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Meropenem-Xeruborbactam: In Vitro Potency against Gram-Negative Bacteria in Comparison with Marketed and Investigational Beta-lactam (BL)/ Beta-lactamase Inhibitor (BLI) Combinations

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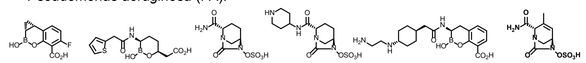
Background

- Several BLI combinations have entered into clinical testing or been approved for use but there are few comparative studies of their in vitro activity.
- **Xeruborbactam (formerly QPX7728)** is a new **ultra-broad-spectrum** beta-lactamase inhibitor based on a cyclic boronic acid pharmacophore with potent activity against serine beta-lactamases, including class A carbapenemases such as KPC, class D carbapenemases such as OXA-48 and OXA-23, and metallo-beta-lactamases such as VIM and NDM.
- **Xeruborbactam** restores the anti-microbial activity of multiple antibiotics against target gram-negative bacteria, Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- **Xeruborbactam** has entered into clinical development.
- The objective of this study was to compare in vitro potency of MEM-XER and other xeruborbactam combinations to that of other investigational and approved BL/BLI combinations in head-to-head testing against recent isolates of carbapenem-resistant *Enterobacterales* (CRE) and *Acinetobacter baumannii* (CRAB) as well as *Pseudomonas aeruginosa* (PA).



Methods:

The test panel of recent worldwide isolates consisted of 521 ESBL-producing *Enterobacterales*, 507 carbapeben-resistant Enterobacterales including 168 MBL producers (157 NDM, 11 VIM, 1 IMP), 505 carbapenem-resistant *A. baumannii*, and 506 *P. aeruginosa* that were representative of current isolates and included strains 101 carbapenem-resistant strains. Xeruborbactam was tested at a fixed 4 or 8 mg/L and other BL/BLI combinations at their established BLI concentrations. MIC testing was conducted blinded to drug identity using CLSI reference methods and controlled using approved quality control bacterial strains and ranges. Enzyme experiments were conducted using 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	Vaborbactam	Avibactam	Relebactam	Taniborbactam	Durlobactam
KPC-2	A	1.4 ± 0.2	56 ± 15	11 ± 3	40 ± 8	32 ± 0.009	1.7 ± 0.4
CTX-M-14	A	0.29 ± 0.06	33 ± 13	0.41 ± 0.13	10 ± 3	1.2 ± 0.5	0.37 ± 0.16
CTX-M-15	A	0.37 ± 0.01	30 ± 4	0.18 ± 0.08	24 ± 1	2.6 ± 0.1	0.21 ± 0.12
SHV-12	A	0.74 ± 0.21	21 ± 4	0.24 ± 0.07	36 ± 6	0.15 ± 0.03	0.74 ± 0.21
TEM-10	A	0.66 ± 0.23	140 ± 40	1.4 ± 0.4	48 ± 7	2.8 ± 0.8	0.99 ± 0.44
P99	C	8.5 ± 2.4	35 ± 15	10 ± 2	14 ± 2	2.4 ± 0.5	0.17 ± 0.08
OXA-48	D	0.22 ± 0.08	1.4 ± 0.5 × 10^4	36 ± 10	1.8 ± 0.1 × 10^3	6.1 ± 0.7	0.72 ± 0.27
OXA-23	D	0.74 ± 0.28	6.6 ± 1.1 × 10^3	1.7 ± 0.4 × 10^3	ND	>2 × 10^4	94 ± 32
NDM-1	B	32 ± 14	>1.6 × 10^5	>1.6 × 10^5	>1.6 × 10^5	31 ± 3	>1.6 × 10^5
VIM-1	B	7.5 ± 2.1	>1.6 × 10^5	>1.6 × 10^5	>1.6 × 10^5	4.5 ± 1.3	>1.6 × 10^5
IMP-1	B	240 ± 30	>1.6 × 10^5	>1.6 × 10^5	>1.6 × 10^5	>2 × 10^4	>1.6 × 10^5

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

	MEM	MEM+ XER (fixed 4 µg/ml)	MEM+ XER (fixed 8 µg/m)	FEP	FEP+XER (fixed 4 µg/m)	FEP+XER (fixed 8 µg/m)	FEP+TAN (fixed 4 µg/m)	TOL-TAZ	TOL-TAZ+XER (fixed 4 µg/m)	TOL-TAZ+XER (fixed 8 µg/m)	ATM	ATM+XER (fixed 4 µg/m)	ATM+XER (fixed 8 µg/m)	PIP-TAZ	MEM-VAB	IMP-REL	CAZ-AVI
ALL (N=1028)																	
MIC_{50}	0.5	≤0.03	≤0.03	64	≤0.03	≤0.03	0.125	8	0.125	0.06	64	64	≤0.03	128	≤0.03	0.125	0.5
MIC_{90}	>64	0.125	0.06	>64	0.5	0.25	2	>64	32	4	>64	>64	0.125	>128	64	16	>32
no MBL (N=860)																	
MIC_{50}	0.06	≤0.03	≤0.03	32	≤0.03	≤0.03	0.125	1	0.125	≤0.03	64	64	≤0.03	32	≤0.03	0.125	0.25
MIC_{90}	64	0.125	0.06	>64	0.25	0.125	2	>64	0.5	0.5	>64	>64	0.125	>128	2	2	2
ESBL (N=521)																	
MIC_{50}	≤0.03	≤0.03	≤0.03	16	≤0.03	≤0.03	0.05	0.5	0.06	≤0.03	32	32	≤0.03	4	≤0.03	0.125	0.25
MIC_{90}	0.06	≤0.03	≤0.03	>64	0.06	≤0.03	0.25	8	0.25	0.125	>64	>64	≤0.03	128	≤0.03	0.25	1
KPC (N=193)																	
MIC_{50}	16	≤0.03	≤0.03	>64	0.06	≤0.03	0.25	64	0.25	0.125	>64	>64	≤0.03	>128	≤0.03	0.125	1
MIC_{90}	>64	0.06	0.06	>64	0.25	0.25	1	>64	0.5	0.5	>64	>64	0.125	>128	0.5	0.5	2
OXA-48-like (N=96)																	
MIC_{50}	16	0.06	≤0.03	>64	0.25	0.06	1	64	0.5	0.25	>64	>64	0.06	>128	16	2	1
MIC_{90}	64	0.125	0.125	>64	1	1	4	>64	1	1	>64	>64	0.25	>128	32	8	2
Non-Carbapenemase-producing CRE (N=50)																	
MIC_{50}	4	0.125	0.06	>64	0.25	0.125	2	64	0.5	0.25	>64	>64	0.125	>128	1	0.25	1
MIC_{90}	16	0.5	0.5	>64	2	0.5	8	>64	2	0.5	>64	>64	0.5	>128	4	1	2
MBL (N=168)																	
MIC_{50}	64	0.06	≤0.03	>64	0.125	≤0.03	1	>64	64	8	>64	>64	≤0.03	>128	64	32	>32
MIC_{90}	>64	2	1	>64	4	0.5	16	>64	>64	64	>64	>64	0.125	>128	>64	>64	>32

MEM, meropenem; XER, xeruborbactam; FEP, cefepime; TAN, taniborbactam; ATM, aztreonam; CAZ, ceftazidime; AVI, avibactam; IMP, imipenem; REL, relebactam;. VAB, vaborbactam; TOL-TAZ, ceftolozane-tazobactam;PIP-TAZ, piperacillin-tazobactam. Taniborbactam, tazobactam, avibactam and relebactam were tested in combination with antibiotics at a fixed 4 µg/ml; vaborbactam was tested in combination with meropenem at a fixed concentration of 8 µg/ml.

Table 3: MICs for Multiple Beta-lactams Alone or With Xeruborbactam and Comparator Combinations vs. Carbapenem-Resistant *Acinetobacter baumannii*

Antibiotics/Activity	MIC_{50}	MIC_{90}	%S
Number of strains=505			
Meropenem	64	65	1.8%
Meropenem-Xeruborbactam (fixed 4 µg/ml)	1	4	99.8%
Meropenem-Xeruborbactam (fixed 8 µg/ml)	0.5	4	100.0%
Sulbactam	16	32	6.1%
Sulbactam-Xeruborbactam (fixed 4) µg/ml	2	4	95.2%
Sulbactam-Xeruborbactam (fixed 8 µg/ml)	1	4	97.2%
Sulbactam-Durlobactam (fixed 4 µg/ml)	1	2	97.6%
Imipenem	64	>64	0.6%
Imipenem-Xeruborbactam (fixed 4 µg/ml)	0.5	2	98.8%
Imipenem-Xeruborbactam (fixed 8 µg/ml)	0.125	1	99.8%
Imipenem-Durlobactam (fixed 4 µg/ml)	8	32	21.6%
Cefepime-Taniborbactam (fixed 4 µg/ml)	>32	>32	1.40%
Ceftazidime-avibactam	32	>32	12.3%

% S: meropenem, MEM and MEM-XER ≤ 8 µg/ml; imipenem, IMP and IMP-BLIs, ≤ 2 µg/ml; sulbactam, SUL and SUL-BLIs ≤ 4 µg/ml; FEP-TAN ≤ 8 µg/ml; CAZ-AVI ≤ 8 µg/ml;

Table 4: MICs for Multiple Beta-lactams Alone or With Xeruborbactam and Comparator Combinations vs. *P. aeruginosa* According to the Resistance Phenotype

	MEM	MEM+XER (fixed 4 µg/ml)	MEM+XER (fixed 8 µg/m)	FEP	FEP+XER (fixed 4 µg/m)	FEP+XER (fixed 8 µg/m)	FEP+TAN (fixed 4 µg/m)	TOL-TAZ	TOL-TAZ+XER (fixed 4 µg/m)	TOL-TAZ+XER (fixed 8 µg/m)	PIP-TAZ	PIP-TAZ+XER (fixed 4 µg/m)	PIP-TAZ+XER (fixed 8 µg/m)	CAZ+AVI	MEM+VAB	IMP+REL
Representative panel ALL (N=506)																
MIC_{50}	0.5	0.5	0.25	4	2	2	2	0.5	0.5	0.5	4	4	4	2	0.5	0.25
MIC_{90}	16	8	8	32	8	8	8	4	1	1	>128	16	16	8	16	2
%S	86.4%	92.5%	92.9%	80.8%	93.5%	94.3%	93.7%	91.5%	98.8%	99.4%	77.1%	90.9%	93.7%	93.5%	80.8%	93.5%
Ceftolozane-tazobctam non-susceptible (MIC≥8 µg/ml, N=43)																
MIC_{50}	16	4	4	32	8	4	8	16	1	1	>128	16	8	8	16	4
MIC_{90}	>64	32	16	>64	64	32	32	>64	8	4	>128	128	32	32	64	32
%S	37.2%	81.4%	83.7%	11.6%	74.4%	81.4%	76.7%	0.0%	86.0%	93.0%	11.6%	65.1%	83.7%	55.8%	25.6%	46.5%
Ceftazidime-avibactam resistant (MIC≥16 µg/ml, N=33)																
MIC_{50}	16	8	8	32	16	8	8	8	2	2	>128	32	32	16	32	2
MIC_{90}	64	32	32	>64	64	32	64	>64	8	4	>128	128	64	32	64	>64
%S	27.3%	51.5%	51.5%	3.0%	48.5%	51.5%	54.5%	42.4%	87.9%	93.9%	9.1%	24.2%	45.5%	0.0%	21.2%	60.6%
Carbapenem-resistant (meropenem MIC≥8 µg/ml, N=101)																
MIC_{50}	16	8	8	16	8	8	8	2	1	1	128	16	16	4	16	2
MIC_{90}	64	32	32	64	32	16	32	32	2	2	>128	32	32	16	64	16
%S	31.7%	62.4%	64.4%	35.6%	71.3%	74.3%	72.3%	66.3%	95.0%	97.0%	26.7%	68.3%	75.2%	74.3%	5.9%	67.3%

% S: meropenem, MEM and MEM+XER ≤8 µg/ml; cefepime, FEP and FEP+BLIs ≤ 8 µg/ml; ceftolozane-tazovactam, TOL-TAZ and TOL-TAZ+XER at BLIs ≤ 4 µg/ml; piperacillin-tazobactam, TOL-TAZ and TOL-TAZ+XER ≤ 16 µg/ml; imipenem-relebactan, IMP-REL ≤ 2 µg/ml, meropenem-vaborbactam, MER-VAB, ≤ 4 µg/ml; ceftazidime-avibactam, CAZ-AVI ≤ 8 µg/ml.

Summary

- Compared to the marketed or investigational BL/BLIs, MEM-XER had the broadest coverage of carbapenem-resistant gram-negative bacteria, with the most differentiating property being activity against multiple strains of MBL-producing CRE and CRAB.
- Compared to the marketed or investigational BL/BLIs, MEM-XER (4 µg/ml or 8 µg/ml) was the most potent agent vs CRE.
- MEM-XER and FEP-TAN were the only BL/BLIs with activity against MBL-producers; based on MIC_{90}, MEM-XER (MIC_{90} of 1-2 mg/L) was 8-16-fold more potent than FEP-TAN (MIC_{90} of 16 mg/L).
- Xeruborbactam significantly increased potency of other beta-lactams against Enterobacterales.
- MEM-XER (4 µg/ml or 8 µg/ml) and SUL-DUR were the only agents with high potency against CRAB, covering >95% of isolates.
- Xeruborbactam but not durlobactam significantly increased potency of carbapenems vs CRAB.
- Coverage of *P. aeruginosa* by MEM-XER (4 µg/ml or 8 µg/ml) was comparable to or exceeded other agents.
- Xeruborbactam (4 µg/ml or 8 µg/ml) in combination with Tol-Taz was the most potent combination vs *P. aeruginosa*
- While xeruborbactam in combination with meropenem had the broadest coverage overall, combinations with other beta-lactams provided superior coverage for some strains and resistance mechanisms.

Table 5: Summary of Comparative Activity of Meropenem-Xerubobactam

Inhibitor Combo	Enterobacterales				Non-Fermenters	
	ESBLs (N=521)	CRE/KPC (N=193)	CRE/OXA-48 (N=96)	CRE/Metallo (N=168)	Pseudomonas (N=506)	Acinetobacter Carbapenem-R (N=505)
Ceftolozane/ Tazobactam	0.5 / 8	64 / >64	64 / >64	>64 / >64	0.5 / 4	>64/>64
Imipenem/ Relebactam	0.125 / 0.5	0.125 / 0.5	2 / 8	32 / >32	0.25 / 2	>16/>16
Ceftazidime/ Avibactam	0.25 / 1	1 / 2	1 / 2	>32 / >32	2 / 8	32/>32
Meropenem/ Vaborbactam	≤0.03 / ≤0.03	≤0.03 / 0.5	16 / 32	64 / >64	0.5 / 16	>32/>32
Cefepime/ Taniborbactam	≤0.06 / 0.25	0.25 / 1	1 / 4	1 / 16	2 / 8	>32/>32
Sulbactam/ Durlobactam	Not tested	Not tested	Not tested	Not tested	Not tested	1 / 2
Meropenem/ Xeruborbactam	≤0.03 / ≤0.03	≤0.03 / 0.06	≤0.03 / 0.125	≤0.03 / 1	0.25 / 8	0.5 / 4

Meropenem with a fixed concentration of xeruborbactam 8 mg/ml shown; other BLIs as in Tables 2 and 3.

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