Saturday – AAR-753

The Novel β-lactamase Inhibitor ETX2514 Restores Sulbactam Activity against Recent, Globally Diverse Clinical Isolates of *Acinetobacter baumannii calcoaceticus* Complex Isolates

S. McLeod[1], M. Huband[2], Y. Edah[2], R. Tommasi[1], and A. Miller[1]

[1]Entasis Therapeutics, Waltham, MA, USA and [2]JMI Laboratories, North Liberty, IA USA

Entasis Therapeutics
1-781-810-0120
sarah.mcleod@entasistx.com

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 combined with sulbactam (ETX2514SUL) is currently in clinical development for the treatment of infections caused by *Acinetobacter baumannii calcoaceticus* complex (ABC) organisms. ABC can cause severe infections that are especially difficult to treat due to increasing resistance to antibacterial therapy. Multiple public health agencies have highlighted ABC infections as among the most urgent threats to human health due to the lack of effective treatments and rising resistance rates. We sought to determine the activity of ETX2514SUL and comparator agents against three recent and geographically diverse collections of ABC isolates.

Methods

The minimal inhibitory concentration (MIC) for each strain was determined following Clinical and Laboratory Standards Institute (CLSI) guidelines, and data analysis was performed using CLSI breakpoint criteria. ETX2514SUL was tested as a titration of sulbactam in the presence of a fixed concentration of 4 mg/L ETX2514. ABC isolates tested included: (1) 101 strains collected during 2013 from Chinese medical centers in 7 cities, (2) 55 strains collected during 2017 from 10 medical centers in 6 Latin American countries and (3) the *Acinetobacter baumannii* panel from the CDC and FDA Antibiotic Resistance Isolate Bank (Atlanta, GA: CDC).

Results

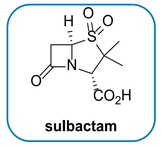
ETX2514SUL was highly active against these diverse collections of ABC isolates, regardless of their resistance determinants. The addition of 4 mg/L ETX2514 decreased the sulbactam MIC_{90} from 64 to 2 mg/L against the Chinese isolates, which exhibited high levels of resistance to other antibiotics, including 78% imipenem (IPM)-resistance. The addition of ETX2514 decreased the sulbactam MIC_{90} from 32 to 0.5 mg/L against the Latin American isolates, 82% of which were resistant to IPM. The activity of ETX2514SUL was also measured against the *A. baumannii* Panel from the CDC and FDA Antibiotic Resistance Isolate Bank, which was chosen to represent a diversity of resistance mechanisms. Against this set, which was 88% IPM-resistant, the addition of ETX2514 decreased the sulbactam MIC_{90} from >64 to 8 mg/L.

Conclusions

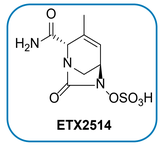
ETX2514SUL demonstrated potent antibacterial activity against geographically diverse, recent, multidrug-resistant ABC isolates. These data support the continued development of ETX2514SUL as a promising new agent for the treatment of antibiotic-resistant infections caused by ABC.

Introduction

ETX2514SUL (sulbactam-ETX2514) is a β-lactam/β-lactamase inhibitor (BL/BLI) combination[1,2] currently in Phase 3 clinical development for the treatment of infections caused by resistant *Acinetobacter baumannii calcoaceticus* complex (ABC) organisms.



sulbactam



ETX2514

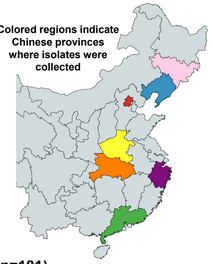
ETX2514 is a novel BLI from a series of diazabicyclooctenones with best-in-class broad spectrum activity against class A, C and D β-lactamases. Sulbactam is an approved BLI with antibacterial activity against *Acinetobacter* spp.

Methods

Broth microdilution susceptibility testing was conducted according to CLSI guidelines[3]. Sulbactam-ETX2514 was tested by dilution of sulbactam in the presence of a fixed concentration of 4 mg/L ETX2514. Testing of the *A. baumannii* isolates from China and Latin America was performed at JMI laboratories.

ETX2514 Restores Sulbactam Activity against *A. baumannii* Isolates Collected from China

101 *A. baumannii* were collected during 2013 from Chinese medical centers in 7 cities (Beijing, Hangzhou, Jilin, ShenYang, Shenzhen, Wuhan and Zhengzhou). Isolates represent a variety of infection types including bloodstream (n=23), pneumonia in hospitalized patients (n=66), and skin and soft tissue (n=12).



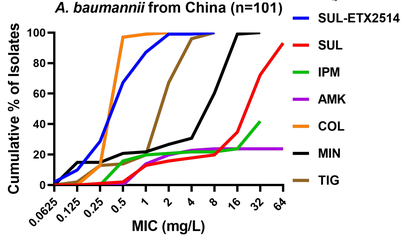
Antimicrobial Agent	Number (cumulative %) of isolates inhibited at MIC (mg/L)											
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Sulbactam			1	1	11	3	2	2	15	38	**21**	7
			1%	2%	12.9%	15.8%	17.8%	19.8%	34.7%	72.3%	**93.1%**	100%
Sulbactam-ETX2514	2	8	19	39	20	**12**	0	1				
	2.0%	9.9%	28.7%	67.3%	87.1%	**99%**	99%	100%				

MIC_{90} values are highlighted with blue squares.

Antimicrobial Agent	mg/L			CLSI*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Sulbactam	32	64	≤0.25 - >64			
Sulbactam-ETX2514	0.5	2	≤0.06 - 8			
Imipenem	>32	>32	≤0.5 - >32	20.8	1.0	78.2
Amikacin	>64	>64	1 - >64	23.8	0	76.2
Ciprofloxacin	>8	>8	≤0.25 - >8	15.8	0	84.2
Colistin	0.5	0.5	≤0.25 - 2	100		0
Minocycline	8	16	≤0.12 - 32	30.7	29.7	39.6
Tigecycline	2	4	0.12 - 8			

*Based on 2019 CLSI breakpoint criteria[4].

***A. baumannii* from China (n=101)**



ETX2514 Restores Sulbactam Activity against *A. baumannii* Isolates Collected from Latin America

55 *A. baumannii* were collected during 2017 from ten medical centers in six Latin American countries (Argentina, Brazil, Chile, Costa Rica, Mexico and Panama). Isolates represent a variety of infection types including bloodstream (n=8), pneumonia in hospitalized patients (n=26), skin and soft tissue (n=14), intra-abdominal (n=2) and urinary tract (n=5).

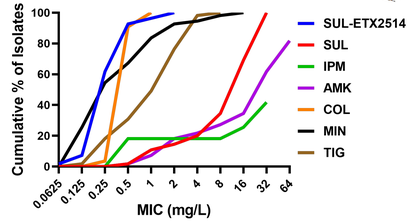
Antimicrobial Agent	Number (cumulative %) of isolates inhibited at MIC (mg/L)									
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32
Sulbactam			0	1	5	2	3	8	19	**17**
			0%	1.8%	10.9%	14.5%	20.0%	34.5%	69.1%	**100%**
Sulbactam-ETX2514	1	3	30	**17**	2	2				
	1.8%	7.3%	61.8%	**92.7%**	96.4%	100%				

MIC_{90} values are highlighted with blue squares.

Antimicrobial Agent	mg/L			CLSI*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Sulbactam	16	32	0.5 - 32			
Sulbactam-ETX2514	0.25	0.5	≤0.06 - 2			
Imipenem	>32	>32	≤0.5 - >32	18.2	0	81.8
Amikacin	32	>64	≤0.5 - >64	34.5	27.3	38.2
Ciprofloxacin	>8	>8	≤0.25 - >8	18.2	1.8	80.0
Colistin	0.5	0.5	≤0.25 - 1	100		0
Minocycline	0.5	4	≤0.12 - 32	92.7	1.8	5.5
Tigecycline	2	4	0.12 - 8			

*Based on 2019 CLSI breakpoint criteria[4].

***A. baumannii* from Latin America (n=55)**



ETX2514 Restores Sulbactam Activity against *Acinetobacter* spp. from the CDC & FDA Antibiotic Resistance Isolate Bank

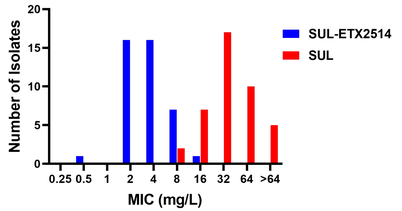
The *Acinetobacter baumannii* Panel was obtained from the CDC and FDA Antibiotic Resistance (AR) Isolate bank.

This panel is comprised of 41 sequenced multidrug-resistant ABC organisms that were chosen to represent a diversity of antimicrobial susceptibilities.

Antimicrobial Agent	Number (cumulative %) of isolates inhibited at MIC (mg/L)								
	0.5	1	2	4	8	16	32	64	>64
Sulbactam					2	7	17	10	**5**
					4.9%	22.0%	63.4%	87.8%	**100%**
Sulbactam-ETX2514	1	0	16	16	**7**	1			
	2.4%	2.4%	41.5%	80.5%	**97.6%**	100%			

MIC_{90} values are highlighted with blue squares.

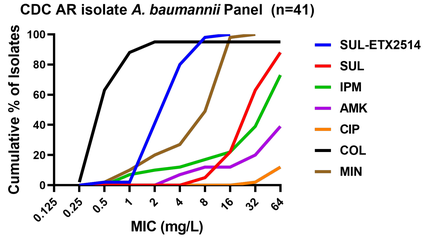
CDC AR isolate *A. baumannii* Panel (n=41)



Antimicrobial Agent	mg/L			CLSI*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Sulbactam	32	>64	8 - >64			
Sulbactam-ETX2514	4	8	0.5 - 16			
Imipenem	64	>64	1 - >64	9.7	2.4	87.8
Amikacin	>64	>64	4 - >64	12.2	7.3	80.5
Ciprofloxacin	>64	>64	32 - >64	0	0	100
Colistin	0.5	2	0.25 - >64	95.1		4.9
Minocycline	16	16	0.5 - 32	26.8	22.0	51.2

*Based on 2019 CLSI breakpoint criteria[4].

CDC AR isolate *A. baumannii* Panel (n=41)



Genotypes of CDC AR Isolates with Sulbactam-ETX2514 MIC values ≥ 8 mg/L

Species	Strain ID	β-lactamase content	MIC (mg/L)						
			SUL-ETX2514	SUL	IPM	AMK	CIP	COL	MIN
A. baumannii	273	ADC-25 [N341S]; OXA-23; OXA-66	8	32	32	>64	>64	1	16
A. baumannii	275	ADC-30 [A245E]; TEM-1; OXA-23; OXA-66	8	32	64	>64	>64	0.5	8
A. baumannii Complex	276	ADC-68-like; TEM-like; OXA-like; PBP3 [H370Y]	8	64	1	64	64	1	0.5
A. baumannii	289	ADC-30; OXA-66 [K42*]; OXA-72	8	32	>64	64	>64	1	16
A. baumannii	295	ADC-30 [A245E]; TEM-1; OXA-23; OXA-66; PBP3 [I387L]	8	64	64	4	>64	0.5	16
A. baumannii	302	ADC-25-like; OXA-23; OXA-82	8	64	>64	>64	>64	1	16
A. baumannii	310	ADC-25-like; OXA-23; OXA-82	8	64	64	>64	>64	2	16
A. baumannii	274	ADC-30; TEM-1; OXA-66; OXA-72	16	64	>64	32	>64	0.5	16

Conclusions

- **ETX2514 restored sulbactam antibacterial activity against a collection of recent ABC clinical isolates from China and Latin America with MIC_{90} values of 2 mg/L and 0.5 mg/L, respectively.**
- **ETX2514 also restored sulbactam antibacterial activity against the multidrug-resistant CDC & FDA AR Isolate ABC Panel.**
- **These data support further development of ETX2514 in combination with sulbactam for the treatment of infections caused by multidrug-resistant *A. baumannii*.**

References

1. Durand-Reville, T. *et al.* (2017) *Nature Microbiol.* 2:17104. **2.** Barnes, M. *et al.* (2019) *MBio.* 10(2): doi: 10.1128/mBio.00159-19. **3.** CLSI M07-A10. 2015. **4.** CLSI M100, 29th ed. 2019.

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