Sulbactam-Durlobactam (SUL-DUR), a targeted β-lactam/β-lactamase inhibitor, for MDR *Acinetobacter* infections

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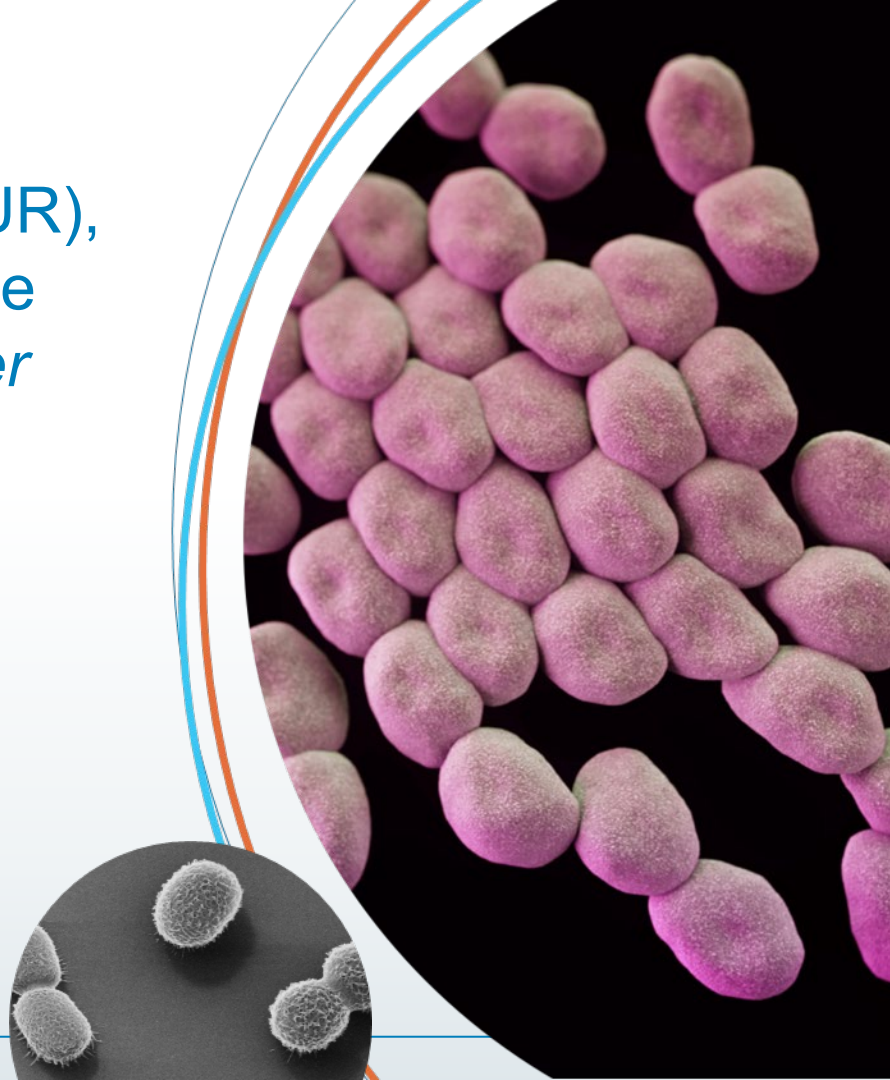
New Agents Discovery Summary Session:
Early New Antimicrobial Agents
Salon GHI, Friday, June 10, 2022



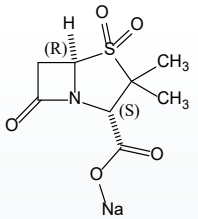
Disclosures

- Alita Miller and Sarah McLeod – full time employees, Entasis Therapeutics

SUL-DUR: a β-Lactam/β-Lactamase Inhibitor Combination in Development For Treatment of Infections Caused by *Acinetobacter baumannii-calcoaceticus*

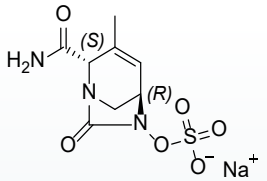
- The *Acinetobacter baumannii-calcoaceticus* (ABC) complex is a group of closely related *Acinetobacter* species that cause serious infections associated with substantial mortality
- *A. baumannii* has been identified by the World Health Organization as a priority pathogen for the development of new antibiotics, due to increasing resistance to existing therapies[1]
  - Carbapenem-resistant *A. baumannii* (CRABC) 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 = 4252 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. Microbiol*. 2021; 12:709974 3. Hackel *et al*. ECCMID 2022 Poster #01106.

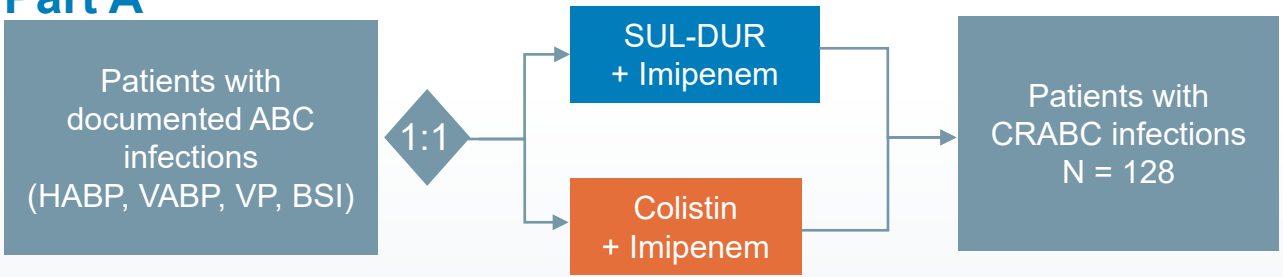
Other SUL-DUR Presentations at 2022 ASM Microbe

Date	Time (Place)	Session	Session Title	Abstract # (Board #)	Presentation Title
6/11/2022	1:45-3:45 (Salon C)	AAR20	Role of the MIC in determining PK/PD targets and STIC	NA	PK/PD of the BLI, DUR, in combination with SUL against ABC
6/12/2022	1:45-3:45 (Salon C)	AAR21	Impact of pre-clinical PK/PD on drug approval	NA	PK/PD of the BLI, DUR, in combination with SUL against ABC
6/10/2022	Poster Hall	AAR01	Surveillance of antimicrobial resistance	3114 (AAR304)	In vitro activity of SUL-DUR against recent ABC isolates from the US
6/10/2022	"	AAR01	Surveillance of antimicrobial resistance	3473 (AAR334)	In vitro activity of SUL-DUR against *A. baumannii* clinical isolates collected in 2020 from China
6/10/2022	"	AAR01	Surveillance of antimicrobial resistance	3490 (AAR326)	Potent activity of SUL-DUR against PDR ABC isolates from a recent 5-year surveillance study (2016-2020)
6/11/2022	"	AAR08	New antimicrobial agents	2776 (AAR451)	In vitro activity of SUL-DUR in combination with other antimicrobial agents
6/11/2022	"	AAR08	New antimicrobial agents	2797 (AAR450)	SUL-DUR is bactericidal against clinical isolates of *A. baumannii*

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



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

Part B - open label

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

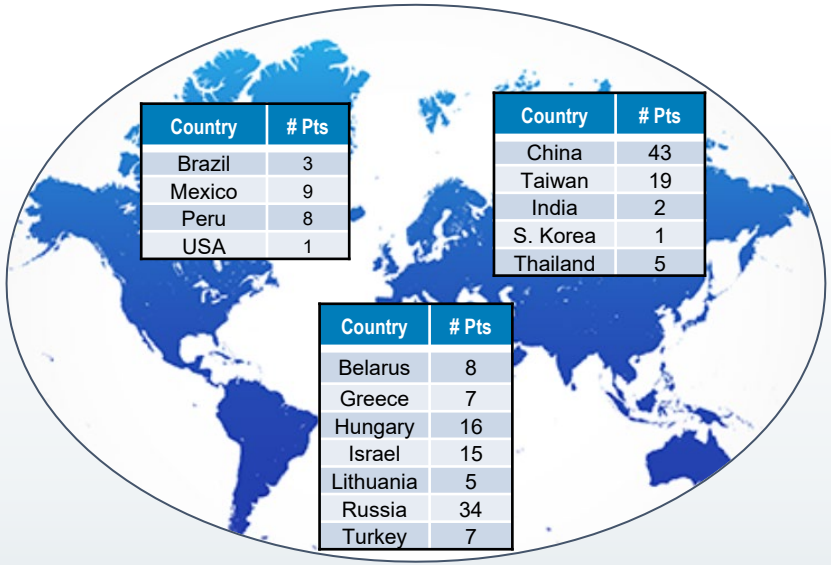
This trial is registered at ClinicalTrials.gov: NCT03894046.

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.

m-MITT Population (N = 183)

128 patients in the CRABC m-MITT population

183 patients from 16 countries enrolled in m-MITT population

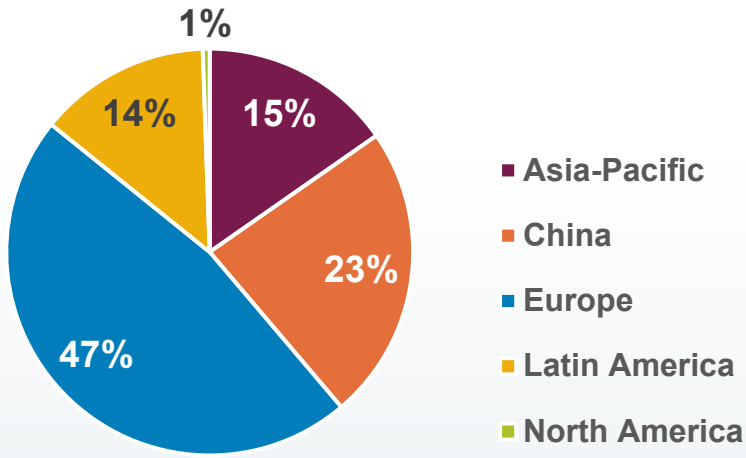


Country	# Pts
Brazil	3
Mexico	9
Peru	8
USA	1

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

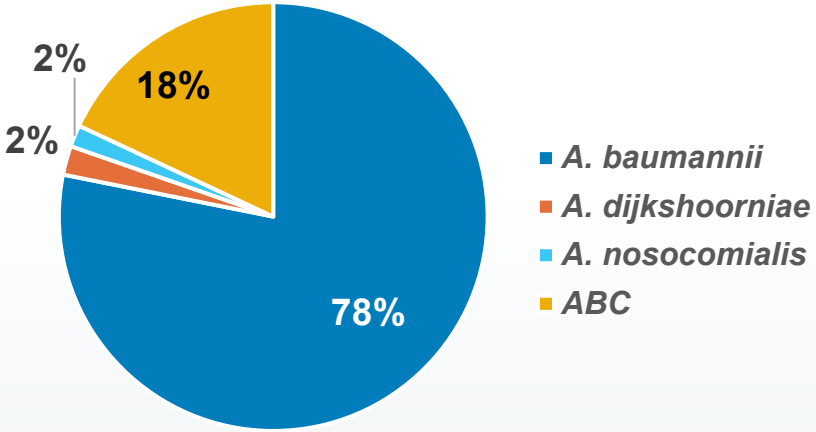


- Almost half from Europe
- Almost one quarter from China

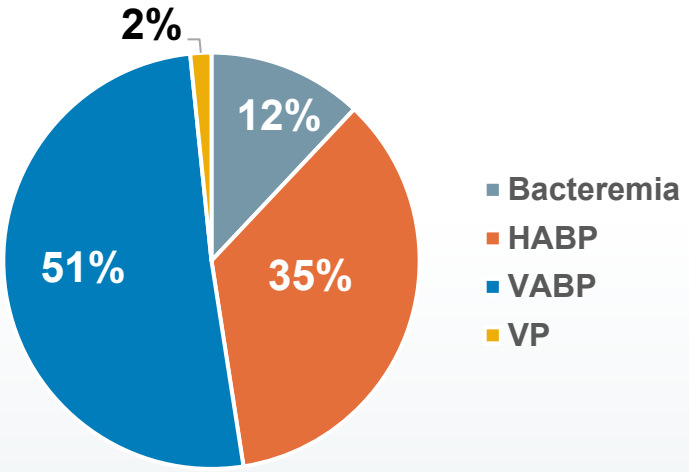
m-MITT population, patients in the ITT (intent-to-treat) population who received any study drug and had an ABC organism isolated at baseline

Demographics of Baseline ABC Isolates

By *Acinetobacter* species



By Infection Type



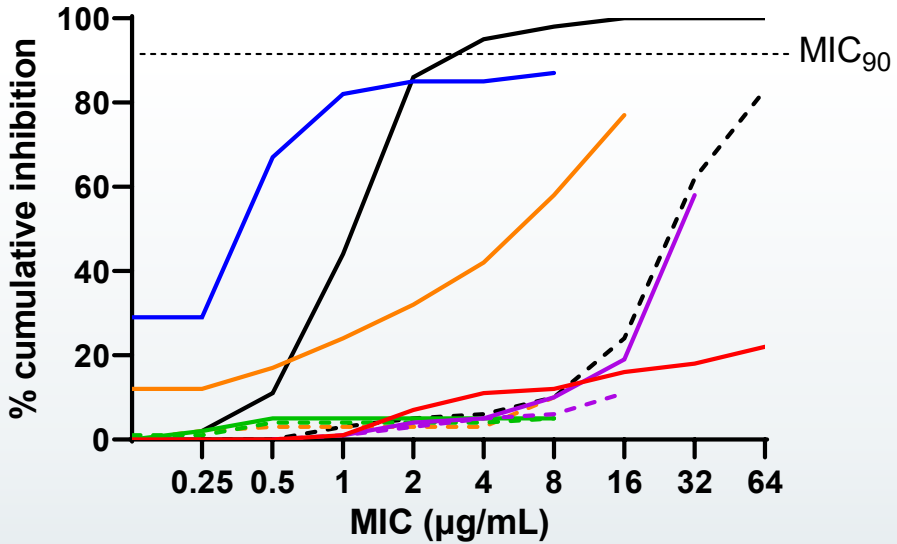
- 67% of patients had monomicrobial ABC infections at baseline

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 (57% and 62%) compared to respiratory isolates (10% and 40%)

* according to CLSI guidelines, except for colistin which lacks susceptible breakpoints. Colistin-non-susceptible defined as ≥4 µg/mL; NA = not applicable

Sulbactam-durlobactam Was Active Across Regions and Infection Types

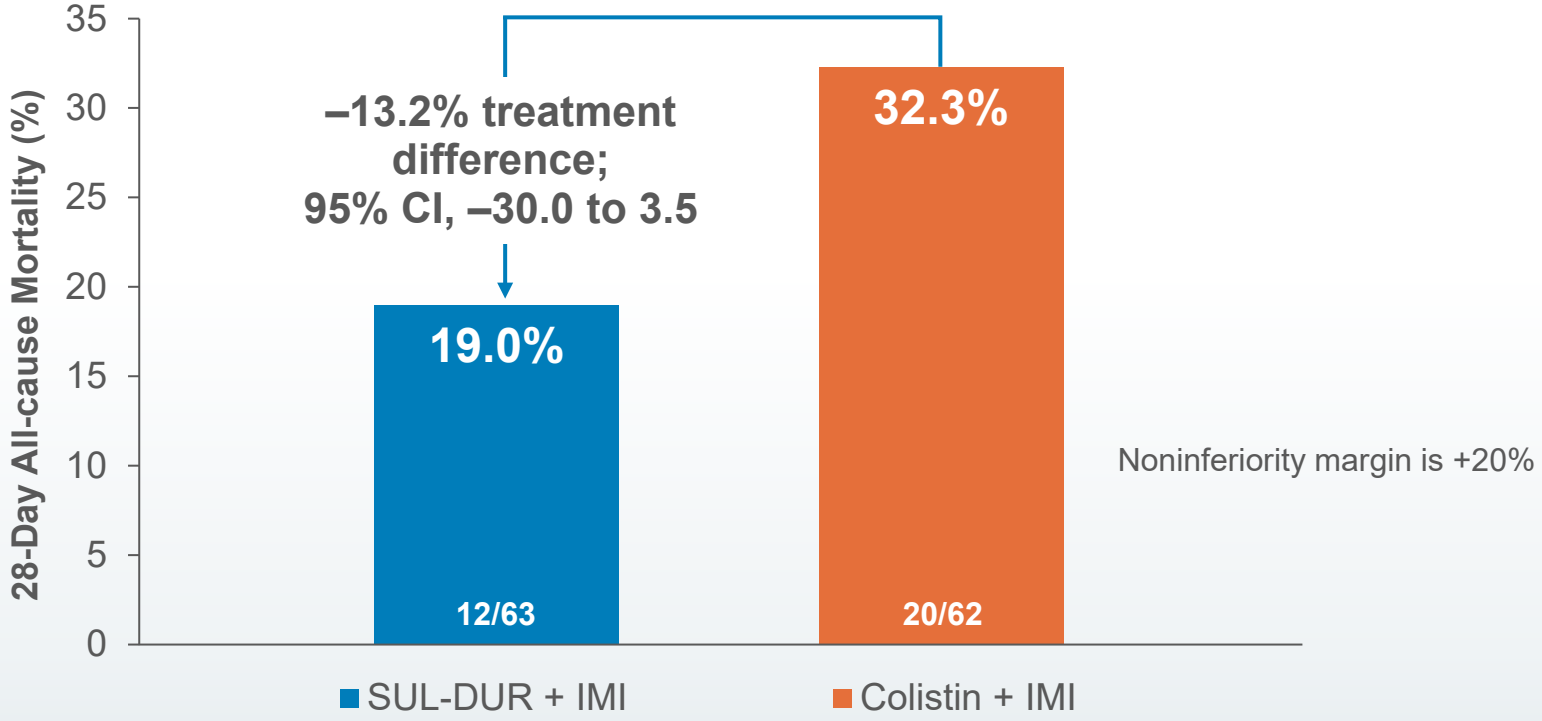
Antibiotic	Region (N)	All	Europe	Latin America	Asia-Pacific	China	USA	Respiratory Infection	Bloodstream Infection
		N = 175	N = 91	N = 16	N = 25	N = 42	N = 1	N = 154	N = 21
Imipenem	MIC_{90} (µg/mL)	>8	>8	>8	>8	>8	NS (MIC >8)	>8	>8
	% NS	96	94	94	96	95		95	96
Sulbactam	MIC_{90} (µg/mL)	>64	64	64	64	>64	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 a 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

Primary Efficacy Endpoint Achieved

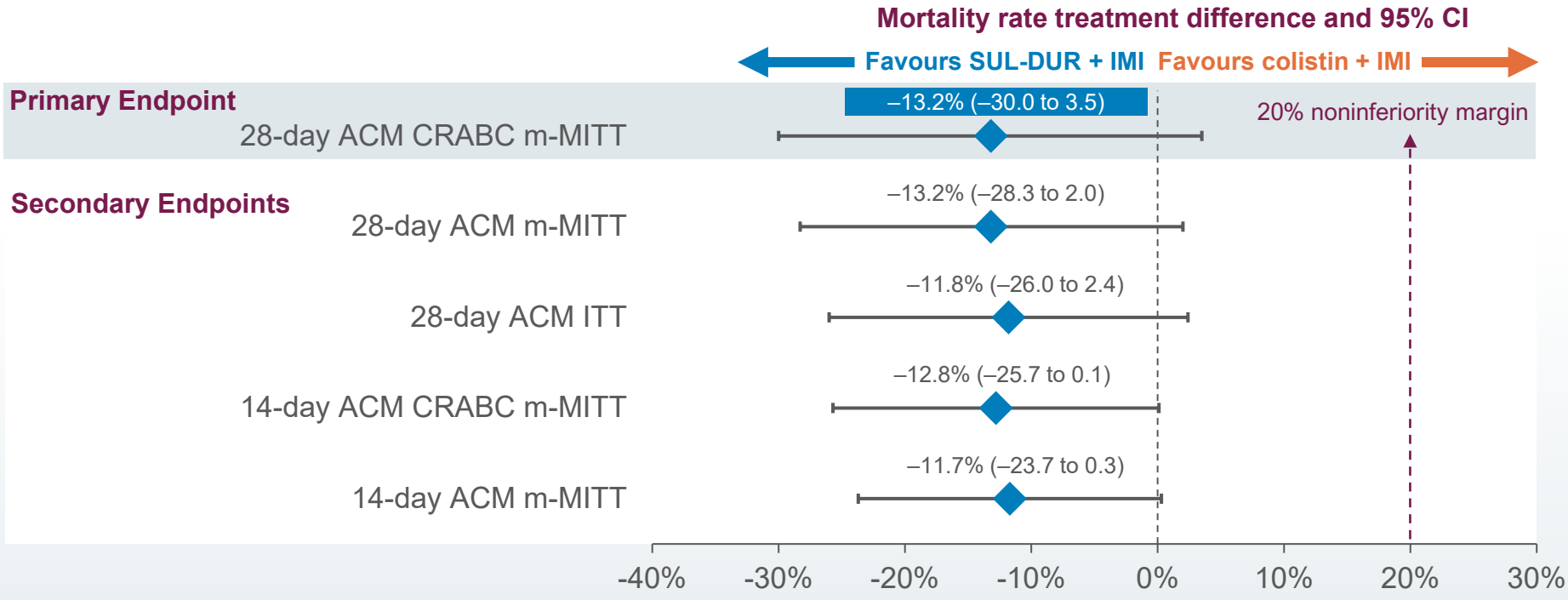
SUL-DUR non-inferior on 28-day all-cause mortality vs colistin in the CRABC m-MITT population



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

All-cause Mortality Consistently Lower With SUL-DUR

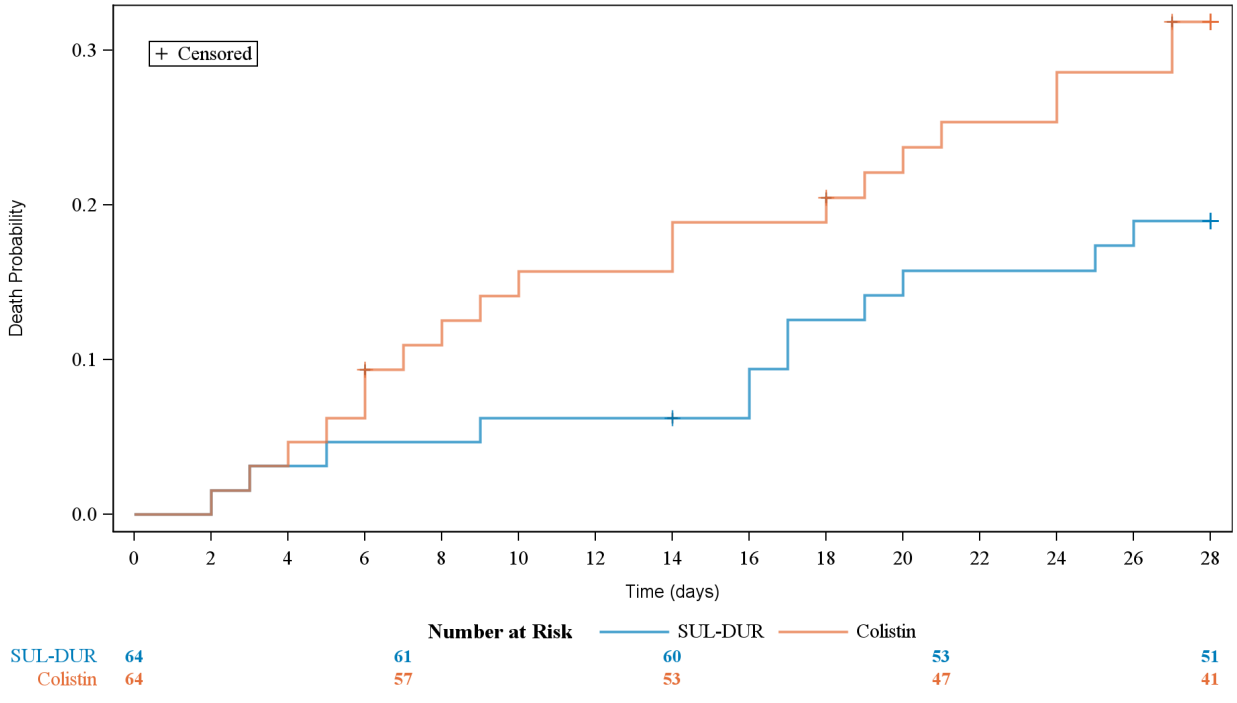
Mortality difference for SUL-DUR vs colistin was consistent across study populations and endpoints



ACM, all-cause mortality.

All-cause Mortality Consistently Lower With SUL-DUR

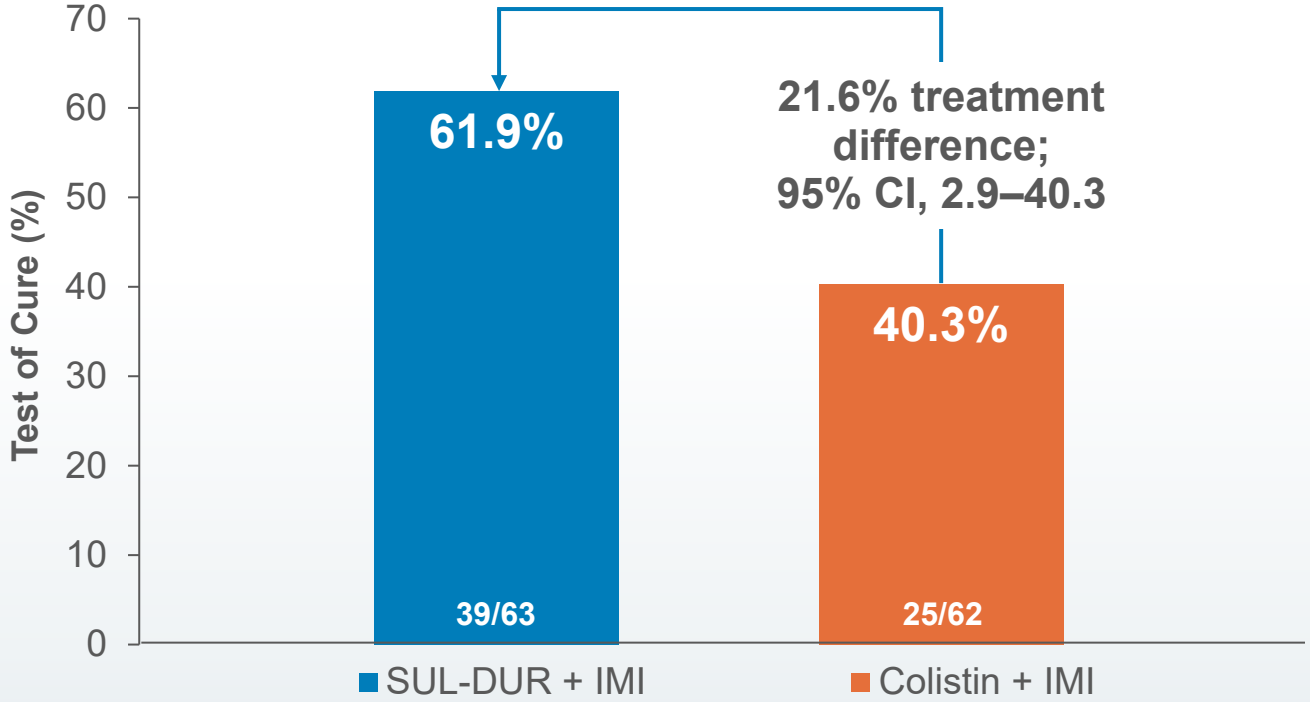
Reduced mortality over time with SUL-DUR treatment



- Between days 6 and 14, more deaths due to the index CRABC infection occurred in the colistin arm.
- Most deaths that occurred before day 6 and after day 14 were not related to the index CRABC infection (and mortality rates were comparable during those time periods).
- These observations suggest that the survival benefit seen between days 6-14 is reflective of the efficacy of SUL-DUR in treating the index CRABC infection during this critical time point.

Statistically Significant Difference in Clinical Cure

SUL-DUR vs colistin at test of cure in the CRABC m-MITT population

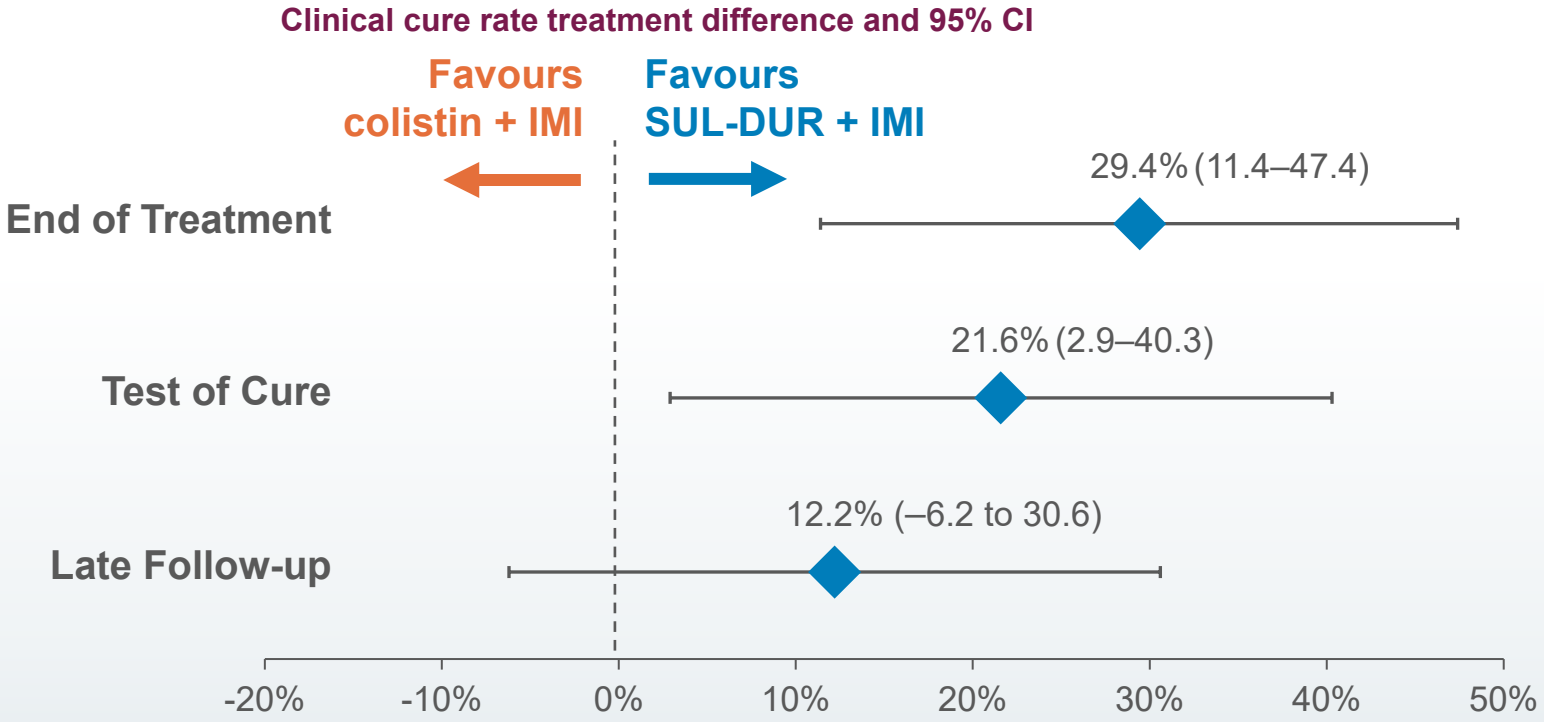


Excludes participants who withdrew consent.

Treatment difference was the difference in clinical cure rate between the 2 treatment arms ([SUL-DUR + IMI] – [colistin + IMI]). The 95% CI (2-sided) was computed using a continuity-corrected Z statistic. Test of cure was 7±2 days after end of treatment.

Clinical Cure Rates Higher with SUL-DUR at All Timepoints

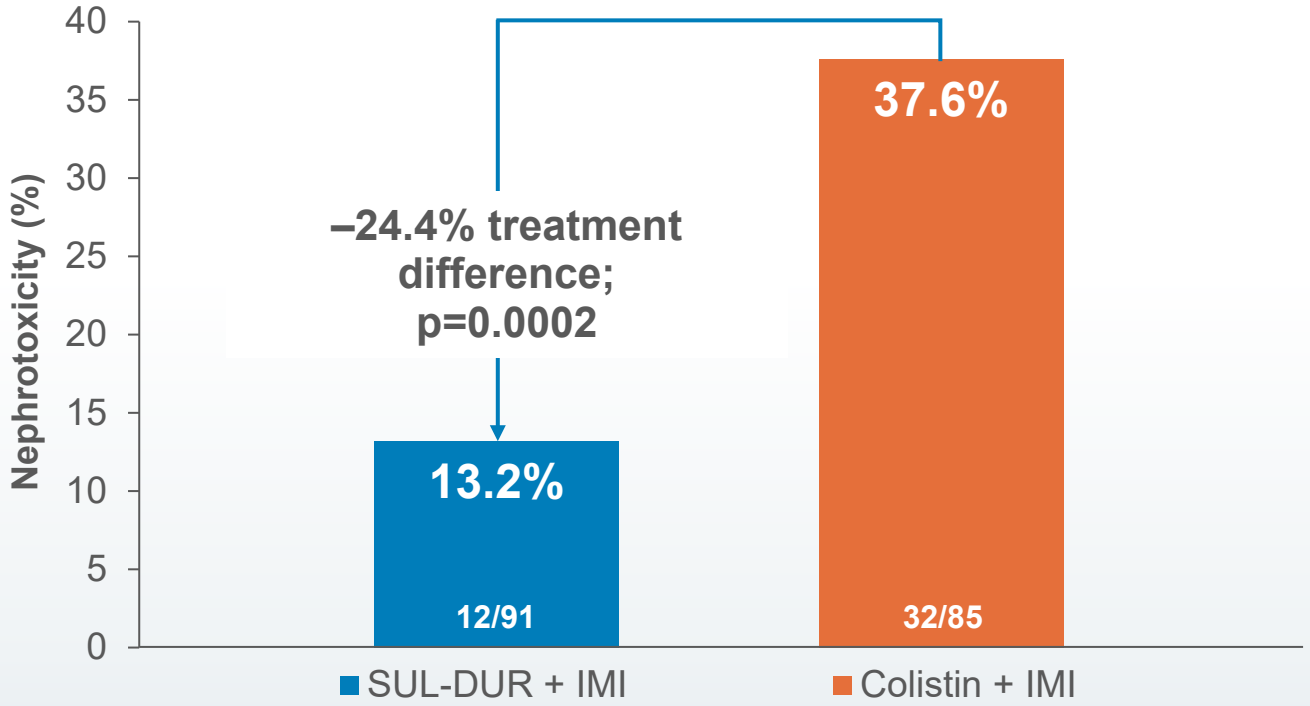
Statistically significant difference in clinical cure at end of treatment and test of cure



Treatment difference was the difference in clinical cure rate between the 2 treatment arms ([SUL-DUR + IMI] – [colistin + IMI]). The 95% CI (2-sided) was computed using a continuity-corrected Z statistic. End of treatment was day of last dose; test of cure 7±2 days after end of treatment; late follow-up 7±2 days after test of cure.

Statistically Significant Reduction in Nephrotoxicity

SUL-DUR vs colistin as measured by the RIFLE classification



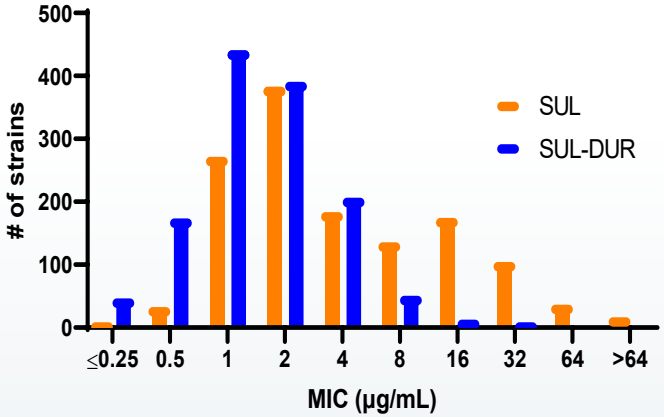
Excludes patients with chronic haemodialysis at baseline. Note: If patients had multiple RIFLE events during post-baseline visits, the patient was counted only once at the highest severity. Please see ECCMID abstract 02145 for additional safety data.
RIFLE measured by creatinine level or glomerular filtration rate. A chi-square test was used to determine statistical significance between treatment groups.

In Vitro Activity of SUL-DUR against 1,271 Recent ABC Isolates from the USA

Antibiotic	MIC (µg/mL)			%S*
	Range	MIC_{50}	MIC_{90}	
SUL-DUR	<0.03 - >64	0.5	2	99*
SUL	0.25 - >64	2	32	NA
Amikacin	<0.5 - >64	2	>64	78
Cefepime	0.25 - >16	4	>16	60
Ciprofloxacin	<0.125 - >4	0.5	>4	61
Colistin	<0.25 - >8	0.5	1	NA
Imipenem	0.06 - >64	0.25	64	68
Meropenem	0.06 - >64	0.5	>64	66
Minocycline	<0.125 - >16	0.25	8	87
Tigecycline	0.03 - 32	0.25	2	NA

*Based on CLSI 2021interpretative criteria; NA, not available. SUL-DUR MICs were interpreted using a preliminary susceptible breakpoint of ≤4 µg/mL.

MIC distribution for SUL vs SUL-DUR against 1,271 US ABC isolates collected between 2016-2020



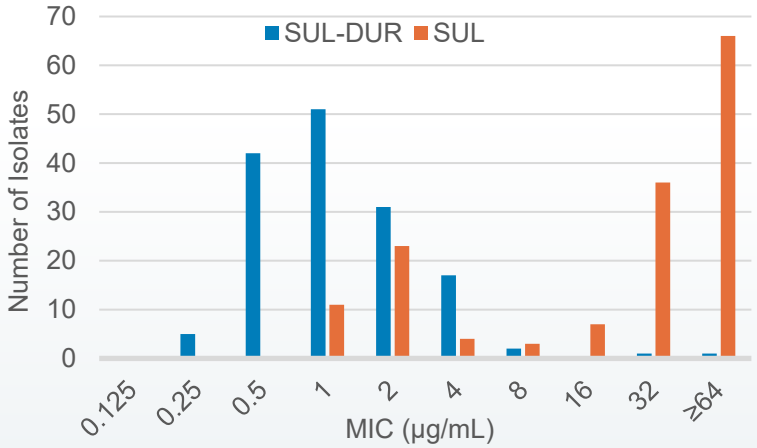
- 99.3% of ABC isolates from the US were inhibited by ≤ 4 µg/mL SUL-DUR, with an MIC_{90} of 2 µg/mL.
- SUL-DUR activity was consistent across ABC species, sources of infection and subsets of resistance phenotypes.
- 7 of the 8 SUL-DUR-non-susceptible isolates encoded either the metallo-β-lactamase NDM-1, which is not inhibited by DUR, or a mutation in PBP3, the target of sulbactam.

In vitro activity of SUL-DUR against 150 recent *A. baumannii* isolates from China

Antibiotic	MIC (µg/mL)			%S*
	Range	MIC_{50}	MIC_{90}	
SUL-DUR	0.25 - >64	1	4	97.3
Sulbactam	1 - >64	32	>64	NA
Imipenem	0.12 - >8	>8	>8	26.7
Cefepime	0.5 - >16	>16	>16	26
Amikacin	1 - >64	>64	>64	37.3
Levofloxacin	≤0.06 - >4	>4	>4	26
Colistin	≤0.25 - 2	0.5	0.5	NA
Minocycline	≤0.12 - >16	8	16	36.7
Tigecycline	0.12 - >4	2	4	NA

*Based on CLSI 2021interpretative criteria; NA, not available. SUL-DUR MICs were interpreted using a preliminary susceptible breakpoint of ≤4 µg/mL.

MIC distribution for SUL vs SUL-DUR against 150 Chinese *A. baumannii* isolates collected in 2020



- This set of isolates had high levels of resistance to other antibiotics, including carbapenems.
- 97.3% of ABC isolates from five provinces in China were inhibited by ≤ 4 µg/mL SUL-DUR, with an MIC_{90} of 4 µg/mL.
- Activity of sulbactam-durlobactam was consistent across provinces and infection types.

In Vitro Activity of SUL-DUR against 95 Pan-Drug Resistant ABC Isolates

- 4,252 geographically diverse, ABC clinical isolates from 2016 to 2020 were tested
- SUL-DUR $MIC_{50/90}$ values were 1/2 µg/mL; 98.2% were inhibited at ≤ 4 µg/mL.
- SUL-DUR activity was consistent across time, geographic region, infection type and antibiotic-resistant subsets.
- 11% of isolates were XDR and 2.2% (N = 95) were pan-drug resistant (PDR)*

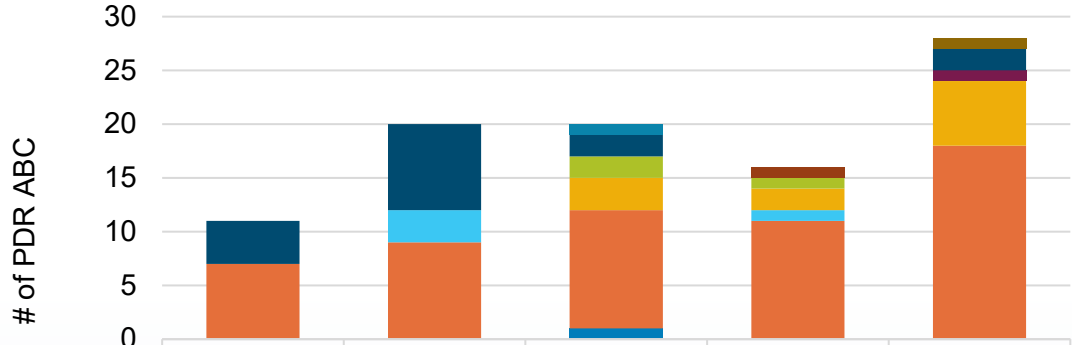
Geographic Region	% total (N = 4,252)	% PDR (N = 95)
North America	29.9	1.0
Europe	41.8	92.6
Latin America	12.5	1.0
Asia	10.7	5.2
South Pacific	3	0.0
Middle East	2.1	0.0

Year	% total (N = 4,252)	% PDR (N = 95)
2016	19.8	11.6
2017	19.4	21.1
2018	21.8	21.1
2019	20.2	16.8
2020	18.7	29.5

*defined as non-susceptibility to all antibiotics tested, excluding tigecycline, which was not included due to lack of approved breakpoints for ABC.

Number and Country of Origin of PDR ABC from SUL-DUR 5-Year Surveillance Program

- The majority of PDR ABC isolates were *A. baumannii* from patients in Europe (primarily from Greece).
- The number of PDR ABC isolates increased over time and spread across the world (from N = 11 over 5 sites in 2016 to 28 at 8 sites in 2020).
- **100% of PDR ABC isolates were inhibited by SUL-DUR at ≤4 µg/mL.**



	2016	2017	2018	2019	2020
USA					1
Argentina			1		
Thailand				1	
Turkey	4	8	2		2
Spain					1
Poland			2	1	
Lithuania			3	2	6
Italy		3		1	
Greece	7	9	11	11	18
Czech Republic			1		

Conclusions

- ABC isolates from patients in ATTACK were highly antibiotic-resistant, but were >95% susceptible to SUL-DUR
- In the ATTACK trial, SUL-DUR met the primary efficacy endpoint of noninferiority to colistin for 28-day all-cause mortality in patients with infections due to CRABC
  - Patients who received SUL-DUR had reduced all-cause mortality at Day 28 (difference –13.2%) and Day 14 (difference –12.8%) relative to the colistin-treated group
  - The survival benefit seen between days 6-14 is reflective of the efficacy of SUL-DUR in treating the CRABC infection at this critical time point
- Patients who received SUL-DUR had significantly higher clinical cure rates at TOC (difference 21.6%) and reduced nephrotoxicity (difference –24.4%) than patients who received colistin
- SUL-DUR *in vitro* activity is consistent across regions, infection types and resistant subsets, including PDR ABC isolates
- 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 the ATTACK trial.