32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Lisbon, Portugal
23–26 April 2022

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

In Vitro Activity of Sulbactam-durlobactam against *Acinetobacter baumannii-calcoaceticus* Complex Isolates from a Five-Year Surveillance Program (2016 –2020)

Sarah McLeod[1], Alita Miller[1], Meredith Hackel[2] and Daniel Sahm[2]

[1]Entasis Therapeutics, Waltham, MA, USA

[2]International Health Management Associates, Inc., Schaumburg, IL, USA

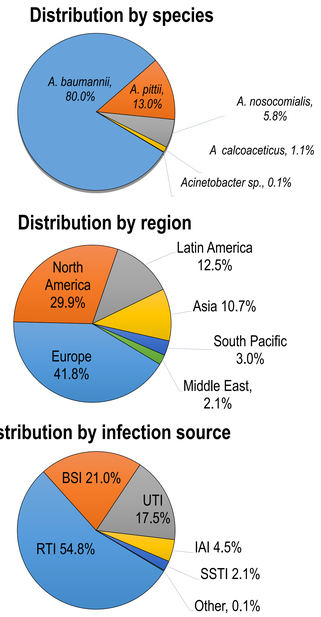
INTRODUCTION

Sulbactam-durlobactam (formerly ETX2514SUL) is a β-lactam–β-lactamase inhibitor combination antibiotic currently under clinical development by Entasis Therapeutics and is designed to treat serious infections caused by *Acinetobacter baumannii-calcoaceticus* complex (ABC) organisms, including multidrug-resistant (MDR) strains [1]. ABC is an increasingly resistant group of organisms commonly isolated from the hospital environment and hospitalized patients that can cause severe and difficult to treat infections. In this study we present the *in vitro* activity of sulbactam-durlobactam (SUL-DUR) against community-associated and hospital-acquired clinical ABC isolates from a geographically diverse global population collected during a five-year surveillance program from 2016 to 2020.

METHODS

4,252 ABC isolates, including (n/% of total) *A. baumannii* (3,401/79.9%), *A. pittii* (552/13.0%), *A. nosocomialis* (248/5.8%), *A. calcoaceticus* (48/1.1%), and *Acinetobacter* spp. (3/<0.1%), were collected during 2016-2020 from geographically diverse medical centers in the United States, Europe, Latin America, Middle East (Israel), and the Asia-Pacific region from varied infection sources (Figure 1). Susceptibility testing was performed according to CLSI M07 guidelines [2]. Sulbactam was tested with durlobactam at a fixed concentration of 4 mg/L. Data analysis was performed using CLSI and EUCAST breakpoint criteria where available [3, 4]. Multidrug resistant (MDR) was defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2021 breakpoints; extensively-drug resistant (XDR) was defined as resistance to at least five of the available antimicrobial drug classes based on 2021 CLSI breakpoints. SUL-DUR MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible) and ≥8 mg/L (resistant).

Figure 1. Distribution of 4,252 *Acinetobacter baumannii-calcoaceticus* complex (ABC) isolates by species, region, and infection source



BSI, bloodstream infection; IAI, intraabdominal infection; RTI, respiratory tract infection; SSTI, skin/soft tissue infection; UTI, urinary tract infection

Table 1. Activity of sulbactam-durlobactam and comparators against 4,252 ABC isolates

Organism (n)	Compound	MIC_{50}	MIC_{90}	Range	%S CLSI	%S EUCAST
ABC (4,252)	Sulbactam-durlobactam	1	2	≤0.03 - >64	98.2[a]	98.2[a]
	Sulbactam	8	64	0.25 - >64	na	na
	Amikacin	4	>64	≤0.5 - >64	58.6	56.5
	Cefepime	16	>16	≤0.12 - >16	44.3	na
	Ciprofloxacin	>4	>4	≤0.12 - >4	44.0	0
	Colistin	0.5	1	≤0.25 - >8	na	95.6
	Imipenem	8	64	0.06 - >64	48.7	48.7
	Meropenem	16	>64	0.06 - >64	47.6	47.6
	Minocycline	0.5	16	≤0.12 - >16	79.1	na
	Tigecycline	0.5	2	0.03 - 32	na	na

$MIC_{50/90}$ and range in mg/L; %S, percent susceptible; na, no breakpoint available

[a] Sulbactam-durlobactam MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible)

Figure 2. MIC distribution of sulbactam-durlobactam and sulbactam for 4,252 ABC isolates

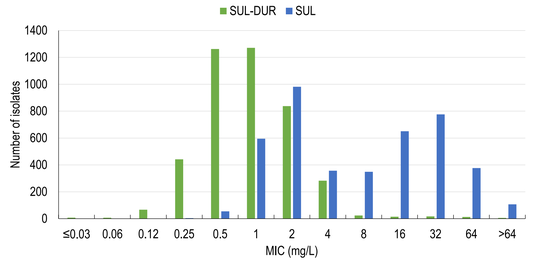


Table 2. Activity of sulbactam-durlobactam against 4,252 ABC isolates by species

Organism (n)	MIC_{50}	MIC_{90}	Range	%S
A. baumannii (3,401)	1	4	≤0.03->64	97.9
A. calcoaceticus (48)	0.5	1	0.12-2	100
A. nosocomialis (248)	0.5	1	≤0.03-8	99.6
A. pittii (552)	0.5	2	0.12-32	99.3
Acinetobacter sp. (3)	nc	nc	≤0.03-0.5	100

$MIC_{50/90}$ and range in mg/L; %S, sulbactam-durlobactam MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible); nc, $MIC_{50/90}$ not calculated for n<15

Table 3. Activity of sulbactam-durlobactam against 4,252 ABC isolates by region

Region (n)	MIC_{50}	MIC_{90}	Range	%S
Asia (456)	1	2	≤0.03->64	98.5
Europe (1,776)	1	4	≤0.03->64	98.6
Latin America (532)	1	4	≤0.03->64	94.4
Middle East (88)	1	2	0.25-32	97.7
North America (1,271)	0.5	2	≤0.03->64	99.3
South Pacific (129)	0.5	2	0.06-64	98.5

$MIC_{50/90}$ and range in mg/L; %S, sulbactam-durlobactam MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible)

Table 4. Activity of sulbactam-durlobactam against 4,252 ABC isolates by year of collection

Region (n)	MIC_{50}	MIC_{90}	Range	%S
2016 (843)	0.5	2	≤0.03 - 64	98.8
2017 (826)	1	4	≤0.03 - >64	97.0
2018 (929)	1	2	≤0.03 - 32	99.3
2019 (859)	1	4	≤0.03 - >64	97.8
2020 (795)	1	2	≤0.03 - >64	98.2

$MIC_{50/90}$ and range in mg/L; %S, sulbactam-durlobactam MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible)

Table 5. Activity of sulbactam-durlobactam against 4,252 ABC isolates by infection source

Infection source (n)	MIC_{50}	MIC_{90}	Range	%S
BSI (893)	1	2	0.06 - >64	98.5
IAI (192)	1	2	0.12 - 32	97.4
RTI (2,328)	1	2	≤0.03 - >64	98.0
SSSI (88)	1	2	0.25 - 16	97.7
UTI (745)	1	2	≤0.03 - >64	98.8
Other (6)	nc	nc	0.5 - 2	100

$MIC_{50/90}$ and range in mg/L; %S, sulbactam-durlobactam MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible); BSI, bloodstream infection; IAI, intraabdominal infection; RTI, respiratory tract infection; SSTI, skin/soft tissue infection; UTI, urinary tract infection

Table 6. Activity of sulbactam-durlobactam against 4,252 ABC isolates by resistance phenotype

Phenotype (n)	MIC_{50}	MIC_{90}	Range	%S
Amikacin R (1,613)	2	4	≤0.03->64	96.9
Ciprofloxacin R (2,352)	1	4	≤0.03->64	97.4
Colistin R (187)	2	4	0.25-64	98.9
Meropenem R (2,180)	1	4	≤0.03->64	96.6
Minocycline R (448)	2	4	0.25-64	97.3
MDR (2,062)	1	4	≤0.03 - >64	96.7
XDR (469)	2	4	0.25 - >64	90.2

$MIC_{50/90}$ and range in mg/L; R, resistant based on 2021 CLSI breakpoints; %S, sulbactam-durlobactam MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible); Multi-drug resistant (MDR) defined as resistance to at least three of the available antimicrobial drug classes based on 2021 CLSI breakpoints; Extremely-drug resistant (XDR) defined as resistance to at least five of the available antimicrobial drug classes based on 2021 CLSI breakpoints

RESULTS

- The addition of durlobactam to sulbactam reduced the MIC_{90} 32-fold against this collection of 4,252 ABC isolates, from 64 mg/L to 2 mg/L. A total of 4,175/4,252 (98.2%) ABC isolates were inhibited by sulbactam-durlobactam at a concentration of ≤4 mg/L (Table 1, Figure 2).
- Colistin and tigecycline were the only two comparators which demonstrated *in vitro* activity equivalent to sulbactam-durlobactam; however, these agents lack susceptibility breakpoints for ABC due to concerns about toxicity and suboptimal PK/PD, respectively[5,6] (Table 1).
- Activity of sulbactam-durlobactam was consistent across species (Table 2), geographical regions (Table 3) years of collection (Table 4), and sources of infection (Table 5).
- Activity was maintained against resistant subsets of ABC isolates, including amikacin-, ciprofloxacin-, colistin-, meropenem-, or minocycline-resistant isolates, and MDR and XDR isolates (MIC_{90} = 4 mg/L for all subsets; >90% sulbactam-durlobactam MIC ≤4 mg/L) (Table 6).

CONCLUSIONS

- Sulbactam-durlobactam demonstrated potent *in vitro* activity against ABC isolates from diverse infections and geographical locations with an MIC_{90} value of 2 mg/L and 98.2% inhibited at ≤4 mg/L.
- These data support the continued development of sulbactam-durlobactam as a potential new treatment option for antibiotic-resistant infections caused by *Acinetobacter baumannii-calcoaceticus* complex.

REFERENCES

1. National Library of Medicine (U.S.). (2019, March -). Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients with Infections Caused *by Acinetobacter baumannii-calcoaceticus* Complex (ATTACK). Identifier NCT03894046. https://clinicaltrials.gov/ct2/show/ NCT03894046.
2. Clinical Laboratory Standards Institute (CLSI), 2018. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eleventh Edition. CLSI document M07-A11 (ISBN 1-56238-836-3). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
3. Clinical and Laboratory Standards Institute (CLSI), 2021. Performance Standards for Antimicrobial Susceptibility Testing. 31st Ed. CLSI Supplement M100 (ISBN 978-1-68440-104-8). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
4. The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints 2022; http://www.eucast.org/clinical_breakpoints/
5. CLSI. 2018. Colistin Breakpoints for *Pseudomonas aeruginosa* and *Acinetobacter* spp. 1st ed. CLSI rationale document MR01. Wayne, PA
6. Isler *et al.* 2019. New Treatment Options against Carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents and Chemother. 63 (1): e01110-18.

CONTACT INFORMATION

Sarah McLeod/ Sarah.McLeod@EntasisTx.com

Entasis Therapeutics 35 Gatehouse Dr., Waltham, MA 02451, USA