Poster #P1183
ECCMID 2019

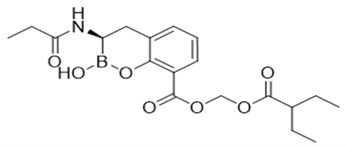
Oral ceftibuten/VNRX-7145 shows comparable activity *in vitro* to IV therapeutics against MDR Enterobacteriaceae

Jodie C. Hamrick, Cassandra L. Chatwin, Kaitlyn J. John, Christopher J. Buns, Luigi Xerri, Greg Moeck, Daniel C. Pevear
VenatoRx Pharmaceuticals, Inc. Malvern, PA 19355 USA.
Contact: hamrick@venatorx.com

Background

VNRX-7145 is a novel cyclic boronate β-lactamase inhibitor (BLI) that undergoes biotransformation in vivo to the active BLI VNRX-5236 with potent inhibitory activity against Ambler class A, C, and D enzymes including those that hydrolyze carbapenems. When combined with ceftibuten, an orally bioavalable cephalosporin, the resulting investigational combination has similar potency in vitro against MDR Enterobacteriaceae as IV β-lactam and β-lactam/BLI antibiotics such as meropenem, meropenem/vaborbactam and ceftazidime/avibactam. This oral combination could allow for earlier discharge from the hospital providing a benefit to the patient and reduction in health care cost.

Structure of VNRX-7145



Methods

Broth microdilution minimum inhibitory concentration (MIC) assays were carried out according to CLSI guidelines. BLIs were fixed at a concentration of 4 mg/L (VNRX-5236, tazobactam, and avibactam) or 8 mg/L (vaborbactam). The antibacterial activity of VNRX-5236 in combination with ceftibuten was compared to ceftibuten alone, meropenem, piperacillin/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, tobramycin, and tigecycline in 193 strains of Enterobacteriaceae expressing Class A ESBL (N=33), Class A KPC (N=77), Class D OXA-48 (39), and Class C (44) enzymes. β-lactamase genes were verified using polymerase chain reaction while gene expression was determined phenotypically. MIC results were interpreted using CLSI M100 Ed. 29 (2019) or EUCAST v9.0 Clinical Breakpoints (2019).

Ceftibuten/VNRX-5236 and comparators in ESBL-expressing Enterobacteriaceae (n = 33)

Test Article	MIC_{50} mg/L	MIC_{90} mg/L	Number of strains at MIC value: ≤ 0.06 mg/L	0.125 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L	8 mg/L	16 mg/L	≥32 mg/L
Ceftibuten	4	≥ 32	0	2	3	2	4	2	8	5	1	6
Ceftibuten + VNRX-5236 (4 mg/L)	0.125	0.25	12	15	4	1	1	0	0	0	0	0
Ceftazidime + avibactam (4 mg/L)	0.5	0.5	2	4	10	15	1	0	0	0	1	0
Meropenem + vaborbactam (8 mg/L)	≤ 0.06	≤ 0.06	31	2	0	0	0	0	0	0	0	0
Piperacillin + tazobactam (4 mg/mL)	16	≥ 32	0	0	0	0	0	5	7	3	3	15
Tobramycin	≥ 32	≥ 32	0	0	0	3	5	2	1	1	4	17
Tigecycline	0.5	2	0	4	10	11	3	3	2	0	0	0
Meropenem	≤ 0.06	0.125	29	1	0	0	1	1	0	1	0	0

Strain set composed of *C. freundii* (1), *E. coli* (11), *K. oxytoca* (3), and *K. pneumoniae* (18)

Ceftibuten/VNRX-5236 and comparators in KPC-expressing Enterobacteriaceae (n = 77)

Test Article	MIC_{50} mg/L	MIC_{90} mg/L	Number of strains at MIC value: ≤ 0.06 mg/L	0.125 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L	8 mg/L	16 mg/L	≥32 mg/L
Ceftibuten	16	≥ 32	0	0	0	2	2	4	7	13	24	25
Ceftibuten + VNRX-5236 (4 mg/L)	0.25	1	10	20	17	22	4	0	2	1	0	1
Ceftazidime + avibactam (4 mg/L)	1	8	0	0	2	10	27	19	7	10	1	1
Meropenem + vaborbactam (8 mg/L)	≤ 0.06	2	40	6	6	7	9	5	3	1	0	0
Piperacillin + tazobactam (4 mg/mL)	≥ 32	≥ 32	0	0	0	0	0	0	1	0	0	76
Tobramycin	≥ 32	≥ 32	0	0	1	3	0	2	0	3	3	65
Tigecycline	1	2	0	0	4	19	34	15	5	0	0	0
Meropenem	≥ 32	≥ 32	1	0	0	1	0	3	4	11	13	44

Strain set composed of *E. cloacae* (4), *E. coli* (4), *K. pneumoniae* (67), and *K. oxytoca* (2)

Ceftibuten/VNRX-5236 and comparators in OXA-48-expressing Enterobacteriaceae (n = 39)

Test Article	MIC_{50} mg/L	MIC_{90} mg/L	Number of strains at MIC value: ≤ 0.06 mg/L	0.125 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L	8 mg/L	16 mg/L	≥32 mg/L
Ceftibuten	16	≥ 32	1	0	0	1	0	0	2	4	13	18
Ceftibuten + VNRX-5236 (4 mg/L)	0.125	2	8	15	6	2	3	1	1	2	0	1
Ceftazidime + avibactam (4 mg/L)	0.5	2	0	1	9	13	10	4	1	0	0	1
Meropenem + vaborbactam (8 mg/L)	2	8	0	2	1	9	3	11	5	4	2	2
Piperacillin + tazobactam (4 mg/mL)	≥ 32	≥ 32	0	0	0	0	0	0	1	0	1	37
Tobramycin	16	≥ 32	0	0	0	3	4	6	1	1	6	18
Tigecycline	0.5	2	0	1	4	16	11	4	1	2	0	0
Meropenem	2	8	1	1	4	6	6	10	3	4	2	2

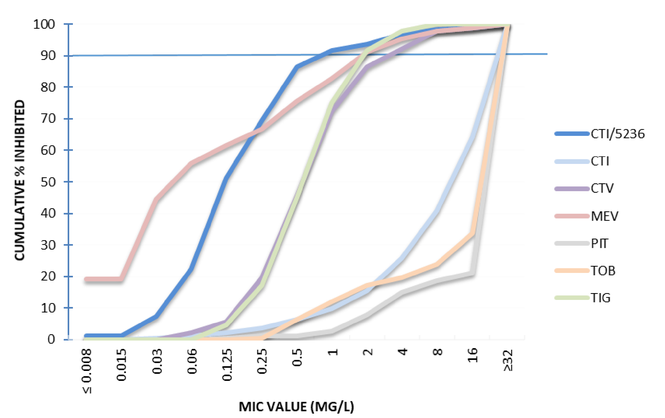
Strain set composed of *E. cloacae* (1), *E. coli* (15), *K. pneumoniae* (22), and *M. morgannii* (1)

Ceftibuten/VNRX-5236 and comparators in AmpC/CMY-expressing Enterobacteriaceae (n = 44)

Test Article	MIC_{50} mg/L	MIC_{90} mg/L	Number of strains at MIC value: ≤ 0.06 mg/L	0.125 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L	8 mg/L	16 mg/L	≥32 mg/L
Ceftibuten	≥ 32	≥ 32	1	0	0	0	1	5	3	7	7	20
Ceftibuten + VNRX-5236 (4 mg/L)	0.25	2	13	6	8	8	2	3	3	0	1	0
Ceftazidime + avibactam (4 mg/L)	0.5	2	2	2	6	12	14	4	3	1	0	0
Meropenem + vaborbactam (8 mg/L)	≤ 0.06	0.25	37	1	3	1	2	0	0	0	0	0
Piperacillin + tazobactam (4 mg/mL)	≥ 32	≥ 32	0	1	1	0	3	5	5	4	1	24
Tobramycin	≥ 32	≥ 32	0	0	0	2	2	0	3	3	6	28
Tigecycline	1	4	0	4	6	8	10	10	4	2	0	0
Meropenem	≤ 0.06	0.5	34	2	2	2	1	0	3	0	0	0

Strain set composed of *C. freundii* (2), *E. aerogenes* (5), *E. cloacae* (5), *E. coli* (8), *K. oxytoca* (2), *K. pneumoniae* (10), *P. mirabilis* (1), *Salmonella spp.* (2), and *S. marcescens* (9)

Cumulative % inhibited across all 193 isolates



- Abbreviations: CTI = ceftibuten, CTI/5236 = ceftibuten + VNRX-5236 fixed at 4 mg/L, CTV = ceftazidime-avibactam, MEV = meropenem-vaborbactam, PIT = piperacillin-tazobactam, TOB = tobramycin, TIG = tigecycline

Conclusions

- VNRX-5236 improved the ceftibuten activity profile to that comparable or superior to recently-approved and legacy IV antibiotics in Enterobacteriaceae expressing serine β-lactamases
- This desirable potency and spectrum of activity supports the development of ceftibuten/VNRX-5236 to address the urgent medical need for oral therapies to combat β-lactamase expressing Enterobacteriaceae

References

- Clinical and Laboratory Standards Institute. 2018. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. M07, 11th Edition.
- Clinical and Laboratory Standards Institute. 2019. Performance standards for antimicrobial susceptibility testing; 29th edition. CLSI Supplement M100S.
- European Committee on Antimicrobial Susceptibility Testing (EUCAST). 2019. Clinical breakpoints for bacteria (v 9.0).
- Bush 2013. The ABCD's of β-lactamase nomenclature. J. Infect. Chemother., 19(4):549-559.
- Drawz and Bonomo 2010. Three Decades of β-lactamase Inhibitors. Clinical Microbiology Reviews., 23(1): p160-201.

This project has been funded in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272201600029C.