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Ceftibuten-Xeruborbactam: In vitro Potency against Enterobacterales in Comparison with Other Oral Beta-lactams (BL) and Beta-lactamase Inhibitor (BLI) Combinations

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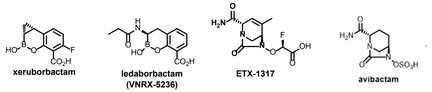
Background

- Oral antibiotics active against extended-spectrum β-lactamase (ESBL) and carbapenemase-producing (CRE) uropathogens are needed.
- New oral antibiotics and beta-lactamase inhibitors have entered into clinical testing, with varying sucess[1].
- Tebipenem completed a Phase 3 trial in cUTIs, but showed reduced efficacy compared to IV ertapenem in ESBL-producing Enterobacterales[2], suggesting that combining it with a beta-lactamase inhibitor may be necessary for improved efficacy against ESBL-producing strains.
- **Xeruborbactam (XER, formerly QPX7728)** is a novel ultra-broad spectrum inhibitor of serine and metallo-beta-lactamases based on a boronic acid pharmacophore[3].
- **Xeruborbatam** can be delivered IV or orally as the isobutyryloxymethyl prodrug[4].
- **Xeruborbactam** potentiates anti-microbial activity of multiple oral beta-lactam antibiotics against ESBL and carbapenemase-producing strains of *Enterobacterales*[5].
- The oral prodrug form of **xeruborbactam** has entered into clinical development.
- The objective of this study was to compare in vitro potency of BUT-XER to that of other investigational oral beta-lactams (BL) or BL/BLI combinations in head-to-head testing against recent isolates of ESBL and carbapenem-resistant Enterobacterales (CRE).



Methods:

The test panel of recent 980 worldwide isolates consisted of 515 ESBL and 465 carbapenem-resistant Enterobacterales including 168 MBL producers (157 NDM, 11 VIM, 1 IMP), 200 KPC producers and 97 isolates producing OXA-48-like beta-lactamases. Xeruborbactam combinations were tested using a fixed concentration of 4 mg/L. Other BL/BLI combinations were tested at their recommended BLI concentrations. MIC testing was conducted blinded to drug identity using CLSI reference methods and controlled using approved quality control bacterial strains and ranges. All enzymes were purified from overexpressing recombinant *E. coli* strains. K_i values of beta-lactamase inhibition for serine beta-lactamases (SBL) and metallo-beta-lactamases (MBL) were determined using nitrocefin (NCF) or imipenem (IMI) as a substrate.

Table 1: K_i values (in nM) of β-lactamase Inhibition by Xeruborbactam and Comparator BLIs

Enzyme	Class	Xeruborbactam	Avibactam	Ledaborbactam (VNRX-5236)	ETX-1317
KPC-2	A	1.4 ± 0.2	11 ± 3	130 ± 11	9.8 ± 1.6
CTX-M-14	A	0.29 ± 0.06	0.41 ± 0.13	2.0 ± 0.1	0.84 ± 0.08
CTX-M-15	A	0.37 ± 0.01	0.18 ± 0.08	3.0 ± 0.3	0.21 ± 0.2
SHV-12	A	0.74 ± 0.21	0.24 ± 0.07	21 ± 3	0.24 ± 0.06
TEM-10	A	0.66 ± 0.23	1.4 ± 0.4	63 ± 13	0.80 ± 0.13
P99	C	8.5 ± 2.4	10 ± 2	6.0 ± 2.0	3.0 ± 0.9
OXA-48	D	0.22 ± 0.08	36 ± 10	6.9 ± 1.9	7.4 ± 1.6
NDM-1	B	32 ± 14	>1.6 × 10^5	>2 × 10^4	>2 × 10^4
VIM-1	B	7.5 ± 2.1	>1.6 × 10^5	>2 × 10^4	>2 × 10^4
IMP-1	B	240 ± 30	>1.6 × 10^5	>2 × 10^4	>2 × 10^4

Nitrocefin was used as a substrate for all the enzymes except NDM-1 and IMP-1; for these two enzymes K_i was determined using imipenem. K_i^{app} values are used for class A, C, and B enzymes, and K_i values are used for class B enzymes.

Results

Table 2: MICs for Multiple Beta-lactams Alone or With Xeruborbactam and Comparator Combinations vs. Enterobacterales According to Beta-lactamase Production

	BUT	BUT+XER	BUT+LED	BUT+AVI	POD	POD+XER	POD+ ETX1317	CDR	CDR+XER	TBP	TBP+XER	CAZ+AVI	MEM-VAB
	ALL (N=980)												
MIC_{50}	16	0.06	0.125	≤0.03	64	0.25	0.125	>64	0.06	0.25	≤0.03	0.5	≤0.03
MIC_{90}	>64	2	>64	>64	64	8	2	>64	4	>64	0.5	64	64
	ESBL (N=515)												
MIC_{50}	8	≤0.03	0.06	≤0.03	64	0.125	0.125	>64	0.02	≤0.03	≤0.03	0.125	≤0.03
MIC_{90}	>64	0.125	0.25	0.06	64	0.5	0.25	>64	0.125	0.125	≤0.03	0.5	≤0.03
	KPC (N=200)												
MIC_{50}	16	0.06	0.25	0.06	64	0.5	0.25	>64	0.25	64	≤0.03	1	≤0.03
MIC_{90}	64	0.25	1	0.25	64	2	2	>64	1	>64	0.5	2	0.5
	OXA-48-like (N=97)												
MIC_{50}	64	0.25	0.5	0.25	64	2	1	>64	1	32	0.25	1	16
MIC_{90}	>64	0.5	2	0.5	64	8	2	>64	4	>64	0.5	2	32
	MBL (N=168)												
MIC_{50}	>64	2	>64	>64	64	16	2*	>64	4	64	0.06	64	64
MIC_{90}	>64	64	>64	>64	64	64	16*	>64	64	>64	4	64	>64

BUT, ceftibuten; XER, xeruborbactam; LED, ledaborbactam (VNRX-5236), AVI, avibactam; POD, cefpodoxime; CDR, cefdinir; TBP, tebipenem; CAZ, ceftazidime; MEM, meropenem; VAB, vaborbactam. Xeruborbactam, ledaborbactam and avibactam were tested in combination with antibiotics at a fixed 4 μg/ml; vaborbactam was tested with meropenem at a fixed 8 μg/ml; cefpodoxime was tested with ETX1317 as a 1:2 ratio.

* Activity of POD-ETX1317 against MBL producers is driven mainly by antibacterial activity of ETX1317 which is not translated to in vivo efficacy[6].

Figure 1: MIC Distribution of BL/BLI Combinations against Various Groups of Enterobacterales

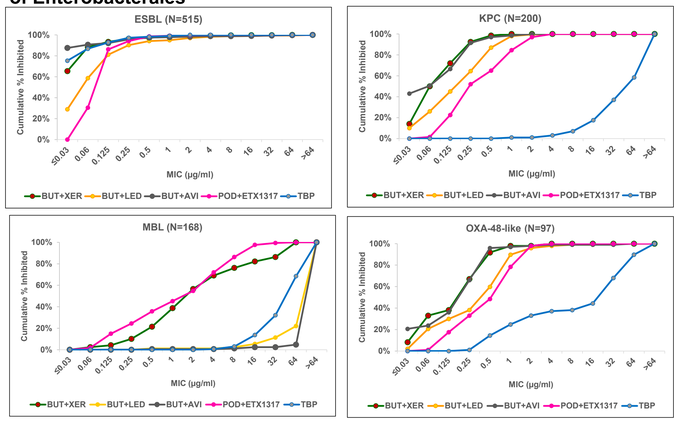
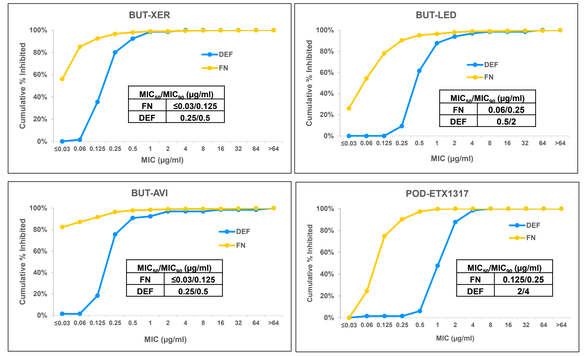


Figure 2: MICs for BL/BLI Combinations vs ESBL and KPC-producing Enterobacterales According to the Phenotypic Assessment of OmpK36 Function



DEF, defective; FN, functional. OmpK36 functional status in ESBL and KPC-producing strains of *Enterobacterales* was assessed based on meropenem-vaborbactam MIC: OmpK36 was considered as functional or defective if MEM-VAB MIC values were ≤0.125 μg/ml (N=651) or ≥0.25 μg/ml, respectively (N=65).

Table 3: Summary of Comparative Activity of Ceftibuten-Xeruborbactam

Beta-lactams and beta-lactam-beta-lactamase inhibitor[1] combinations	In Vitro Potency (MIC_{50}/MIC_{90}, mg/L) Against Enterobacterales				
	Beta-lactamase production				
	ALL (N=980)	ESBLs (N=515)	KPC (N=200)	OXA-48 like (N=97)	MBL (N=168)
Ceftibuten	16 / >64	8 / >64	16 / 64	64 / >64	>64 / >64
Ceftibuten/Xeruborbactam	0.06 / 2	≤0.03 / 0.125	0.06 / 0.25	0.25 / 0.5	2 / 64
Ceftibuten/Avibactam	≤0.03 / >64	≤0.03 / 0.06	0.06 / 0.25	0.25 / 0.5	64 / >64
Ceftibuten/Ledaborbactam (VNRX-5236)	0.125 / >64	0.06 / 0.25	0.25 / 1	0.25 / 2	64 / >64
Cefpodoxime	64 / 64	64 / 64	64 / 64	64 / 64	64 / 64
Cefpodoxime/ETX1317	0.125 / 2	0.125 / 0.25	0.25 / 2	1 / 2	2 / 16*
Tebipenem	0.5 / >64	≤0.03 / 0.125	64 / >64	32 / >64	64 / >64

[1] Xeruborbactam, avibactam and VNRX-5236 were tested with ceftibuten at fixed 4 mg/L; cefpodoxime was tested with ETX-1317 at 1:2 ratio.

Summary

- Xeruborbactam significantly increased activity of all oral beta-lactams against Enterobacterales.
- Compared to the investigational BL/BLIs and tebipenem, BUT-XER had the broadest antimicrobial profile, with activity against ESBL and all carbapenemase producing isolates.
- BUT-XER and BUT-AVI were the most potent BL/BLIs against ESBL producers with a potency comparable to that of the carbapenem tebipenem.
- BUT-XER and BUT-AVI were also the most potent BL/BLIs against CRE that produced serine carbapenemases (e.g. KPC or OXA-48-like enzymes). Tebipenem did not have activity against these isolates.
- BUT-XER and BUT-AVI were the least affected by defects in major porin OmpK36 compared to other BL/BLI combinations.
- BUT-XER and POD-ETX1317 were the only BL/BLIs with activity against MBL-producers; however, activity of POD-ETX1317 was mainly due to antibacterial activity of ETX1317 which is not translated to in vivo efficacy.
- In vitro potency and spectrum of ceftibuten-xeruborbactam combined with the potential for once-daily administration of the combination warrants further clinical development.

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