Poster # WMF21-0293

ETX0462 is a Novel PBP Inhibitor with Potent Activity against Recent, Global, Gram-Negative Clinical Isolates

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Abstract

Background: Penicillin binding proteins (PBPs), which are required for the synthesis of the bacterial cell wall, are the target of β-lactam antibiotics; however, the clinical prevalence and diversity of β-lactamases (enzymes that hydrolyze the β-lactam ring) is limiting the clinical utility of even the latest generation of β-lactams. ETX0462 is a novel, non-β-lactam inhibitor of PBP1a and PBP3 which was rationally designed based on the diazabicyclooctane (DBO) chemotype. The goal of this study was to determine the *in vitro* antibacterial activity of ETX0462 against recent, global, Gram-negative clinical isolates.

Methods: Clinical isolates were collected as part of the SENTRY surveillance program in 2017-2018 from Asia/West Pacific, Europe, Latin America and North America. Isolates were collected from bloodstream, intra-abdominal, pneumonia in hospitalized patients, skin/soft tissue and urinary tract sources of infection. The susceptibility of ETX0462 and comparator agents was measured for 911 Gram-negative isolates (200 *Acinetobacter baumannii-calcoaceticus* complex (ABC), 204 *Escherichia coli*, 201 *Klebsiella pneumoniae*, 205 *Pseudomonas aeruginosa* and 101 *Stenotrophomonas maltophilia*) by broth microdilution. The minimal inhibitory concentrations (MICs) for each strain was determined following CLSI guidelines at JMI Laboratories.

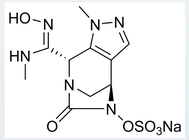
Results: Against 205 *P. aeruginosa* isolates, ETX0462 was the most potent agent tested with MIC_{50}/MIC_{90} values of 0.5/1 mg/L (MIC range ≤0.06 – 4 mg/L). ETX0462 had a similar level of potency against 204 *E. coli* with MIC_{50}/MIC_{90} values of 0.25/1 mg/L (MIC range 0.12 – 16 mg/L). ETX0462 was also very active against *S. maltophilia* (n=101) with MIC_{50}/MIC_{90} values of 2/2 mg/L (MIC range 0.25 – 2 mg/L). Against 201 *K. pneumoniae* and 200 ABC isolates, ETX0462 had MIC_{50}/MIC_{90} values of 0.5/4 mg/L and 2/4 mg/L, respectively. Of particular note was the activity of ETX0462 against the non-fermenting organisms (*A. baumannii*, *P. aeruginosa* and *S. maltophilia*), which was equally potent across geographical regions and infection sources and against carbapenem-resistant isolates.

Conclusions: The novel DBO compound ETX0462 demonstrated potent *in vitro* antibacterial activity against a variety of recent, global, Gram-negative clinical isolates. In particular, the potent activity of ETX0462 against the non-fermenting species was stable across the globe and against isolates from different infection types, as well as against carbapenem-resistant isolates for which effective therapeutic options are limited.

Introduction

The discovery of the diazabicyclooctane (DBO) chemotype has led to the development of several potent β-lactamase inhibitors, such as avibactam, relebactam and durlobactam[1]. Several DBOs also inhibit PBP2, one of the enzymes required for bacterial cell wall synthesis, which results in intrinsic antibacterial activity. However, the high frequency of resistance and the lack of *in vivo* efficacy, has limited use as a monotherapy[2-4]. These liabilities have been attributed to relying solely on PBP2 as a mode of inhibition, which triggers stringent response pathways that compensate for the loss of PBP2 activity[5].

ETX0462 is a DBO that has been rationally designed to alter the spectrum of target inhibition from PBP2 to PBP1 and PBP3, resulting in a preclinical candidate with potent *in vitro* activity as well as *in vivo* efficacy. This study measures the *in vitro* antibacterial activity of ETX0462 and comparator agents against 911 clinically important Gram-negative pathogens collected as part of the SENTRY surveillance program in 2017-2018.

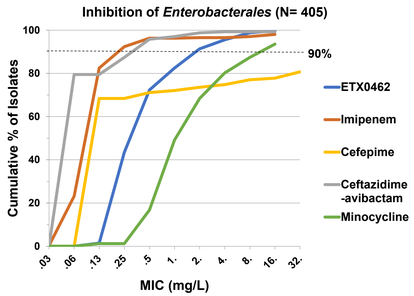


ETX0462

ETX0462 Antibacterial Activity Against Recent, Global *Enterobacterales* Clinical Isolates

Antimicrobial Agent/ Species	N	mg/L			%S* (CLSI)
		MIC_{50}	MIC_{90}	Range	
Enterobacterales					
ETX0462	405	0.5	2	0.12 - >16	NA
cefepime	405	≤0.25	>32	≤0.25 - >32	74
ceftazidime-avibactam	405	≤0.12	0.5	≤0.12 - >16	99
ceftolozane-tazobactam	405	≤0.25	2	≤0.25 - >8	91
imipenem	405	0.12	0.25	≤0.03 - >16	96
imipenem-relebactam	405	0.12	0.25	≤0.03 - 16	99
minocycline	405	2	16	≤0.25 - >16	80
E. coli					
ETX0462	204	0.25	1	0.12 - 16	NA
cefepime	204	≤0.25	>32	≤0.25 - >32	79
ceftazidime-avibactam	204	≤0.12	0.25	≤0.12 - 4	100
ceftolozane-tazobactam	204	≤0.25	0.5	≤0.25 - >8	98
imipenem	204	0.12	0.12	≤0.03 - 0.25	100
minocycline	204	1	16	≤0.25 - >16	82
K. pneumoniae					
ETX0462	201	0.5	4	0.25 - >16	NA
cefepime	201	≤0.25	>32	≤0.25 - >32	68
ceftazidime-avibactam	201	≤0.12	0.5	≤0.12 - >16	99
ceftolozane-tazobactam	201	≤0.25	>8	≤0.25 - >8	84
imipenem	201	0.12	0.5	0.06 - >16	93
imipenem-relebactam	201	0.12	0.25	0.06 - 16	97
minocycline	201	2	16	≤0.25 - >16	79

*%S, percent susceptible according to CLSI guidelines (M100, S31); for imipenem-relebactam, FDA breakpoints were applied; NA, none available



*Enterobacterales** by Geographical Region	N	ETX0462 (mg/L)		
		MIC_{50}	MIC_{90}	Range
North America	130	0.25	2	0.12 - >16
Latin America	84	0.5	2	0.25 - 8
Europe	123	0.5	2	0.12 - >16
Asia-W. Pacific	68	0.5	8	0.12 - 16

**Enterobacterales* = *E. coli* and *K. pneumoniae*

Study Design

Category	Number
Species	
Acinetobacter baumannii-calcoaceticus	200
Escherichia coli	204
Klebsiella pneumoniae	201
Pseudomonas aeruginosa	205
Stenotrophomonas maltophilia	101
Region	
North America	272
Latin America	185
Europe	270
Asia-W. Pacific	184

Category	Number
Infection Type	
Bloodstream	307
Intra-abdominal	50
Pneumonia in hospitalized patients	249
Skin/soft tissue	142
urinary tract	157
other	6
Year Collected	
2017	456
2018	455

Susceptibility testing was performed by broth microdilution following CLSI guidelines[6] at JMI Laboratories. Interpretive criteria for comparator agents were based on CLSI M100 S31[7].

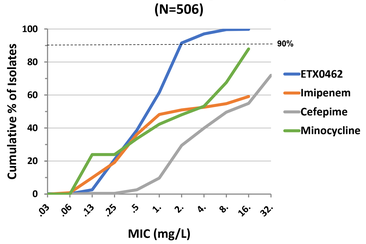
Acknowledgements

Partially supported by Coop. Agreement 4500002444 from ASPR/BARDA, Wellcome Trust and Germany's Fed. Min. of Education and Research, administrated by CARB-X. The content does not necessarily represent official views of the Dept. of Health and Human Services Office of the Asst. Secretary for Preparedness and Response, other funders, or CARB-X.

ETX0462 Antibacterial Activity against Recent, Global, Clinical Isolates of Non-Fermenting Species

Antimicrobial Agent/ Species	N	mg/L			%S* (CLSI)
		MIC_{50}	MIC_{90}	Range	
P. aeruginosa					
ETX0462	205	0.5	1	≤0.06 - 4	NA
cefepime	205	2	16	≤0.25 - >32	83
ceftazidime-avibactam	205	2	8	0.25 ->16	95
ceftolozane-tazobactam	205	0.5	2	≤0.25 - >8	91
imipenem	205	1	16	0.06 - >16	80
imipenem-relebactam	205	0.25	2	0.06 - >16	90
minocycline	205	16	>16	1 - >16	NA
A. baumannii					
ETX0462	200	2	4	0.25 - >16	NA
cefepime	200	32	>32	0.5 - >32	38
ceftazidime-avibactam	200	16	>16	1 - >16	NA
ceftolozane-tazobactam	200	8	>8	≤0.25 - >8	NA
imipenem	200	8	>16	0.06 - >16	47
imipenem-relebactam	200	8	>16	0.06 - >16	47
minocycline	200	0.5	16	≤0.25 - >16	78
S. maltophilia					
ETX0462	101	2	2	0.25 - 2	NA
cefepime	101	32	>32	2 - >32	NA
ceftazidime-avibactam	101	16	>16	0.5 - >16	NA
ceftolozane-tazobactam	101	>8	>8	≤0.25 - >8	NA
imipenem	101	>16	>16	>16 - >16	NA
imipenem-relebactam	101	>16	>16	8 - >16	NA
minocycline	101	0.5	2	≤0.25 - 4	100

*%S, percent susceptible according to CLSI guidelines (M100, S31); for imipenem-relebactam, FDA breakpoints were applied; NA, none available



Category by Non-fermenting Species*	N	ETX0462 (mg/L)		
		MIC_{50}	MIC_{90}	Range
All	506	1	2	≤0.06 - >16
North America	142	1	2	0.12 - 8
Latin America	101	1	4	0.12 - 8
Europe	147	1	2	≤0.06 - >16
Asia-W. Pacific	116	1	4	0.12 - 16
Bloodstream infection	173	1	2	≤0.06 - >16
Pneumonia (hospitalized)	145	1	4	0.12 - 8
Intra-abdominal infection	31	0.5	2	0.12 - 4
Urninary tract infection	73	1	2	0.12 - 8
Skin/soft tissue infection	78	1	4	0.25 - 8
Carbapenem non-susceptible *P. aeruginosa*	41	1	2	0.12 - 2
Carbapenem non-susceptible *A. baumannii*	106	2	8	0.25 - >16

Conclusions

- **ETX0462 is a novel DBO that has been designed to target PBP1 and PBP3 to achieve antibacterial activity as a single agent.**
- **In this study, ETX0462 was shown to have potent *in vitro* antibacterial activity against clinical isolates collected globally in 2017-2018.**
- **The activity of ETX0462 was most notable against *A. baumannii*, *P. aeruginosa* and *S. maltophilia*. Treatment options for these pathogens is limited due to increasing prevalence of antibiotic resistance.**
- **ETX0462 had a MIC_{90} of 1 mg/L against a collection of 205 *P. aeruginosa* isolates, a MIC_{90} of 4 mg/L against *200 A. baumannii* isolates and a MIC_{90} of 2 mg/L against 101 *S. maltophilia* isolates.**
- **ETX0462 inhibited a collection of 204 *E. coli* isolates with a MIC_{90} of 1 mg/L and collection of 201 *K. pneumoniae* isolates with a MIC_{90} of 4 mg/L.**
- **Activity of ETX0462 was maintained across geographical areas, sites of infection and carbapenem-resistant subsets.**

References

1. Vazquez-Ucha *et al.* (2020) Int J Mol Sci. 21:9308 **2.** Levy *et al.* (2019) J Med Chem. 62:4742-4754 **3.** Kidd *et al.* (2020) JAC 75: 149-155 **4.** O'Donnell *et al.* (2020) ACS Infect Dis doi:10.1021/acsinfecdis.0c00019 **5.** Doumith *et al.* (2016) JAC 71:2810-2814 **6.** CLSI M07, 11th ed. 2018. **7.** CLSI M100, 31st ed. 2021.