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Restoration of Sulbactam Activity by the Novel β-lactamase Inhibitor ETX2514 Against Recent Global Clinical Isolates of *Acinetobacter baumannii calcoaceticus* Complex Isolates

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Abstract

Background

ETX2514 is a novel, diazabicyclooctenone β-lactamase inhibitor with broad-spectrum activity against Ambler class A, C and D serine β-lactamases. ETX2514 restores β-lactam activity against multidrug-resistant Gram-negative bacteria. ETX2514 combined with sulbactam (ETX2514SUL) is currently in clinical development for the treatment of infections caused by *Acinetobacter baumannii calcoaceticus* complex (ABC). ABC can cause severe infections that are especially difficult to treat due to increasing resistance to antibacterial therapy. We sought to determine the relative potency of ETX2514SUL against geographically diverse ABC isolates collected in 2017.

Methods

875 ABC isolates including 685 *A. baumannii*, 6 *A. calcoaceticus*, 38 *A. nosocomialis*, and 146 *A. pitii* were chosen for testing. Isolates were collected during 2017 from geographically diverse medical centers in the United States, Europe, Latin America, and the Asia-Pacific region. Susceptibility testing was performed according to CLSI guidelines, and data analysis was performed using CLSI and EUCAST breakpoint criteria. Select isolates were subjected to whole genome sequencing with an Illumina MiSeq instrument and genomic analysis using CLCBio Genomics Workbench v9.5.

Results

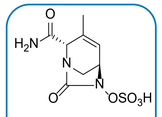
ETX2514SUL was highly active against this collection of ABC isolates. In surveillance of 875 global isolates from 2017, the addition of 4 mg/L ETX2514 decreased the sulbactam MIC_{90} from 64 mg/L to 4 mg/L. This level of potency was found to be consistent across organisms, regions, sources of infection and subsets of resistance phenotypes. 48% of the isolates were found to be non-susceptible to the carbapenem meropenem. Overall only 4.4% of the isolates were non-susceptible to colistin; however, prevalence of colistin non-susceptible isolates varied widely depending on the country. Whole genome sequencing of isolates with elevated ETX2514SUL MIC values revealed that these isolates either encoded for the metallo-β-lactamase NDM-1, which ETX2514 does not inhibit, or for single amino acid changes near the active site of PBP3, the primary target of sulbactam.

Conclusions

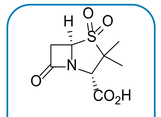
ETX2514SUL demonstrated potent antibacterial activity against recent, geographically diverse clinical isolates of ABC, including MDR isolates. These data support the continued development of ETX2514SUL for the treatment of antibiotic-resistant infections caused by ABC.

Introduction

ETX2514SUL (sulbactam-ETX2514) is a β-lactam/β-lactamase inhibitor combination currently in clinical development for the treatment of resistant *A. baumannii* infections[1].



ETX2514



sulbactam

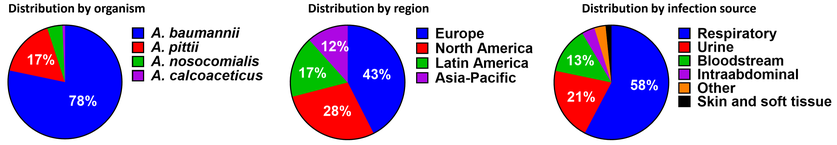
ETX2514 is a novel β-lactamase inhibitor (BLI) from a series of diazabicyclooctenones with potent broad spectrum activity against class A, C and D β-lactamases. Sulbactam is an approved BLI with antibacterial activity versus *Acinetobacter* spp. through inhibition of PBP3.

Methods

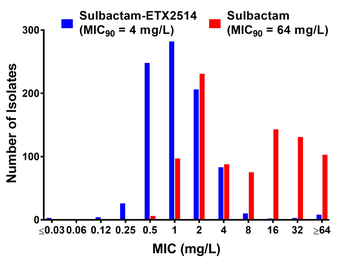
Broth microdilution susceptibility testing was conducted according to CLSI guidelines using cation-adjusted Mueller-Hinton broth[2,3]. ETX2514SUL was tested by dilution of sulbactam in the presence of 4 mg/L ETX2514. MIC testing of the 875 global ABC isolates was performed at IHMA laboratories. An Illumina MiSeq instrument was used for whole genome sequencing and genomic analysis was done with CLCBio Genomics Workbench v9.5.

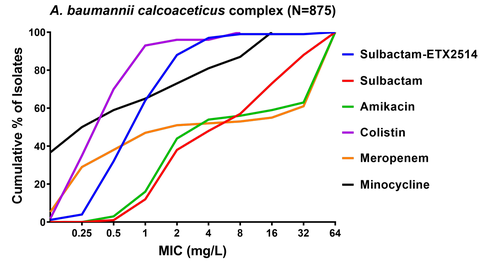
2017 ETX2514SUL Global Surveillance Study Design

875 *Acinetobacter baumannii calcoaceticus* (ABC) complex isolates



ETX2514 Restores Sulbactam Activity Against Geographically Diverse ABC from 2017





		Number (cumulative %) of isolates inhibited at MIC (mg/L)											
Antimicrobial	**%S***	**≤0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**≥64**
Sulbactam	**NA**				1	6	97	231	88	75	143	131	**103†**
						1%	12%	38%	48%	57%	73%	88%	**100%**
Sulbactam-ETX2514	**NA**	3		4	26	248	282	206	**83**	10	2	3	8
				1%	4%	32%	64%	88%	**97%**	99%	99%	99%	100%
Amikacin	**59**					29	115	242	84	24	24	32	**325†**
						3%	16%	44%	54%	56%	59%	63%	**100%**
Cefepime	**45**			3		9	33	153	141	59	**477†**		
						1%	5%	23%	39%	45%	**100%**		
Ciprofloxacin	**46**			234	117	39	10	7	**468†**				
				27%	40%	45%	46%	47%	**100%**				
Colistin	**96**				302	314	**196**	25	6	32			
					35%	70%	**93%**	96%	96%	100%			
Imipenem	**52**			27	366	19	21	23	6	10	15	94	**294†**
				3%	45%	47%	49%	52%	53%	54%	56%	66%	**100%**
Meropenem	**51**	1	5	29	218	82	75	32	13	9	14	59	**338†**
			1%	4%	29%	38%	47%	51%	52%	53%	55%	61%	**100%**
Minocycline	**81**			315	122	76	59	69	65	**57**	**112**		
				36%	50%	59%	65%	73%	81%	**87%**	**100%**		
Tigecycline	**NA**	11	81	143	140	160	227	**91**	19	**3**			
		1%	11%	27%	43%	61%	87%	**97%**	100%	100%			

*Based on 2018 CLSI breakpoint criteria[3]. NA = not available. MIC_{90}s are highlighted with blue squares. †Top concentration tested so MIC_{90} could not be determined.

- ~50% of ABC from this set are carbapenem non-susceptible.
- ETX2514 effectively restores sulbactam activity. The addition of 4 mg/L ETX2514 decreased the sulbactam MIC_{90} from ≥64 mg/L to 4 mg/L.

Activity of ETX2514SUL by Species, Geographical Region and Infection Source

Species	**N**	**Sulbactam-ETX2514 (mg/L)**		
		MIC_{50}	**MIC_{90}**	**Range**
A. baumannii	**685**	**1**	**4**	**≤0.03 - 64**
Other *Acinetobacter* spp.	**190**	**0.5**	**2**	**≤0.03 - 4**
Carbapenem-non-susceptible	**433**	**2**	**4**	**0.12 - >64**
Colistin-non-susceptible	**38**	**2**	**4**	**0.25 - 16**
Geographical Region	**N**	**MIC_{50}**	**MIC_{90}**	**Range**
Europe	**372**	**1**	**4**	**≤0.03 - 64**
North America	**249**	**1**	**2**	**0.12 - 8**
Latin America	**152**	**1**	**4**	**≤0.03 - >64**
Asia/South Pacific	**102**	**1**	**2**	**0.25 - 64**
Infection Source	**N**	**MIC_{50}**	**MIC_{90}**	**Range**
Respiratory	**505**	**1**	**4**	**≤0.03 - >64**
Urinary	**180**	**1**	**2**	**0.12 - >64**
Bloodstream	**116**	**1**	**4**	**≤0.03 - 8**
Intra-abdominal	**32**	**1**	**2**	**0.25 - 8**

- **Sulbactam-ETX2514 potency was consistent across *Acinetobacter* species, geographical regions and sources of infection.**
- **Sulbactam-ETX2514 maintained a MIC_{90} of 4 mg/L among carbapenem and colistin non-susceptible isolates.**
- **Only 23/875 isolates (2.6%) had a MIC ≥ 8 mg/L, which were subjected to whole genome sequencing.**
- **8 of 23 isolates encoded NDM-1, which ETX2514 does not inhibit.**
- **14 of 23 isolates encoded mutations in PBP3, the target of sulbactam: PBP3 A515V (n=2), T526S (n=7), F548I (n=2), V146I (n=1), Q488K (n=1), K235N (n=1).**
- **Further characterization of the effect of these mutations on sulbactam PBP3 binding is in progress.**

Profile of Select Isolates with Reduced Susceptibility to ETX2514SUL

Strain ID	**Species**	**Country**	**Sequence type (Oxford/Pasteur)**	**Whole Genome Sequencing Results**	**MIC (mg/L)**					
					AMK	**COL**	**MEM**	**MIN**	**SUL**	**SUL-ETX2514**
ARC6820	*A. baumannii*	Argentina	ST1806, 208 / PST2	ADC-25; OXA-23; OXA-66; **PBP3 [T526S]**	4	0.5	64	8	64	8
ARC6803	*A. baumannii*	Belgium	ST1089 / PST85	ADC-80 [V119E]; ADC-96 [V119E, A248V]; OXA-94; **NDM-1**	4	≤0.25	>64	0.1199	>64	64
ARC6823	*A. baumannii*	Greece	ST1816, 195 / PST2	ADC-73; OXA-23; OXA-66 ; AdeA [Tn insertion]; PBP1A [W343*]; **PBP3 [A515V]**	>64	2	64	16	32	8
ARC6810	*A. baumannii*	Guatemala	PST1	ADC-53 [A236V]; TEM-1; CTX-M-15; OXA-24; OXA-69; AdeC [P29L]; **PBP3 [T526S]**	>64	1	>64	1	64	8
ARC6815	*A. baumannii*	Guatemala	ST514 / PST103	ADC-97-like; TEM-1; OXA-70; **NDM-1**; MtgA [F12I]; **PBP3 [N337Y, T526S]**	64	≤0.25	>64	0.25	>64	>64
ARC6806	*A. baumannii*	Italy	ST1806, 208 / PST2	ADC-73; TEM-1; OXA-23; OXA-66; **PBP3 [A515V]**	>64	1	>64	16	>64	8
ARC6799	*A. baumannii*	Spain	ST1489 / PST25	ADC-5 [G239S, N341T]; OXA-23; OXA-64; AdeS [Tn insertion]; **PBP3 [T526S]**; DacD [T188S]	64	1	64	>16	64	32
ARC6801	*A. baumannii*	Thailand	ST355 / PST16	ADC-169; OXA-58; OXA-402; VEB-1; **NDM-1**	64	0.5	>64	0.5	64	32
ARC6804	*A. baumannii*	Turkey	ST1809, 451 / PST2	ADC-73; OXA-23; OXA-66; **PBP3 [A515V]**	>64	4	64	16	64	8
ARC6805	*A. baumannii*	USA	ST1701 / PST2	ADC-25; OXA-23; OXA-66; **PBP3 [F548I]**	>64	0.5	64	8	64	8

AMK = amikacin; COL = colistin; MEM = meropenem; MIN = minocycline and SUL = sulbactam

Conclusions

- **ETX2514 restores sulbactam antibacterial activity against a global collection of 875 *A. baumannii calcoaceticus* complex clinical isolates collected in 2017 with a MIC_{90} of 4 mg/L.**
- **Activity of ETX2514SUL was consistent across regions, sources of infection and subset of resistance phenotypes.**
- **Less susceptible isolates encoded either a metallo-β-lactamase or a mutation in PBP3.**
- **These data support development of ETX2514 in combination with sulbactam for the treatment of infections caused by multidrug-resistant *A. baumannii calcoaceticus* complex.**

Disclosures

S. McLeod, S. Moussa, R. Tommasi and A. Miller are employees of Entasis Therapeutics. M. Hackel is an employee of IHMA, Inc.

References

1. Durand-Reville, T. et *al.* (2017) Nature Microbiol. 2:17104. **2.** CLSI M07-A10. 2015. **3.** CLSI M100, 28th ed. 2018.

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