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In Vitro Activity of Ceftibuten in Combination with VNRX-7145 and Comparators against 1,066 UTI Isolates Non-susceptible to Amoxicillin-clavulanate and Levofloxacin

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INTRODUCTION

VenatoRx is currently developing VNRX-7145, a novel oral beta-lactamase inhibitor in combination with ceftibuten to treat gram-negative infections resistant to front-line oral agents. VNRX-7145 undergoes biotransformation *in vivo* to the active beta-lactamase inhibitor, VNRX-5236. VNRX-5236 was tested in combination with ceftibuten against 1,066 *Enterobacteriaceae* isolates non-susceptible to amoxicillin-clavulanate and levofloxacin from urinary tract infections (UTI).

MATERIALS & METHODS

A total of 1,066 *Enterobacteriaceae* UTI isolates non-susceptible to amoxicillin-clavulanate and levofloxacin using CLSI 2017 breakpoints [1] were collected globally from 2014 to 2016. Isolates were from community- and hospital-associated sources, distributed globally (region [n/percent of total]: Africa [16/1.5], Asia [116/10.9], Europe [506/47.5], Latin America [246/23.1], Middle East [75/7.0], North America [62/5.8], and South Pacific [45/4.2]). Minimal inhibitory concentration (MIC) values were determined following CLSI guidelines [2]. Sixty-one isolates were previously tested and found to be positive for KPC enzymes. As ceftibuten/VNRX-5236 breakpoints have not yet been established, the ceftibuten CLSI susceptible breakpoint of ≤8 µg/mL was applied for comparative purposes.

RESULTS

Table 1. *In Vitro* Activity of Ceftibuten/VNRX-5236 Against *Enterobacteriaceae* Isolates from Urinary Tract Infections

Organism, phenotype (n)	Compound	%S	%I	%R	µg/mL		
					MIC_{50}	MIC_{90}	Range
Enterobacteriaceae (1066)	Ceftibuten/VNRX-5236*	94.5	1.0	4.5	≤0.25	2	≤0.25 - > 32
	Ceftibuten	58.3	13.0	28.8	8	> 32	0.12 - > 32
	Amoxicillin-clavulanate	0.0	46.1	53.9	32	> 64	16 - > 64
	Ceftazidime-avibactam	97.2	0.0	2.8	0.25	2	≤0.03 - > 32
	Ceftolozane-tazobactam	55.9	8.3	35.8	2	> 8	≤0.25 - > 8
	Levofloxacin	0	0	100	> 4	> 4	4 - > 4
	Piperacillin-tazobactam	32.7	22.0	45.3	64	> 64	≤0.5 - > 64
Enterobacteriaceae, ceftibuten NS (445)	Ceftibuten/VNRX-5236*	86.7	2.5	10.8	≤0.25	32	≤0.25 - > 32
	Ceftibuten	0.0	31.0	69.0	32	> 32	16 - > 32
	Amoxicillin-clavulanate	0.0	27.0	73.0	32	> 64	16 - > 64
	Ceftazidime-avibactam	93.3	0.0	6.7	0.5	4	≤0.03 - > 32
	Ceftolozane-tazobactam	26.5	9.2	64.3	> 8	> 8	≤0.25 - > 8
	Levofloxacin	0	0	100	> 4	> 4	4 - > 4
	Piperacillin-tazobactam	13.3	17.1	69.7	> 64	> 64	2 - > 64
Enterobacteriaceae, KPC-positive (61)	Ceftibuten/VNRX-5236*	95.1	3.3	1.6	≤0.25	2	≤0.25 - 32
	Ceftibuten	45.9	29.5	24.6	16	> 32	0.12 - > 32
	Amoxicillin-clavulanate	0.0	1.6	98.4	> 64	> 64	16 - > 64
	Ceftazidime-avibactam	98.4	0.0	1.6	1	2	0.25 - 16
	Ceftolozane-tazobactam	1.6	0.0	98.4	> 8	> 8	0.5 - > 8
	Levofloxacin	0	0	100	> 4	> 4	> 4 - > 4
	Piperacillin-tazobactam	0.0	1.6	98.4	> 64	> 64	32 - > 64
Enterobacteriaceae, ESBL-positive (634)	Ceftibuten/VNRX-5236*	96.9	0.2	3.0	≤0.25	0.5	≤0.25 - > 32
	Ceftibuten	56.9	16.1	27.0	8	> 32	0.12 - > 32
	Amoxicillin-clavulanate	0.0	61.7	38.3	16	64	16 - > 64
	Ceftazidime-avibactam	100	0	0	0.25	1	≤0.03 - 8
	Ceftolozane-tazobactam	54.3	9.5	36.3	2	> 8	≤0.25 - > 8
	Levofloxacin	0	0	100	> 4	> 4	4 - > 4
	Piperacillin-tazobactam	28.1	25.7	46.2	64	> 64	≤0.5 - > 64

%S, I, R, percent susceptible, intermediate, resistant; *as ceftibuten/VNRX-5236 breakpoints have not yet been established, the ceftibuten CLSI susceptible breakpoint of ≤8 µg/mL was applied for comparative purposes.

Figure 1a. Distribution of 1,066 *Enterobacteriaceae* by Species

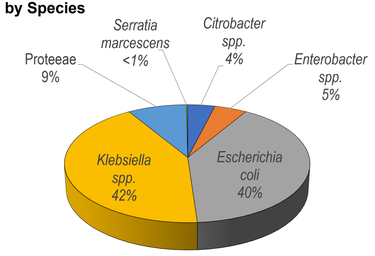


Figure 1b. Distribution of 1,066 *Enterobacteriaceae* by Molecular Characterization

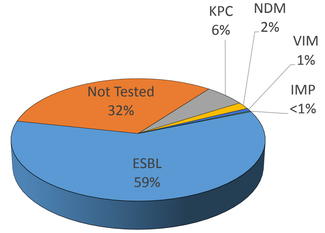
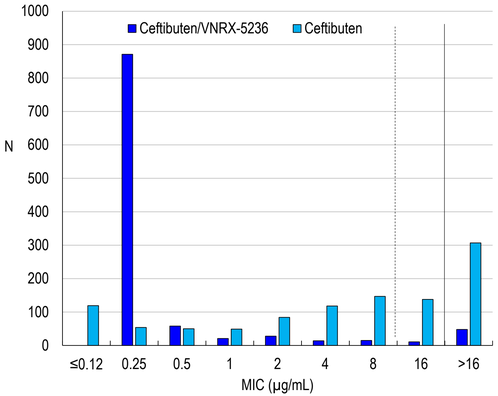
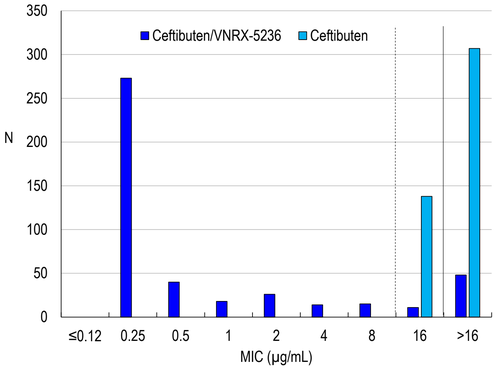


Figure 2. Ceftibuten and Ceftibuten/VNRX-5236 MIC Distributions Against 1,066 *Enterobacteriaceae* Non-susceptible to Amoxicillin-clavulanate and Levofloxacin



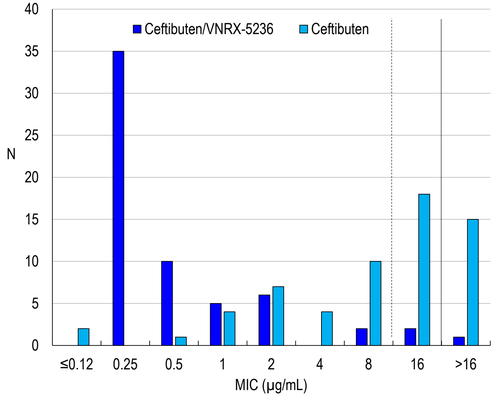
The dashed and solid lines indicate the CLSI ceftibuten susceptible and intermediate breakpoints, respectively.

Figure 3. Ceftibuten and Ceftibuten/VNRX-5236 MIC Distributions Against 445 *Enterobacteriaceae* Non-susceptible to Amoxicillin-clavulanate, Levofloxacin and ceftibuten



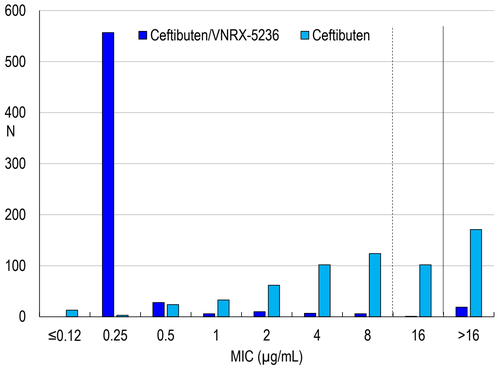
The dashed and solid lines indicate the CLSI ceftibuten susceptible and intermediate breakpoints, respectively.

Figure 4. Ceftibuten and Ceftibuten/VNRX-5236 MIC Distributions Against 61 KPC-producing *Enterobacteriaceae* Non-susceptible to Amoxicillin-clavulanate and Levofloxacin



The dashed and solid lines indicate the CLSI ceftibuten susceptible and intermediate breakpoints, respectively.

Figure 5. Ceftibuten and Ceftibuten/VNRX-5236 MIC Distributions Against 634 ESBL-producing *Enterobacteriaceae* Non-susceptible to Amoxicillin-clavulanate and Levofloxacin



The dashed and solid lines indicate the CLSI ceftibuten susceptible and intermediate breakpoints, respectively.

RESULTS SUMMARY

- The MIC_{90} value for ceftibuten/VNRX-5236 was 2 µg/mL, compared to >32 µg/mL for ceftibuten alone against all *Enterobacteriaceae* (Table 1, Figure 2).
- 94.5% of isolates were inhibited by ceftibuten/VNRX-5236 at ≤8 µg/mL, and 89.1% were inhibited at 1 µg/mL compared to 58.3% susceptible to ceftibuten alone.
- Ceftibuten/VNRX-5236 activity was similar against KPC- producing isolates, with an MIC_{90} value of 2 µg/mL, 95.1% inhibited at ≤8 µg/mL and 82.0% inhibited at 1 µg/mL, compared to an MIC_{90} of >32 µg/mL and 45.9% susceptible to ceftibuten alone (Table 1, Figure 4).
- Ceftibuten/VNRX-5236 maintained activity against ESBL-producing isolates with an MIC_{90} value of 0.5 µg/mL and 96.9% inhibited at ≤8 µg/mL and 93.2% inhibited at ≤1 µg/mL.

CONCLUSIONS

- Ceftibuten in combination with VNRX-5236 exhibited potent *in vitro* activity against recent resistant UTI isolates, including KPC-positive strains.
- Because this orally-available drug combination exhibited substantial potential for the treatment of infections caused by isolates non-susceptible to currently marketed antimicrobials, further development is warranted.

REFERENCES

1. Clinical and Laboratory Standards Institute. 2015. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Tenth Edition*. CLSI document M07-A10 Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2017. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seventh Informational Supplement*. CLSI Document M100S 2017. Wayne, PA.

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