INNOVIVA Specialty Therapeutics™

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In Vitro Activity of Sulbactam-Durlobactam against Global Clinical *Acinetobacter baumannii-calcoaceticus* Complex Isolates Collected in 2024

Sarah M. McLeod[1*], Samir H. Moussa, Mark Estabrook[2], and Meredith Hackel[2]

[1]Innoviva Specialty Therapeutics, Inc., Waltham, MA, USA
[2]IHMA, Inc., Schaumburg, IL, USA

*corresponding author: Sarah.McLeod@istx.com

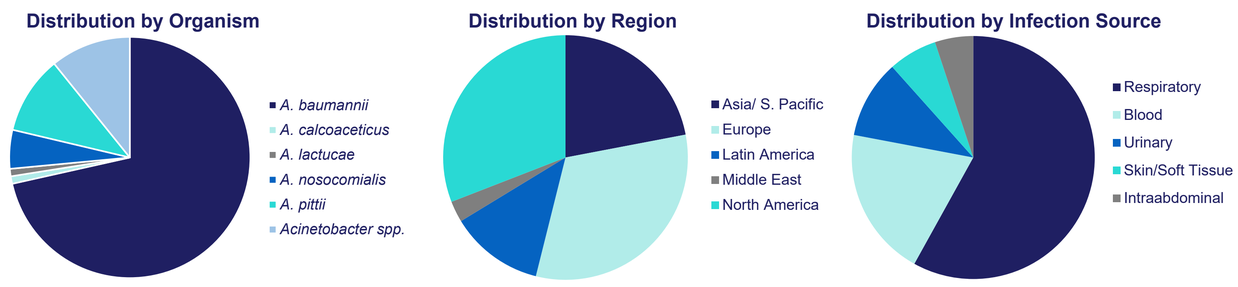
Background:

- Sulbactam-durlobactam (SUL-DUR) is a targeted β-lactam/β-lactamase inhibitor combination approved by the US FDA in May 2023 for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex (ABC) in adults 18 years of age and older[1]
- Durlobactam (DUR) is a diazabicyclooctane (DBO) β-lactamase inhibitor with broad spectrum activity against serine β-lactamases from Ambler classes A, C and D[2]
- Sulbactam (SUL) is a β-lactam penicillin derivative β-lactamase inhibitor with intrinsic antibacterial activity against *Acinetobacter* spp. through the inhibition of PBP3[3]
- *In vitro* activity of SUL-DUR against 799 geographically diverse ABC isolates collected in 2024 was measured

Methods:

- 799 unique *Acinetobacter baumannii-calcoaceticus* complex (ABC) isolates were collected during 2024 from 153 medical centers in 45 countries
- Identities of all isolates were confirmed using MALDI-TOF spectrometry (Bruker Daltonics, Billerica, MA, USA)
- Susceptibility was performed by broth microdilution at IHMA (Schaumburg, IL, USA) according to CLSI guidelines[4]
- SUL-DUR non-susceptible isolates were subjected to whole genome sequencing

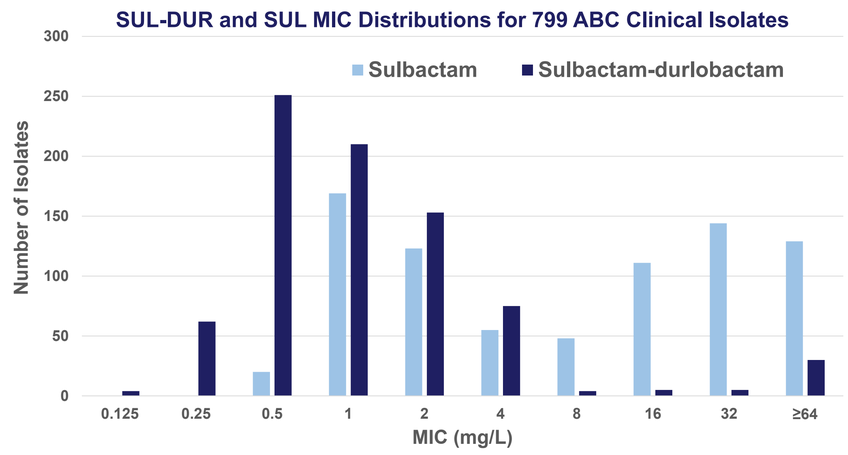
Study Design:



Results:

Antibiotic Susceptibility of *Acinetobacter baumannii-calcoaceticus* Complex Clinical Isolates

- DUR restored SUL activity: addition of 4 mg/L DUR decreased the SUL MIC_{90} 16-fold from 64 mg/L to 4 mg/L
- 94.5% of 799 global ABC clinical isolates collected in 2024 were susceptible to SUL-DUR based on CLSI interpretive criteria[5]
- ~55% of isolates were carbapenem non-susceptible



Antibacterial Agent	mg/L			%S (CLSI[5])	%S (EUCAST[6])
	MIC_{50}	MIC_{90}	MIC Range		
Sulbactam-durlobactam	1	4	0.12 - >64	94.5	NA
Sulbactam	8	64	0.5 - >64	NA	NA
Amikacin	4	>64	≤0.5 - >64	57.1	57.1
Ciprofloxacin	>4	>4	≤0.06 - >4	43.3	NC
Colistin	0.5	0.5	≤0.25 - >4	0	96.9
Cefiderocol	0.5	2	≤0.03 - >32	95.4	NA
Imipenem	32	>32	0.12 - >32	45.2	45.2
Meropenem	32	>32	0.06 - >32	44.7	44.7
Minocycline	1	16	≤0.12 - >16	54.1	IE
Tigecycline	1	2	0.06 - 8	NA	IE

IE= Insufficient Evidence; NA= Not Available; NC=Not Calculated as dilution range did not cover susceptible breakpoint; %S = Percent susceptible

SUL-DUR Activity against Subsets of Isolates

- SUL-DUR *in vitro* activity was consistent across *Acinetobacter* species, geographical regions and sources of infection
- ~90% of carbapenem-resistant isolates were susceptible to SUL-DUR
- Among the 37 cefiderocol-non-susceptible isolates (by CLSI criteria[5]), ~60% were susceptible to SUL-DUR

Species	N	SUL-DUR (mg/L)			%S (CLSI[5])
		MIC_{50}	MIC_{90}	MIC Range	
A. baumannii	571	1	4	0.12 - >64	93.2
Other *Acinetobacter* spp.	228	0.5	2	0.12 - >64	97.8
Carbapenem-resistant*	438	2	8	0.25 - >64	89.95
Colistin-resistant*	25	2	32	0.5 - 64	88.0
Cefiderocol-non-susceptible*	37	4	>64	0.5 - >64	59.5
Geographical Region	**N**	**MIC_{50}**	**MIC_{90}**	**MIC Range**	**%S**
Europe	255	1	4	0.25 - >64	94.9
North America	247	1	2	0.12 - >64	99.2
Asia / South Pacific	176	0.5	8	0.25 - >64	89.2
Latin America	99	2	4	0.25 - 64	93.9
Infection Source	**N**	**MIC_{50}**	**MIC_{90}**	**MIC Range**	**%S**
Respiratory	463	1	4	0.12 - >64	94.6
Urinary	83	1	4	0.12 - >64	92.8
Bloodstream	159	1	4	0.12 - >64	93.1
Skin / Soft Tissue	52	0.5	2	0.25 - 4	100
Intraabdominal	41	1	4	0.25 - 64	95.1

*based on CLSI interpretive criteria[5] %S = Percent susceptible

Profile of SUL-DUR Non-Susceptible Isolates

44 isolates were identified as non-susceptible to SUL-DUR (MIC > 4 mg/L)

- All were carbapenem-resistant
- 88.6% (39/44) of isolates were *A. baumannii*
  - 1 *A. nosocomialis*, 1 *A. pittii*, 3 *Acinetobacter* spp.
- Majority of isolates originated from Thailand (31.8%) and Romania (20.5%)
- 79.5% encoded a metallo-β-lactamase (MBL): NDM-5 (14/35) or NDM-1 (21/35)
- Non-MBL-encoding isolates (20.5%) encoded amino acid substitution near the active site of PBP3 (mostly T526S)

SUL-DUR Resistance Determinant	No. of Isolates	MLST(s)*	Origin (n of isolates)	SUL-DUR MIC Range (mg/L)	Other Encoded Resistance Mechanisms
NDM-5 (MBL)	14	2	Thailand (13), US (1)	32 - >64	• β-lactamases: ○ ADC-73, OXA-23, OXA-66, +/- TEM-1 • PBP3 A515V (14/14) • Efflux: • AdeS G186V (13/14) • AdeR and AdeS disrupted (1/14)
NDM-1 (MBL)	21	2, 108, 126, 193, 457, 570, 600, 654, novel	US, Greece, Guatemala, Colombia, Germany, Qatar, Italy, Malaysia, Thailand (each 1); Jordan (3); Romania (9)	16 - >64	• β-lactamases: ○ ADC-73, ADC-20, ADC-50, ADC-132, ADC-32, or ADC-165 ○ OXA-23, OXA-66 or OXA-336, +/- TEM-1 • PBP3 A515V (15/21) • PBP3 Q488K (1/21) • Efflux: • AdeS G186V (15/21) • AdeR, AdeS and/or AdeN disrupted (10/21) • AdeJ mutations (2/21)
PBP3 T526S	7	2, 25, 734	Argentina (3), Turkey (1), China (4), Guatemala (1)	8 - 32	• β-lactamases: ○ ADC-73, ADC-25, ADC-30, ADC-259 or ADC-novel ○ OXA-23; OXA-66 (4/7) ○ OXA-23; OXA-64 (1/7) ○ OXA-23; OXA69 (1/7)
PBP3 A515V (without an MBL)	2	2	Argentina (1), China (1)	8 - 16	• β-lactamases: ○ ADC-73, OXA-23, OXA-66 (2/2) • Efflux: • AdeS G186V (1/2) • AdeS G186V; disrupted AdeN (1/2)

*MLST = Multi-Locus Sequence Type based on the Pasteur Scheme

Conclusions:

- SUL-DUR demonstrated potent antibacterial activity against recent, geographically diverse clinical isolates of ABC, including carbapenem-resistant isolates, in the first full year following introduction of SUL-DUR into the US market in 2023
- Addition of durlobactam to sulbactam reduced the MIC_{90} 16-fold from 64 mg/L to 4 mg/L
- Activity of SUL-DUR was consistent across *Acinetobacter* species, geographical regions and sources of infection
- The majority SUL-DUR non-susceptible isolates (79.5%) encoded for metallo-β-lactamases NDM-1 or NDM-5, which durlobactam does not inhibit
- Among the SUL-DUR non-susceptible isolates negative for NDM, all encoded a PBP3 variant with a single amino acid substitution (majority T526S) near the active site serine, which has been shown to reduce sulbactam binding affinity[7]
- All SUL-DUR non-susceptible isolates had alterations in genes associated with efflux, but always in combination with other genetic determinants known to decrease susceptibility to SUL-DUR, making assessment of the contribution to efflux hard to determine
- These data support the use of SUL-DUR for the treatment of antibiotic-resistant infections caused by *Acinetobacter baumannii-calcoaceticus* complex

References:

1. Xacduro®, 2023. Sulbactam for injection; durlobactam for injection prescribing information. Entasis Therapeutics Inc., Waltham, MA

2. Durand-Réville *et al. (*2017) Nat Microbiol. 2:17104

3. Penwell WF, *et al.* (2015) Antimicrob Agents Chemother. 59:1680–1689

4. M07-A12 (2024) Clinical and Laboratory Standards Institute, Wayne, PA

5. M100Ed35 (2025) Clinical Laboratory Standards Institute, Wayne, PA

6. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 16.0. 2026

7. Moussa SH *et al.* (2023) Antimicrob Agents Chemother. 67:10.1128/aac.00665-23

Presented at 36th ESCMID Global 2026, Munich, Germany