Characterisation of *Acinetobacter baumannii-calcoaceticus* complex (ABC) pathogens isolated at baseline from patients enrolled in the ATTACK Phase III trial

Alita A. Miller*, Sarah M. McLeod, Daria Chabas, Gabrielle Poirier, David Altarac

Entasis Therapeutics, Waltham, MA, USA

*corresponding author,
alita.miller@entasistx.com

Presented at 32nd ECCMID, 23–26 April 2022, Lisbon, Portugal

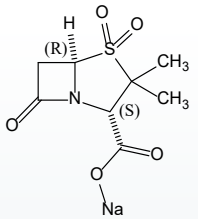
Disclosures

- Alita Miller, Sarah McLeod, Daria Chabas and David Altarac are employees of, and own stock in, Entasis Therapeutics
- Gabrielle Poirier is a former employee of Entasis Therapeutics when the study was conducted, and owns stock in Entasis Therapeutics
- The ATTACK trial was funded by Entasis Therapeutics
- Zai Labs (China) provided financial and operational support for the ATTACK trial in China

SUL-DUR: a β-lactam/β-lactamase Inhibitor Combination For the Treatment of Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex

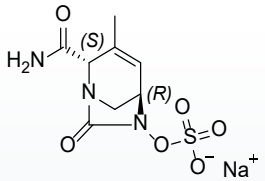
- The *Acinetobacter baumannii-calcoaceticus* (ABC) complex is a group of closely related *Acinetobacter* species that cause serious infections associated with substantial mortality
- *A. baumannii* has been identified by the World Health Organization as a priority pathogen for the development of new antibiotics, due to increasing resistance to existing therapies[1]
  - Carbapenem-resistant *A. baumannii* is the fourth leading cause of death attributable to antimicrobial resistance globally[1]

Sulbactam



- Penicillin derivative with intrinsic activity against ABC
- Clinically used as a β-lactamase inhibitor, often in combination with cefoperazone or ampicillin to treat *A. baumannii*
- β-lactamase–mediated resistance is common[2] (MIC_{90} >64 mg/L; N = 4,252 global clinical isolates[3]

Durlobactam (ETX2514)



- Diazabicyclooctane β-lactamase inhibitor
- Potent inhibitor of class A, C, and D β-lactamases
- Restores sulbactam activity in vitro and in vivo

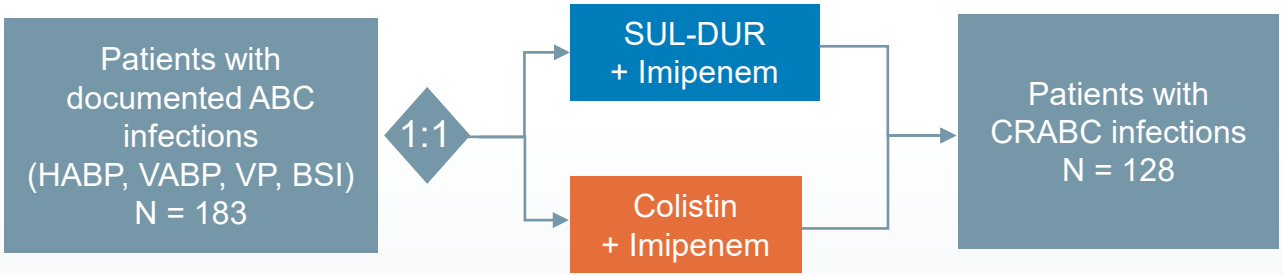
MIC_{90}, minimum inhibitory concentration that inhibits 90% of the microbial strains; SUL-DUR, sulbactam-durlobactam

1. Antimicrobial Resistance Collaborators. *Lancet.* 2022:399;629-655. 2. Shapiro et al. *Front. Biochem*:2021; 12:709974. 3. Hackel et al ECCMID 2022 Poster 01106

ATTACK: Study Design

- ATTACK was a Phase 3, multinational, randomised controlled trial conducted to evaluate the efficacy and safety of SUL-DUR versus colistin, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to ABC, including carbapenem-resistant strains

Part A (Oral presentation 02060)



- Primary efficacy analysis: 28-day all-cause mortality in CRABC m-MITT population
- Primary safety analyses: Nephrotoxicity, AEs

Part B - open label (Poster 02093)

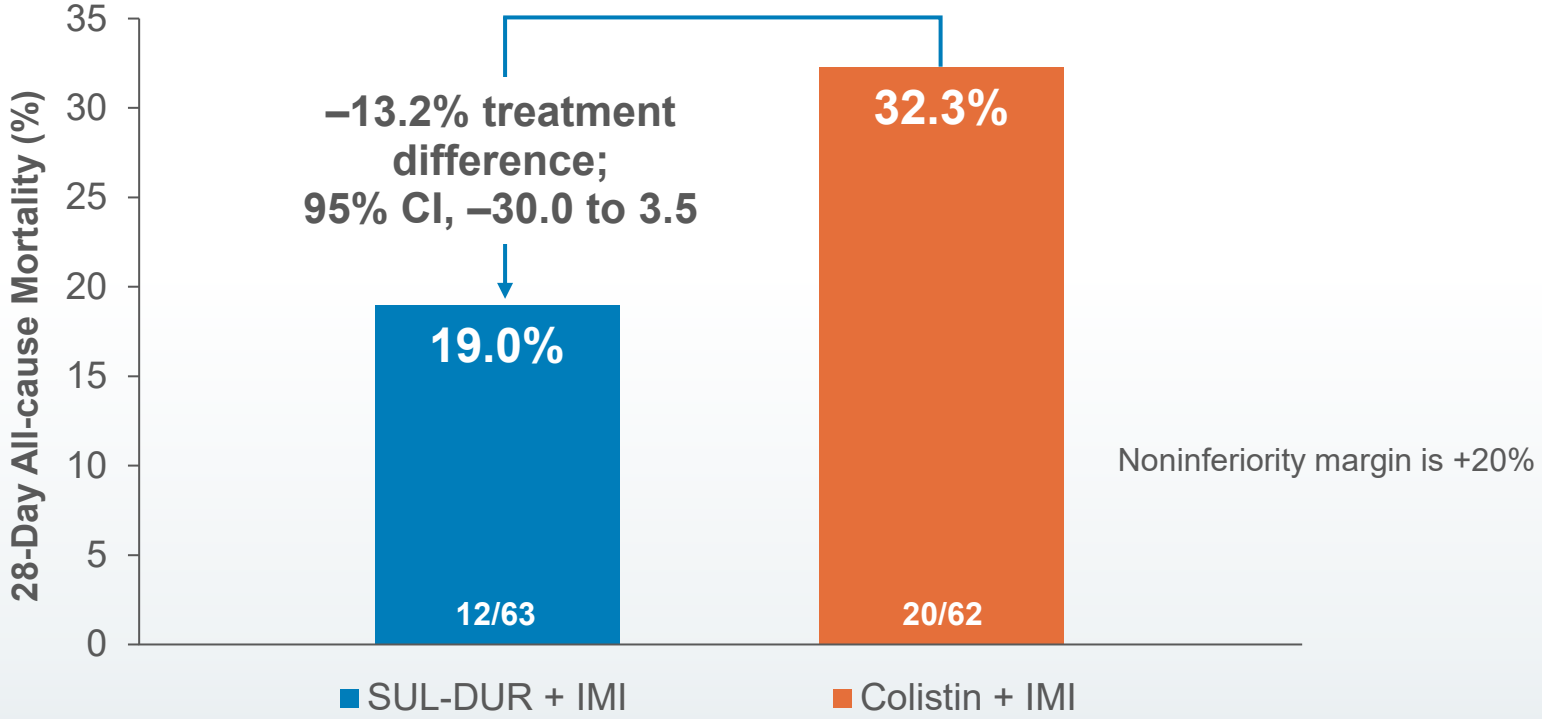
Patients with colistin-resistant CRABC infections or colistin intolerance (treated with SUL-DUR + Imipenem)
N = 28

This trial is registered at ClinicalTrials.gov: NCT03894046.

BSI, bloodstream infection; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; m-MITT population, patients in the ITT (intent-to-treat) population who received any study drug and had an ABC organism isolated at baseline; HABP, hospital-acquired bacterial pneumonia; SUL-DUR, sulbactam-durlobactam; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia; AEs, adverse events.

Primary Efficacy Endpoint Achieved

SUL-DUR noninferior on 28-day all-cause mortality vs colistin in the CRABC m-MITT population

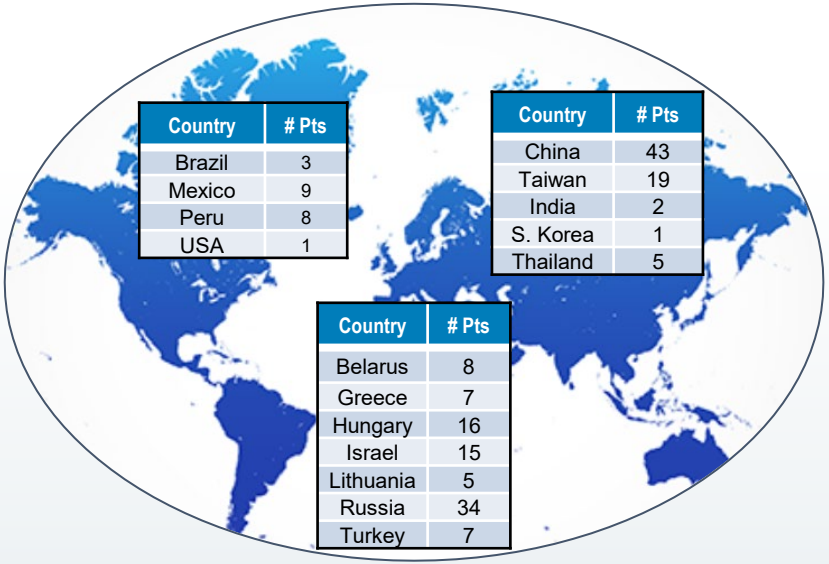


Excludes participants who withdrew consent. Participants with missing survival status were treated as a death.
CI, confidence interval.

Oral presentation 02060
26/04/2022 Hall G 9:30-11:30 CET

Baseline ABC Isolates (m-MITT Population)

183 patients from 16 countries enrolled in m-MITT population

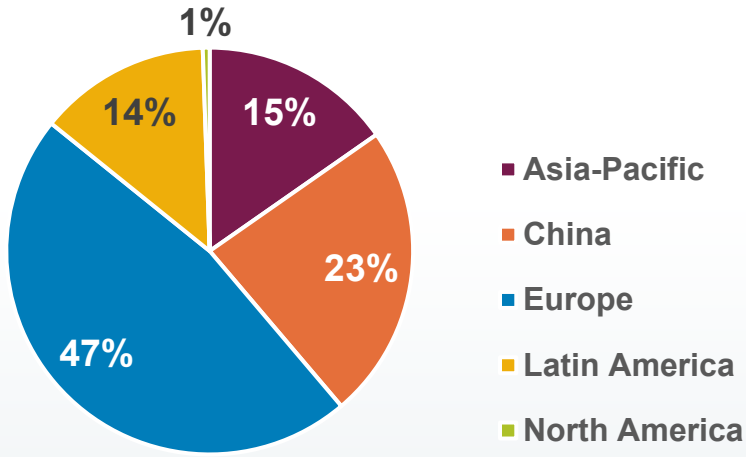


Country	# Pts
Brazil	3
Mexico	9
Peru	8
USA	1

Country	# Pts
China	43
Taiwan	19
India	2
S. Korea	1
Thailand	5

Country	# Pts
Belarus	8
Greece	7
Hungary	16
Israel	15
Lithuania	5
Russia	34
Turkey	7

Percent of Patients by Region

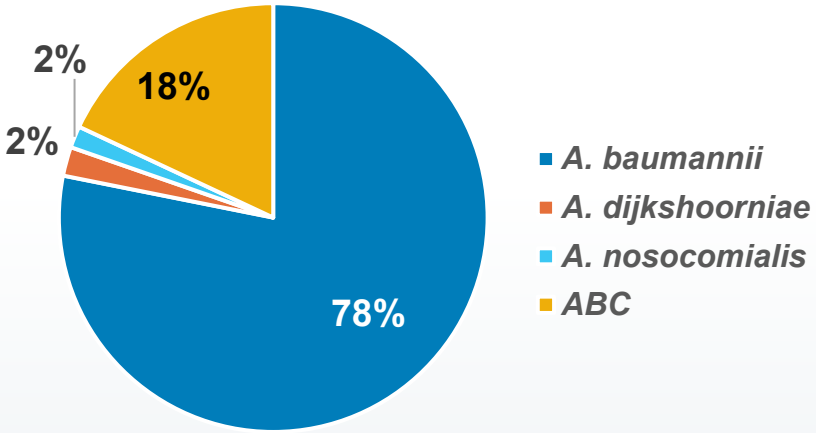


- Almost half from Europe
- Almost one quarter from China

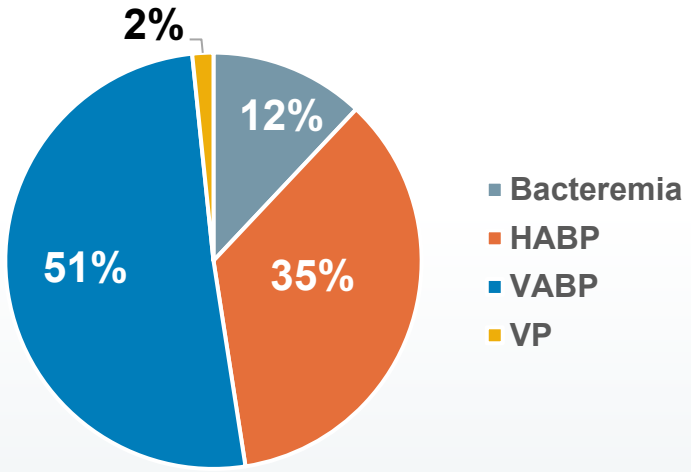
m-MITT population, patients in the ITT (intent-to-treat) population who received any study drug and had an ABC organism isolated at baseline

Demographics of Baseline ABC Isolates

By *Acinetobacter* species



By Infection Type



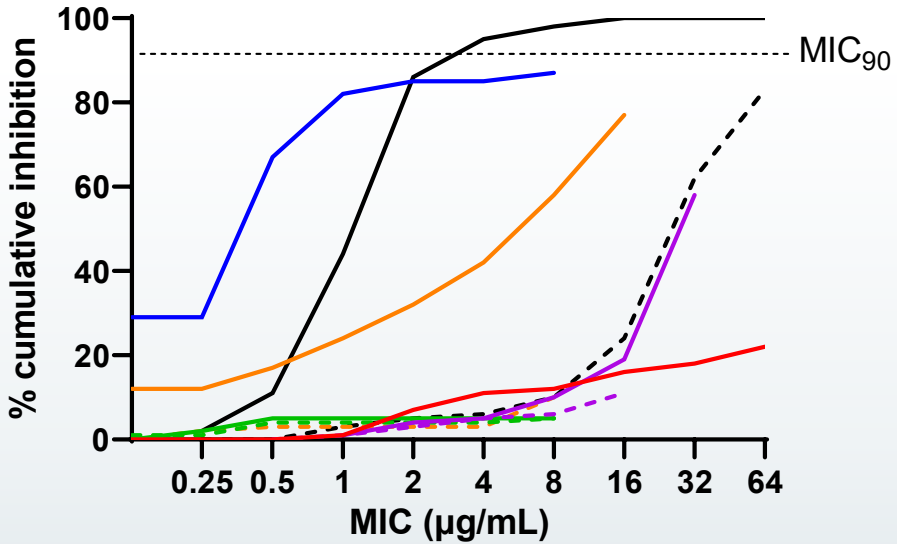
- 67% of patients had monomicrobial ABC infections at baseline (see Poster 02091)

m-MITT population, patients in the ITT (intent-to-treat) population who received any study drug and had an ABC organism isolated at baseline; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia

Antibiotic Susceptibility of Baseline ABC Isolates

N = 175 characterized by central lab; N = 8 characterized by local labs

- 96% MDR[1], 84% XDR[1], 15% PDR[2]
  - *96% non-susceptible to carbapenems*
  - *17% non-susceptible to colistin*
- 4.6% non-susceptible to sulbactam-durlobactam
  - based on preliminary breakpoint of 4 µg/mL*



	$MIC_{50/90}$	%NS (CLSI)
AMK	>64/>64	85
FEP	>16/>16	95
CPZ-SUL	32/>32	NA
COL	0.5/>8	17
IPM	>8/>8	96
MEM	>8/>8	96
LVX	>4/>4	96
MIN	4/16	43
SUL	32/>64	95*
SUL-DUR	2/4	4.6*

AMK, amikacin; FEP, cefepime; CPZ-SUL, cefoperazone-sulbactam (2:1); COL, colistin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; SUL, sulbactam; DUR, durlobactam, NS, non-susceptible; [1]MDR, multidrug-resistant; XDR, extensively drug-resistant (as defined by Magiorakos *et al*., *Clin. Microb. Infect.* 2012 18:268-81) [2]PDR, pan-drug resistant, non-susceptible to all approved agents tested; *preliminary susceptibility breakpoint for sulbactam-durlobactam is 4 µg/mL based on O'Donnell *et al*, 2019 ECCMID Poster P1953, Rodvold *et al*. AAC 2018; 62:e01089

Antibiotic Resistance Patterns Across Regions and Infection Types

Antibiotic / % Non-susceptible*	All	Europe	Latin America	Asia-Pacific	China	USA	Respiratory Infection	Bloodstream Infection
	N = 175	N = 91	N = 16	N = 25	N = 42	N = 1	N = 154	N = 21
Amikacin	85%	92%	87%	76%	88%	NS (MIC = 64)	87%	95%
Colistin	17%	30%	0	4%	0	NA (MIC = 0.5)	10%	57%
Imipenem	96%	94%	94%	96%	95%	NS (MIC >8)	95%	96%
Minocycline	42%	49%	56%	4%	28%	NS (MIC = 16)	40%	62%
Sulbactam	95%	93%	94%	96%	95%	NA (MIC = 16)	94%	95%

- High rates of antibiotic resistance were observed across regions, except for colistin, which was variable
  - *Colistin non-susceptibility ranged from 30% in Europe to 0% in Latin America and China*
- Blood isolates had notably higher colistin and minocycline non-susceptibility rates (59% and 62%) compared to respiratory isolates (10% and 40%)

* according to CLSI guidelines (CLSI does not recognize susceptible breakpoints for colistin. Colistin-non-susceptible defined as ≥4 µg/mL); NA = not applicable

Sulbactam-durlobactam Was Active Across Regions and Infection Types

Antibiotic	Region (N)	All	Europe	Latin America	Asia-Pacific	China	USA	Respiratory Infection	Bloodstream Infection
		N = 175	N = 91	N = 16	N = 25	N = 42	N = 1	N = 154	N = 21
Imipenem	MIC_{90} (µg/mL)	>8	>8	>8	>8	>8	NS (MIC >8)	>8	>8
	% NS	96	94	94	96	95		95	96
Sulbactam	MIC_{90} (µg/mL)	>64	64	64	64	>64	NA (MIC = 16)	>64	>64
	% NS*	95	93	94	96	95		94	95
Sulbactam-durlobactam	MIC_{90} (µg/mL)	4	4	2	2	8	NA	4	4
	% NS*	4.6	2	0	4	11.9	NA	4.5	4.8

- Only 8 of 175 ABC isolates had SUL-DUR MIC values > 4 µg/mL
  - N = 7 with SUL-DUR MIC values of 8 µg/mL (4 in China, 1 each in Taiwan, Greece, Israel)
  - N = 1 with SUL-DUR MIC value of 16 µg/mL (from China)
- All encoded PBP3 variants that confer resistance to sulbactam
  - None encoded genes for metallo-β-lactamase (which durlobactam does not inhibit)

NS, non-susceptible; *preliminary susceptibility breakpoint for sulbactam-durlobactam is 4 µg/mL based on O'Donnell *et al*, 2019 ECCMID Poster P1953, Rodvold *et al.* AAC 2018; 62:e01089

Sulbactam-durlobactam Was Active Across Resistant Subsets

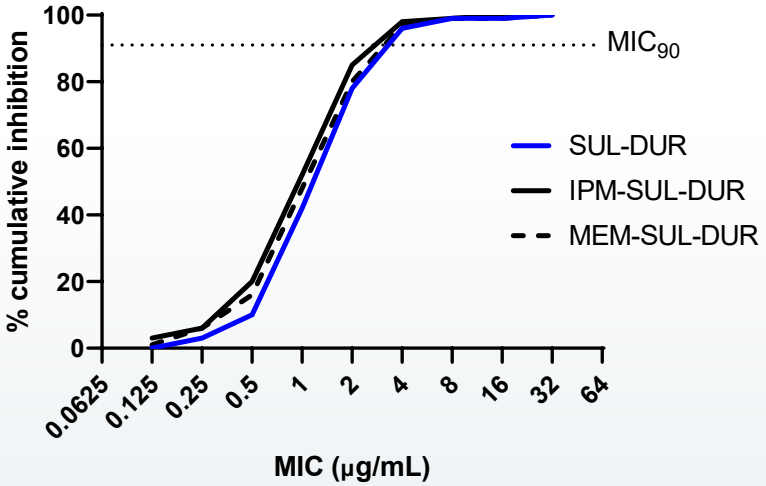
Category	ABC baseline isolates, N (%)	Sulbactam-durlobactam MIC (µg/mL)		
		Range	MIC_{50}	MIC_{90}
ALL	175 (100%)	0.25 - 16	2	4
CARB-R	168 (96%)	0.5 - 16	2	4
COL-NS	30 (17%)	1 - 8	2	4
MIN-NS	75 (43%)	1 - 8	2	4
MDR*	168 (96%)	0.5 - 16	2	4
XDR*	148 (85%)	0.5 - 16	2	4
PDR	26 (15%)	1 - 8	2	4

CARB-R, carbapenem-resistant: COL-NS, colistin-non-susceptible, MIN-NS, minocycline-non-susceptible, MDR, multidrug-resistant; XDR, extensively drug-resistant; PDR, pan-drug resistant (non-susceptible to all approved agents tested) *as defined by Magiorakos *et al.*, *Clin. Microb. Infect.* 2012 18:268-81

Addition of Carbapenems Had Minimal Effect on SUL-DUR Activity in Vitro

- Because all patients received imipenem as background therapy in ATTACK, susceptibility to sulbactam, durlobactam and imipenem alone or in double or triple combinations was tested to determine relative contribution of each against all 175 baseline ABC isolates.
  - *Meropenem combinations were also tested*

Antibacterial Agent or Combination	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Sulbactam	0.25 - >64	32	64
Durlobactam	0.25 - >64	64	>64
Sulbactam-Durlobactam	0.25 - 32	2	4
Imipenem	0.12 - >64	64	>64
Meropenem	0.12 - >64	64	>64
Imipenem-Durlobactam	0.12 - 64	16	32
Meropenem-Durlobactam	0.06 - >64	16	32
Sulbactam-Imipenem (1:1)	0.12 - 64	16	32
Sulbactam-Meropenem (1:1)	0.06 - >64	32	32
Sulbactam-Imipenem (1:1) + Durlobactam	0.12 - 16	1	4
Sulbactam-Meropenem (1:1) + Durlobactam	0.12 - 32	2	4



- The only active double combination was sulbactam-durlobactam
- Addition of either imipenem or meropenem had minimal effect on overall sulbactam-durlobactam activity
  - 3 of 8 ABC isolates with SUL-DUR MIC > 4 µg/mL had IPM-SUL-DUR or MEM-SUL-DUR MIC = 4 µg/mL

Conclusions

- ABC baseline isolates from the ATTACK Phase 3 trial were highly antibiotic resistant
  - 96% multidrug-resistant, 84% extensively drug-resistant, 15% pan drug-resistant
- Only 8 of 175 (4.6%) had sulbactam-durlobactam MIC values above its preliminary breakpoint (4 µg/mL)
  - 7 isolates with MIC = 8 µg/mL, 1 with MIC = 16 µg/mL
- Addition of carbapenems had minimal effect on overall sulbactam-durlobactam activity
- The second most active antibiotic in vitro was colistin, to which 17% of ABC isolates were non-susceptible, followed by minocycline (43% non-susceptible)
  - CLSI does not recognize susceptibility breakpoints for colistin
- In global surveillance studies, sulbactam-durlobactam demonstrated potent in vitro activity against 4,252 ABC isolates (MIC_{90} = 2 mg/L, 98.2% inhibited at ≤4 µg/mL [Poster 01106])
- If approved, SUL-DUR could be an important treatment option for infections caused by ABC including carbapenem-resistant and multidrug-resistant strains

Thank You

We would like to extend our heartfelt thanks to all the patients and their families, as well as the investigators involved in this study.

Other ATTACK TRIAL Presentations at ECCMID 2022

- **Abstract 02060:** Altarac D, *et al*. Efficacy and safety of sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections: a global, randomised, active-controlled phase 3 trial (ATTACK).
- **Abstract 02093:** Altarac D, *et al*. Efficacy and safety of sulbactam-durlobactam (SUL-DUR) therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections in the open label Part B of the ATTACK phase 3 trial.
- **Abstract 02145:** Lewis D, *et al*. Safety profile of sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections from the global, randomised, active-controlled phase 3 trial (ATTACK).
- **Abstract 01106:** Hackel, *et al*. In vitro activity of sulbactam-durlobactam against *Acinetobacter baumannii-calcoaceticus* complex isolates from a five-year surveillance program (2016 –2020)
- **Abstract 02091:** Miller A, *et al*. Characterisation of co-infecting gram-negative pathogens isolated in addition to *Acinetobacter baumannii-calcoaceticus* complex (ABC) at baseline from patients enrolled in the ATTACK phase 3 trial.