composed of the following species

Testing used reference 96-well panels manufactured by JMI Laboratories

Organism /						No	of isolat	es and cu	mulative	% inhibit	ed at MIC	(mg/L)	of:							
organism group (no. of isolates)	≤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	MIC ₅₀	MIC ₉₀
Enterobacteriaceae (2	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 pneumonia	e carbape	nemase ^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)										I	I			/						
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

$\leq 0.12 - >2$ $\leq 0.015 - >3$ $\leq 0.015 - >3$ $0.06 - 32$ $0.05 - >64$ $0.25 - >25$ $\leq 0.12 - >25$ $\leq 0.12 - >25$ $\leq 0.03 - >6$ $\leq 0.12 - >25$ $\leq 0.03 - >6$ $\leq 0.03 - >6$ $\leq 0.015 - >64$ $\leq 0.03 - >6$ $\leq 0.015 - >64$ $\leq 0.012 - >64$ $\leq 0.012 - >64$ $\leq 0.015 - >64$ $\leq 0.015 - >64$ $\leq 0.015 - >64$ $\leq 0.006 - 32$ $\leq 0.012 - 31$ $\leq 0.012 - 31$ $\leq 0.012 - 31$ $\leq 0.003 - 21$ $\leq 0.012 - 31$ $\leq 0.003 - 21$ $\leq 0.012 - 64$ $\leq 0.012 - 64$ $\leq 0.015 - 256$ $\leq 0.03 - 0.256$	%S 56 40.5 32 98.5 98.5 98.5 98.5 38.0 6 7.8 56 27.8 56 27.8 56 27.8 64 58.5 8 49.8 6 31.7 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 98.1 96.2 98.1 96.2 96.2 6 64.2 952.8 96.2 4 84.0 2 100.0 4 76.0 6 20.0 14.0 14.0	% 8.8 0.0 10.7 7.3 10.2° 6.3 11.2° 4.4 11.2 4.4 11.2 4.4 11.2 4.4 11.2 4.4 11.2 4.4 11.3° 11.3° 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.1.3° 1.1.3° 1.1.3° 1.9 3.8 <th>%R 50.7 1.5 1.15 1.13 92.5 3.8 3.8 11.3 92.5 5.7 0.0 0.0 3.8 3.8 3.8 3.8 11.3 92.5 5.7 0.0 0.0 35.8 47.2 10.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0</th> <th>%S 7.3 94.6 98.5 34.1 4.9 22.9 64.9 61.0 22.4 29.9 64.3 98.5 96.2 67.9 0.0 94.3 96.2 67.9 0.0 94.3 95.2 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0</th> <th>% 3.9 3.9 2.9 9.3 8.3 16.6 5.9 4.4 5.7 1.9 1.1.3 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 </th>	%R 50.7 1.5 1.15 1.13 92.5 3.8 3.8 11.3 92.5 5.7 0.0 0.0 3.8 3.8 3.8 3.8 11.3 92.5 5.7 0.0 0.0 35.8 47.2 10.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0	%S 7.3 94.6 98.5 34.1 4.9 22.9 64.9 61.0 22.4 29.9 64.3 98.5 96.2 67.9 0.0 94.3 96.2 67.9 0.0 94.3 95.2 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0	% 3.9 3.9 2.9 9.3 8.3 16.6 5.9 4.4 5.7 1.9 1.1.3 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0 9.4 0.0
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$\leq 0.03 - >6$ $\leq 0.12 - >6$ $\leq 0.03 - >16$ $\leq 0.03 - >16$ $\leq 0.03 - >16$ $\leq 0.05 - >4$ $= 0.06 - 32$ $= 0.06 - 32$ $= 0.06 - 32$ $= 0.06 - 32$ $\leq 0.12 - 32$ $\leq 0.12 - 32$ $\leq 0.12 - 32$ $\leq 0.12 - 32$ $\leq 0.03 - 22$ $\leq 0.03 - 24$ $= 0.005 - 24$ $= 0.06 - 2$ $= 0.06 - 2$ $= 0.05 \text{ to } >64$ $= 0.25 - >25$ $= 0.03 - 0.25$ $= 0.03 - 0.25$ $= 0.03 - 0.25$	54 58.5 8 49.8 6 31.7 29.9 32 96.2 96.2 96.2 96.2 96.2 1.9 2 2 83.0 2 96.2 98.1 2 98.1 2 96.2 98.1 2 96.2 98.1 2 96.2 1.9 2 1.9 2 1.9 2 1.0 4 52.8 4 84.0 2 100.0 4 76.0 56 20.0 14.0 14.0	6.3 11.2 4.4 3.8 0.0 15.1 5.7 11.3 ° 1.9 3.8 0.0 6.0 0.0 15.1 1.9 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 0.0 1.9 3.8 1.9 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 0.0 1.8.0 1.8.0	$\begin{array}{c c} & 35.1 \\ & 39.0 \\ & 63.9 \\ & 70.1 \\ \hline \\ & 92.5 \\ & 3.8 \\ & 3.8 \\ & 3.8 \\ & 3.8 \\ & 3.8 \\ & 3.8 \\ & 3.8 \\ & 3.8 \\ & 3.8 \\ \hline \\ & 11.3 \\ & 92.5 \\ & 5.7 \\ & 0.0 \\ & 5.7 \\ \hline \\ & 0.0 \\ & 0.0 \\ & 35.8 \\ & 47.2 \\ \hline \\ & 47.2 \\ \hline \\ & 10.0 \\ & 0.0 \\ \hline \\ & 0.0 \\ & 0.0 \\ \hline \\ & 6.0 \\ \hline \\ & 62.0 \\ \end{array}$	$\begin{array}{c c} 64.9 \\ 61.0 \\ 22.4 \\ 29.9 \\ \end{array} \\ \begin{array}{c c} 0.0 \\ 94.3 \\ 96.2 \\ 67.9 \\ 0.0 \\ 67.9 \\ 0.0 \\ 79.2 \\ 100.0 \\ 79.2 \\ 100.0 \\ 50.9 \\ 52.8 \\ \end{array} \\ \begin{array}{c c} 24.0 \\ 52.8 \\ \end{array} \\ \begin{array}{c c} 24.0 \\ 98.0 \\ 100.0 \\ 68.0 \\ 12.0 \\ \end{array}$	8.3 16.6 5.9 4.4 5.7 1.9 11.3 0.0 0.0 9.4 0.0 9.4 0.0 9.4 0.0
$\leq 0.12 - >3$ $0.03 - >10$ $\leq 0.5 - >4$ $3 - >256$ $\leq 0.015 - >3$ $0.06 - 32$ $- 1 \text{ to } >64$ $4 - >256$ $\leq 0.12 - 33$ $\leq 0.12 - 33$ $\leq 0.03 - 24$ $\leq 0.12 \text{ to } 26$ $\leq 0.03 - >4$ $\leq 0.12 - 64$ $\leq 0.03 - 256$ $\leq 0.03 - 256$ $\leq 0.03 - 0.25$	8 49.8 6 31.7 29.9 3.8 32 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 98.1 2 96.2 98.1 2 96.2 98.1 2 96.2 98.1 2 96.2 1.9 2 1.9 2 1.0 4 84.0 2 100.0 4 76.0 56 20.0 14.0 14.0	11.2 4.4 4.4 3.8 0.0 3.8 0.0 15.1 5.7 11.3 ^e 1.9 3.8 0.0 3.8 0.0 6.0 0.0 6.0 0.0	$ \begin{array}{c c} 39.0\\ 63.9\\ 70.1\\ 92.5\\ 3.8\\ 3.8\\ 3.8\\ 3.8\\ 3.8\\ 3.8\\ 3.8\\ 3.8$	61.022.429.90.094.396.267.90.079.2100.079.2100.050.952.824.098.0100.068.012.0	16.6 5.9 4.4 5.7 1.9 11.3 0.0 0.0 9.4 0.0 9.4 0.0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	6 31.7 29.9 3.8 32 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 96.2 98.1 2 96.2 98.1 2 96.2 98.1 2 96.2 98.1 98.1 2 96.2 4 84.0 2 100.0 4 84.0 2 100.0 4 76.0 50 20.0 14.0 14.0	4.4 4.4 4.4 4 3.8 0.0 10 15.1 5.7 11.3 ^e 1.9 3.8 1.9 3.8 0.0 4 3.8 0.0 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 3.8 1.9 1.9 3.8 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9	63.9 70.1 92.5 3.8 3.8 3.8 11.3 92.5 5.7 0.0 0.0 35.8 47.2 10.0 0.0 0.0 0.0 6.0 6.0 62.0	 22.4 29.9 0.0 94.3 96.2 67.9 0.0 79.2 100.0 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0 	5.9 4.4 5.7 5.7 1.9 11.3 0.0 0.0 9.4 0.0 9.4 0.0
$\leq 0.5 - >4$ $= 4 - >256$ $\leq 0.015 - >32$ $= 0.06 - 32$ $= 1 \text{ to } >64$ $= 4 - >256$ $\leq 0.12 - 32$ $\leq 0.12 - 32$ $\leq 0.03 - 22$ $\leq 0.03 - 24$ $= 40.025 - >44$ $= 0.006 - 22$ $= 0.015 - 32$ $= 0.006 - 22$ $= 0.006 - 22$ $= 0.5 \text{ to } >64$ $= 0.25 - >25$ $= 1 - >256$ $= 0.03 - 0.24$	29.93.83296.296.296.296.273.61.9283.0298.1296.2664.252.8484.02100.0100.0100.0476.05620.014.0	A second seco	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	29.9 0.0 94.3 96.2 67.9 0.0 79.2 100.0 100.0 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0	4.4 4.4 5.7 1.9 11.3 0.0 0.0 9.4 0.0 9.4 0.0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	3.83296.296.296.273.61.9283.0298.1296.2664.252.852.8484.02100.0100.0100.0476.05620.014.0	3.8 0.0 10.0 11.1 11.3° 11.3° 1.9 3.8 0.0 1.9 3.8 0.0 1.9	92.53.83.811.392.55.70.00.035.847.210.00.00.06.06.062.0	0.094.396.267.90.079.2100.0100.050.952.824.098.0100.068.012.0	5.7 1.9 11.3 0.0 0.0 9.4 0.0 9.4 0.0
$ \leq 0.015 - >3 \\ 0.06 - 32 \\ 1 \text{ to } >64 \\ 4 - >256 \\ \leq 0.12 - 33 \\ \leq 0.03 - 2 \\ \leq 0.03 - 2 \\ \leq 0.03 - 2 \\ \leq 0.12 \text{ to } 2 \\ \leq 0.12 \text{ to } 2 \\ \leq 0.5 - >4 \\ 1 \\ \leq 0.015 - 3 \\ 0.06 - 2 \\ 0.5 \text{ to } >6 \\ 3 \\ 0.25 - >25 \\ 1 - >256 \\ \leq 0.03 - 0.2 \\ \end{cases} $	32 96.2 96.2 96.2 73.6 1.9 2 83.0 2 98.1 2 96.2 98.1 96.2 98.1 96.2 98.1 96.2 98.1 98.1 2 96.2 6 64.2 52.8 100.0 4 84.0 2 100.0 4 76.0 56 20.0 14.0 14.0	0.0 15.1 15.1 5.7 11.3° 1.9 3.8 0.0 6.0 0.0 18.0 18.0	3.8 3.8 11.3 92.5 5.7 0.0 0.0 0.0 35.8 47.2 10.0 0.0 0.0 6.0 62.0	94.396.267.90.079.2100.0100.050.952.824.098.0100.068.012.0	5.7 1.9 11.3 0.0 0.0 9.4 0.0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2 96.2 73.6 1.9 2 83.0 2 98.1 2 96.2 6 64.2 52.8 52.8 4 84.0 2 100.0 4 76.0 56 20.0 14.0 14.0	15.1 5.7 11.3 ° 1.9 3.8 0.0 3.8 0.0 6.0 0.0 4 5.7 1.9 5.7 1.9 5.7 1.9 5.7 5.7 5.7 5.7 5.7 5.7 5.7 5.7 5.7 5.7	3.8 11.3 92.5 5.7 0.0 0.0 35.8 47.2 10.0 0.0 0.0 6.0 62.0	96.2 67.9 0.0 79.2 100.0 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0	5.7 1.9 11.3 0.0 0.0 9.4 0.0 9.4 0.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	73.6 1.9 2 83.0 2 98.1 2 96.2 6 64.2 4 52.8 4 84.0 2 100.0 4 76.0 56 20.0 14.0 14.0	15.1 5.7 11.3° 1.9 3.8 0.0 3.8 0.0 6.0 0.0 18.0 18.0	$ \begin{array}{c cccc} 11.3 \\ 92.5 \\ 5.7 \\ 0.0 \\ 0.0 \\ 0.0 \\ 35.8 \\ 47.2 \\ \hline 10.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 6.0 \\ 62.0 \\ \end{array} $	67.9 0.0 79.2 100.0 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0	5.7 1.9 11.3 0.0 0.0 9.4 0.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.9283.0298.1296.2664.252.8484.02100.0100.0100.0476.05620.014.0	5.7 11.3 ° 1.9 3.8 0.0 0.0 6.0 0.0 6.0 0.0	$ \begin{array}{cccc} 92.5 \\ 5.7 \\ 0.0 \\ 0.0 \\ 35.8 \\ 47.2 \\ 10.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 6.0 \\ 62.0 \\ \end{array} $	0.079.2100.0100.050.952.824.098.0100.068.012.0	1.9 11.3 0.0 0.0 9.4 0.0
$ \begin{array}{r llllllllllllllllllllllllllllllllllll$	2 83.0 2 98.1 2 96.2 6 64.2 52.8 52.8 4 84.0 2 100.0 4 76.0 56 20.0 14.0 14.0	11.3 ^e 1.9 3.8 0.0 6.0 6.0 0.0 18.0 18.0	5.7 0.0 0.0 35.8 47.2 10.0 0.0 0.0 6.0 62.0	79.2 100.0 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0	11.3 0.0 0.0 9.4 0.0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2 98.1 2 96.2 6 64.2 4 52.8 4 84.0 2 100.0 100.0 100.0 4 76.0 56 20.0 14.0 14.0	1.9 3.8 0.0 6.0 0.0 18.0 18.0	0.0 0.0 35.8 47.2 10.0 0.0 0.0 6.0 62.0	100.0 100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0	0.0 0.0 9.4 0.0
$\leq 0.12 \text{ to } 2$ $\leq 0.12 \text{ to } 2$ $\leq 0.03 - >10$ $\leq 0.5 - >4$ $\leq 0.12 - 6$ $\leq 0.015 - 2$ $0.06 - 2$ $0.5 \text{ to } >64$ $0.25 - >25$ $1 - >256$ $\leq 0.03 - 0.2$	2 96.2 6 64.2 4 52.8 4 84.0 2 100.0 100.0 4 76.0 56 20.0 14.0	3.8 0.0 6.0 0.0 18.0 18.0	0.0 35.8 47.2 10.0 0.0 0.0 6.0 62.0	100.0 50.9 52.8 24.0 98.0 100.0 68.0 12.0	0.0 9.4 0.0 8.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	6 64.2 52.8 4 84.0 2 100.0 100.0 4 76.0 56 20.0 14.0	0.0 0.0 6.0 0.0 18.0 18.0 18.0	35.8 47.2 10.0 0.0 0.0 6.0 62.0	50.9 52.8 24.0 98.0 100.0 68.0 12.0	9.4 0.0 8.0
$\leq 0.5 - >4$ $\leq 0.12 - 6$ $\geq 0.015 - 2$ $= 0.06 - 2$ $= 0.5 \text{ to } >64$ $= 0.25 - >25$ $= 1 - >256$ $\leq 0.03 - 0.2$	4 52.8 4 84.0 2 100.0 100.0 4 76.0 56 20.0 14.0	6.0 0.0 18.0 18.0	47.2 10.0 0.0 0.0 6.0 62.0	52.8 24.0 98.0 100.0 68.0 12.0	8.0
$ \begin{array}{c} \leq 0.12 - 6 \\ \leq 0.015 - 2 \\ = 0.06 - 2 \\ 0.5 \text{ to } > 6 \\ = 0.25 - > 25 \\ = 1 - > 256 \\ = 0.03 - 0.2 \\ \end{array} $	4 84.0 2 100.0 100.0 4 76.0 56 20.0 14.0	6.0 0.0 18.0 18.0	10.0 0.0 0.0 6.0 62.0	24.0 98.0 100.0 68.0 12.0	8.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	4 84.0 2 100.0 100.0 4 76.0 56 20.0 14.0	6.0 0.0 18.0 18.0	10.0 0.0 0.0 6.0 62.0	24.0 98.0 100.0 68.0 12.0	8.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	2 100.0 100.0 4 76.0 56 20.0 14.0	0.0 0.0 18.0 18.0	0.0 0.0 6.0 62.0	98.0 100.0 68.0 12.0	8.0
$ \begin{array}{c} 0.06 - 2 \\ 0.5 \text{ to } > 64 \\ 0.25 - > 25 \\ 1 - > 256 \\ 5 \leq 0.03 - 0.25 \\ \end{array} $	100.0 1000.0 100000000	18.0 18.0	0.0 6.0 62.0	100.0 68.0 12.0	8.0
$ \begin{array}{c} 0.5 \text{ to } > 64 \\ 0.25 - > 25 \\ 1 - > 256 \\ 6 \leq 0.03 - 0.2 \end{array} $	4 76.0 56 20.0 14.0	18.0 18.0	6.0 62.0	68.0 12.0	8.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	56 20.0 14.0	18.0	62.0	12.0	
1 - >256 $\leq 0.03 - 0.2$	14.0	TOIO	0210	7710	X ()
$\leq 0.03 - 0.2$		20 0 e	66.0	20	20.0
	25 100.0	0.0	0.0	100.0	0.0
<0.12 to 2	2 940	6.0	0.0	100.0	0.0
0.03 - >10	6 28.0	4.0	68.0	22.0	4.0
<0.5 - >4	32.0		68.0	32.0	2.0
2 -> 256	48.0	10.0	42.0	0.0	
< 0.015 - 3	8 100.0	0.0	0.0	92.0	
0.25 – 16	<u>98.0</u>		2.0	98.0	
- 16 to >64	2.0	4.0	94.0	0.0	2.0
$6 \qquad 8 - > 256$	0.0	2.0	98.0	0.0	0.0
1 - >256	2.0	4.0 ^e	94.0	2.0	0.0
0.06 - >64	4 6.0	10.0	84.0	16.0	26.0
1 to >8	2.0	4.0	94.0	6.0	30.0
0.25 - >10	6 18.0	6.0	76.0	4.0	8.0
<0.5 - >4	18.4		81.6	18.4	10.2
0.5 - >25	6 28.8	15.4	55.8	5.8	
<0.015 - >	32 98.1	0.0	1.9	94.2	
0 12 - 4	100.0		0.0	100.0	
64 to > 64		5.8	94.2	0.0	0.0
0.5 - >25	6 9.6	3.8	86.5	77	1 9
0.5 > 25	6 9.6	5.8 ^e	84.6	5.8	5.8
0.12 - >6	4 28.8	13.5	57.7	42.3	7 7
$< 0.12 \pm 0.00$	8 5.8	20.8	63.5	36.5	36.5
	6 15.0	7 7	76.0	11.5	1.0
		1.1	Q16		5.9
6 0.03 - >1 <0.5	LO.4		04.0	10.4	0.0
	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccc} 6 & 1 - > 256 & 2.0 \\ \hline 0.06 - > 64 & 6.0 \\ 1 \text{ to } > 8 & 2.0 \\ \hline 0.25 - > 16 & 18.0 \\ \leq 0.5 - > 4 & 18.4 \\ \hline & & & \\ 8 & 0.5 - > 256 & 28.8 \\ \leq 0.015 - > 32 & 98.1 \\ 0.12 - 4 & 100.0 \\ \hline & 64 \text{ to } > 64 & 0.0 \\ \hline & 0.5 - > 256 & 9.6 \\ \hline & 0.5 - > 256 & 9.6 \\ \hline & 0.12 - > 64 & 28.8 \\ \leq 0.12 \text{ to } > 8 & 5.8 \\ \hline & 0.03 - > 16 & 15.4 \\ \leq 0.5 - > 4 & 15.4 \\ \end{array}$	6 $1 - > 256$ 2.0 4.0° 4 $0.06 - > 64$ 6.0 10.0 1 to >8 2.0 4.0 5 $0.25 - > 16$ 18.0 6.0 $\leq 0.5 - > 4$ 18.4 6.0 3 $0.5 - > 256$ 28.8 15.4 $\leq 0.015 - > 32$ 98.1 0.0 $0.12 - 4$ 100.0 $0.12 - 4$ 100.0 64 to > 64 0.0 5.8 6 $0.5 - > 256$ 9.6 3.8 6 $0.5 - > 256$ 9.6 5.8° $0.12 - > 64$ 28.8 13.5 ≤ 0.12 to > 8 5.8 30.8 5.8 $0.03 - > 16$ 15.4 7.7 $\leq 0.5 - > 4$ 15.4	6 $1 - > 256$ 2.0 4.0° 94.0 4 $0.06 - > 64$ 6.0 10.0 84.0 1 to >8 2.0 4.0 94.0 5 $0.25 - > 16$ 18.0 6.0 76.0 $\leq 0.5 - > 4$ 18.4 81.6 3 $0.5 - > 256$ 28.8 15.4 55.8 $\leq 0.015 - > 32$ 98.1 0.0 1.9 $0.12 - 4$ 100.0 0.0 4 64 to > 64 0.0 5.8 94.2 5 $0.5 - > 256$ 9.6 3.8 86.5 6 $0.5 - > 256$ 9.6 5.8° 84.6 $0.12 - > 64$ 28.8 13.5 57.7 ≤ 0.12 to > 8 5.8 30.8 63.5 6 $0.03 - > 16$ 15.4 7.7 76.9 $\leq 0.5 - > 4$ 15.4 7.7 84.6	6 $1 - > 256$ 2.0 4.0° 94.0 2.0 4 $0.06 - > 64$ 6.0 10.0 84.0 16.0 1 to >8 2.0 4.0 94.0 6.0 $0.25 - > 16$ 18.0 6.0 76.0 4.0 $\leq 0.5 - > 4$ 18.4 81.6 18.4 $\leq 0.5 - > 4$ 18.4 81.6 18.4 $\leq 0.5 - > 256$ 28.8 15.4 55.8 5.8 $\leq 0.015 - > 32$ 98.1 0.0 1.9 94.2 $0.12 - 4$ 100.0 0.0 100.0 100.0 64 to > 64 0.0 5.8 94.2 0.0 $0.5 - > 256$ 9.6 3.8 86.5 7.7 6 $0.5 - > 256$ 9.6 5.8° 84.6 5.8 $0.12 - > 64$ 28.8 13.5 57.7 42.3 ≤ 0.12 to > 8 5.8 30.8 63.5 36.5 $0.03 - >16$ 15.4 7.7 76.9 11.5

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

% R
92.7 ^b
 5.4 ^b
1.5
 62.0
92.2
 67.8
26.8
 22.4
71.7
 65.7
100.0 ^b
5.7 b
3.8
26.4
 98.1
9.4
0.0
0.0
39.6
47.2
76.0 ^b
2.0 ^b
0.0
24.0
80.0
78.0
0.0
 0.0
74.0
66.0
100.0 ^b
8.0 ^b
2.0
98.0
100.0
98.0
58.0
64.0
88.0
71.4
94.2 ^b
5.8 ^b
0.0
100.0

90.4

88.5

50.0 26.9

86.5

78.8

Results

- Overall, ceftibuten/VNRX-5236 (MIC_{50/90}, 0.12/1 mg/L) MIC results were 256fold 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 piperacillintazobactam (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 (\leq 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 MIC₉₀ values 4- to 8-fold lower than ceftazidimeavibactam (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)</p>
- While ceftibuten/VNRX-5236 had an MIC₉₀ value 8-fold lower than ceftazidimeavibactam against KPC producers, these 2 combinations had similar MIC₉₀ 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 $\leq 1 \text{ mg/L}$ 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

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