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In vitro Activity of Ceftibuten in Combination with VNRX-5236 against Clinical Isolates of *Enterobacterales* Collected in 2018-2020

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DISCLOSURES

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INTRODUCTION

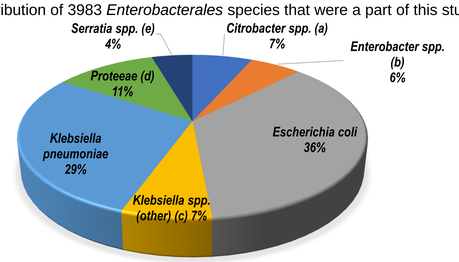
Oral antimicrobial agents effective against Gram negative bacteria that are becoming increasing resistant to available drugs are urgently needed, especially for urinary tract infections that can be managed on an outpatient basis. Ceftibuten in combination with VNRX-7145 is under development as an oral treatment for complicated urinary tract infections caused by serine β-lactamase-producing *Enterobacterales*, including isolates carrying ESBLs and serine carbapenemases. *In vivo*, VNRX-7145 (VNRX-5236 etzadroxil) is cleaved into to the active enzyme inhibitor, VNRX-5236. This study assessed the *in vitro* activity of ceftibuten/VNRX-5236 and comparator agents against 3,893 isolates of *Enterobacterales* from a 2018-2020 global culture collection.

MATERIALS & METHODS

- MICs of ceftibuten with VNRX-5236 fixed at 4 mg/L and comparators were determined following the ISO 20776-1:2019 reference method against 3,893 *Enterobacterales* [1].
- Isolates were from community and hospital infections collected from 229 clinical sites globally in 52 countries in 2018-2020.
- *In vitro* activity interpretation employed EUCAST 2021 breakpoints [2] except where otherwise noted.
- As ceftibuten/VNRX-5236 breakpoints have not yet been established, the ceftibuten breakpoint of ≤1 mg/L was applied for comparison purposes; the provisional breakpoint of ≤0.125 mg/L was applied for tebipenem [3].
- All isolates with ceftibuten/VNRX-5236 MIC values ≥2 µg/mL were interrogated by either WGS (n=99) or PCR followed by Sanger sequencing (n=62) for β-lactamase genes as previously described [4]. An additional set of isolates with ceftibuten/VNRX-5236 MIC values < 2 mg/L were examined by PCR/Sanger (n=275) or WGS (n=4).

RESULTS

Figure 1. Distribution of 3983 *Enterobacterales* species that were a part of this study



[a]*Citrobacter* spp. isolates consist of (n): *C. amalonaticus* (4); *C. braakii* (14); *C. farmeri* (2); *C. freundii* (149); *C. koseri* (84); *C. sedlakii* (2); *Citrobacter* sp. (3); *C. youngae* (1)
[b]*Enterobacter* spp. isolates consist of (n): *E. asburiae* (10); *E. bugandensis* (21); *E. cloacae* (138); *E. cloacae* complex, unable to further speciate (12); *E. kobei* (1); *E. ludwigii* (1); *Enterobacter* sp. (20); *E. xiangfangensis* (19)
[c]Includes (n): *K. aerogenes* (91), *K. oxytoca* (183), *K. variicola* (1).
[d]Includes (n): *Morganella morganii* (88); *Proteus mirabilis* (181); *Proteus vulgaris* (77); *Providencia alcalifaciens*, (1) *Providencia rettgeri* (43); *Providencia stuarti* (45).
[e]Includes (n): *Serratia liquefaciens* (2); *Serratia marcescens* (101); *Serratia* sp. (68); *Serratia ureilytica* (5).

Figure 2. Distribution of 3983 *Enterobacterales* that were a part of this study by global region from which they originated

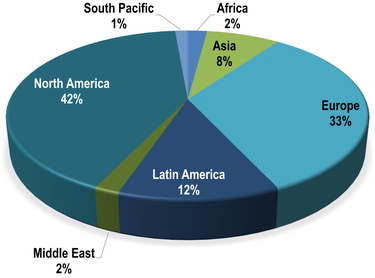
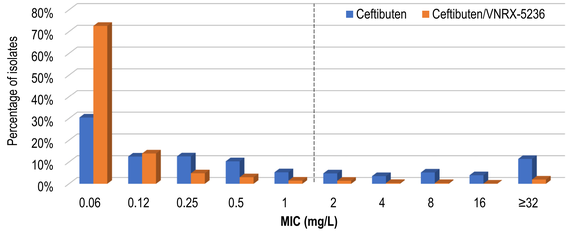
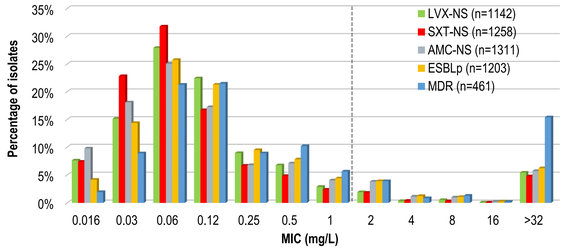


Figure 3. MIC distribution of ceftibuten and ceftibuten/VNRX-5236 against 3893 *Enterobacterales* collected globally



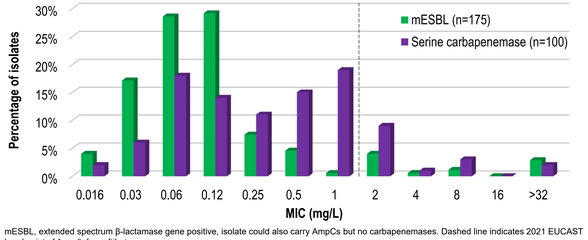
Dashed line indicates 2021 EUCAST breakpoint of 1 mg/L for ceftibuten.

Figure 4. MIC distribution of ceftibuten/VNRX-5236 against resistant phenotypes



NS, non-susceptible; LVX, levofloxacin; SXT, trimethoprim-sulfamethoxazole; AMC, amoxicillin clavulanate (CLSI 2021 breakpoints used to define non-susceptible group); ESBLp, phenotypic ESBL defined as ceftazidime and/or cefepime MIC ≥2 mg/L; MDR defined as resistance to at least one agent from ≥3 drug classes based on CLSI M100 [5]. Dashed line indicates 2021 EUCAST breakpoint of 1 mg/L for ceftibuten.

Figure 5. MIC distribution of ceftibuten/VNRX-5236 against ESBL positive and serine carbapenemase positive *Enterobacterales*



mESBL, extended spectrum β-lactamase gene positive, isolate could also carry AmpCs but no carbapenemases. Dashed line indicates 2021 EUCAST breakpoint of 1 mg/L for ceftibuten.

Table 1. *In vitro* activity of ceftibuten/VNRX-5236 and comparator agents against *Enterobacterales* collected globally

Phenotype / Genotype (n)	Drug	MIC_{50}	MIC_{90}	%Sus	%Int	%Res
All (n=3893)	Ceftibuten	0.25	32	71.2	na	28.8
	Ceftibuten/VNRX-5236	0.06	0.25	95.9	na	4.1
	Amoxicillin-clavulanate	4	32	na	na	na
	Cefazolin	16	>32	0.0	45.2	54.8
	Cefixime	0.5	>8	64.0	na	36.0
	Ceftazidime	0.5	>16	69.9	4.9	25.2
	Imipenem	0.25	2	94.1	2.2	3.7
	Levofloxacin	0.12	>8	70.6	4.5	24.9
	Meropenem	0.06	0.12	95.8	1.1	3.2
	Nitrofurantoin	32	>128	73.2	na	26.8
	Tebipenem	0.03	0.25	85.8	na	14.2
	Trimethoprim-sulfa	≤0.25	>4	67.7	1.1	31.2
LVX-NS (n=1142)	Ceftibuten	4	>32	38.5	na	61.5
	Ceftibuten/VNRX-5236	0.06	1	91.7	na	8.3
	Amoxicillin-clavulanate	8	>32	na	na	na
	Cefazolin	>32	>32	0.0	20.0	80.0
	Cefixime	>8	>8	30.9	0.0	69.1
	Ceftazidime	16	>16	32.7	6.5	60.9
	Imipenem	0.25	8	86.3	2.6	11.0
	Levofloxacin	>8	>8	0.0	15.2	84.8
	Meropenem	0.06	16	87.3	2.6	10.1
	Nitrofurantoin	32	>128	64.8	na	35.2
	Tebipenem	0.06	>4	73.6	na	26.4
	Trimethoprim-sulfa	>4	>4	31.3	2.0	66.6
SXT-NS (n=1258)	Ceftibuten	2	>32	45.6	na	54.4
	Ceftibuten/VNRX-5236	0.06	0.5	92.6	na	7.4
	Amoxicillin-clavulanate	8	>32	na	na	na
	Cefazolin	>32	>32	0.0	25.6	74.4
	Cefixime	>8	>8	38.2	na	61.8
	Ceftazidime	8	>16	44.3	5.6	50.2
	Imipenem	0.25	4	87.8	2.5	9.7
	Levofloxacin	2	>8	37.7	9.1	53.2
	Meropenem	0.06	4	89.3	2.1	8.6
	Nitrofurantoin	32	>128	69.6	na	30.4
	Tebipenem	0.03	>4	78.5	na	21.5
	Trimethoprim-sulfa	>4	>4	0.0	3.4	96.6
AMC-NS (n=1311)	Ceftibuten	2	>32	46.9	na	53.1
	Ceftibuten/VNRX-5236	0.06	2	88.1	na	11.9
	Amoxicillin-clavulanate	32	>32	0.0	32.6	67.4
	Cefazolin	>32	>32	0.0	2.0	98.0
	Cefixime	4	>8	34.1	na	65.9
	Ceftazidime	2	>16	47.9	7.9	44.2
	Imipenem	0.5	8	85.0	4.2	10.8
	Levofloxacin	0.25	>8	61.8	6.0	32.3
	Meropenem	0.12	8	87.6	3.0	9.4
	Nitrofurantoin	64	>128	59.0	na	41.0
	Tebipenem	0.12	>4	67.1	na	32.9
	Trimethoprim-sulfa	≤0.25	>4	62.7	1.5	35.8
ESBLp (n=1203)	Ceftibuten	8	>32	18.1	na	81.9
	Ceftibuten/VNRX-5236	0.12	2	87.2	na	12.8
	Amoxicillin-clavulanate	16	>32	na	na	na
	Cefazolin	>32	>32	0.0	2.8	97.2
	Cefixime	>8	>8	8.5	na	91.5
	Ceftazidime	>16	>16	2.7	15.8	81.5
	Imipenem	0.25	8	85.4	2.9	11.6
	Levofloxacin	4	>8	34.1	8.6	57.3
	Meropenem	0.06	16	86.3	3.5	10.2
	Nitrofurantoin	64	>128	68.7	na	31.3
	Tebipenem	0.06	>4	72.1	na	27.9
	Trimethoprim-sulfa	>4	>4	40.3	1.4	58.3
MDR (n=461)	Ceftibuten	16	>32	6.1	na	93.9
	Ceftibuten/VNRX-5236	0.12	>32	78.3	na	21.7
	Amoxicillin-clavulanate	16	>32	na	na	na
	Cefazolin	>32	>32	0.0	0.4	99.6
	Cefixime	>8	>8	2.2	na	97.8
	Ceftazidime	>16	>16	1.7	2.4	95.9
	Imipenem	0.5	>16	66.2	4.3	29.5
	Levofloxacin	>8	>8	5.4	4.1	90.5
	Meropenem	0.12	64	64.9	8.5	26.7
	Nitrofurantoin	64	>128	53.1	na	46.9
	Tebipenem	0.12	>4	55.7	na	44.3
	Trimethoprim-sulfa	>4	>4	21.9	2.2	75.9
ESBLm (n=175)	Ceftibuten	8	>32	9.1	na	90.9
	Ceftibuten/VNRX-5236	0.12	0.5	91.4	na	8.6
	Amoxicillin-clavulanate	8	16	na	na	na
	Cefazolin	>32	>32	0.0	0.0	100.0
	Cefixime	>8	>8	0.6	na	99.4
	Ceftazidime	>16	>16	1.7	5.1	93.1
	Imipenem	0.12	0.5	98.9	0.6	0.6
	Levofloxacin	>8	>8	18.9	8.6	72.6
	Meropenem	0.06	0.25	95.4	4.6	0.0
	Nitrofurantoin	32	>128	68.0	na	32.0
	Tebipenem	0.03	0.25	86.9	na	13.1
	Trimethoprim-sulfa	>4	>4	22.9	1.1	76.0
Serine carbapenemase (n=100)	Ceftibuten	32	>32	8.0	na	92.0
	Ceftibuten/VNRX-5236	0.25	2	85.0	na	15.0
	Amoxicillin-clavulanate	>32	>32	na	na	na
	Cefazolin	>32	>32	0.0	0.0	100.0
	Cefixime	>8	>8	4.0	na	96.0
	Ceftazidime	>16	>16	1.0	1.0	98.0
	Imipenem	8	>16	20.2	8.1	71.7
	Levofloxacin	>8	>8	12.0	5.0	83.0
	Meropenem	32	>64	12.0	18.0	70.0
	Nitrofurantoin	>128	>128	25.0	na	75.0
	Tebipenem	>4	>4	1.0	na	99.0
	Trimethoprim-sulfa	>4	>4	19.0	4.0	77.0

Ceftibuten/VNRX-5236, ceftibuten with VNRX-5236 fixed at 4 mg/L; Ceftibuten/VNRX-5236 MICs were interpreted using the ceftibuten breakpoint of ≤1 mg/L for comparison purposes only; provisional breakpoint of ≤0.125 mg/L was applied for tebipenem [3]; na, no breakpoint available; NS, non-susceptible; LVX, levofloxacin; SXT, trimethoprim-sulfamethoxazole; AMC, amoxicillin clavulanate (CLSI 2021 breakpoints [5] used to define non-susceptible group); ESBLm, extended spectrum β-lactamase gene positive, isolate could also carry AmpCs but no carbapenemases; ESBLp, phenotypic ESBL defined as ceftazidime and/or cefepime MIC ≥2 mg/L; MDR defined as resistance to at least one agent from ≥3 drug classes based on CLSI M100 [5]. Serine carbapenemases included KPC-2 (n=46), KPC-3 (n=18), KPC-33 (n=1), OXA-48 (n=17), OXA-181 (n=5), OXA-244 (n=1), and OXA-232 (n=12).

RESULTS SUMMARY

- Against the full collection of *Enterobacterales*, the addition of VNRX-5236 reduced ceftibuten MIC_{90} values from 32 mg/L to 0.25 mg/L and increased the percentage inhibited at ≤1 mg/L from 71.2% to 95.9% (Table 1, Figure 3).
- Ceftibuten/VNRX-5236 exhibited strong *in vitro* activity against isolates that were non-susceptible to common orally-administered antimicrobials, including levofloxacin, trimethoprim-sulfamethoxazole and amoxicillin-clavulanic acid with 91.7%, 92.6%, and 88.1% of the respective populations inhibited at ≤1 µg/mL (Table 1 and Figure 4). Tebipenem inhibited 73.6%, 69.6% and 67.1% of these subsets, respectively.
- Versus the phenotypically positive ESBL (cefepime and/or ceftazidime MIC≥2 mg/L) and multi-drug resistant (MDR) isolates, ceftibuten/VNRX-5236 showed good activity with 87.2% and 78.3% of the populations inhibited at ≤1 µg/mL, respectively (Table 1 and Figure 4). Tebipenem inhibited 72.1%, and 55.7% of these subsets, respectively.
- Ceftibuten/VNRX-5236 maintained activity against genotypically positive ESBL isolates (MIC_{90}, 0.5 mg/L; 91.4% inhibited at ≤1 mg/L) (Table 1, Figure 5) and serine carbapenemase-positive isolates (85.0 % inhibited at ≤1 mg/L) (Table 1, Figure 5).

CONCLUSIONS

Ceftibuten/VNRX-5236 exhibited promising *in vitro* activity against recent *Enterobacterales* and may have potential as an oral treatment option for complicated infections, including those caused by serine β-lactamase-expressing *Enterobacterales* (ESBL, KPC, OXA-48-like) for which there are currently few oral treatment options available.

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