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Efficacy of Sulbactam-Durlobactam versus Colistin in Patients with XDR or PDR *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Infections

Alita Miller, PhD

Chief Scientific Officer

Entasis Therapeutics

alita.miller@entasistx.com

Disclosures

- David Altarac, Alita Miller, Sarah McLeod, Adam Shapiro, Khurram Rana and Drew Lewis are employees of Entasis Therapeutics
- Gabrielle Poirier and Daria Chabas were employees of Entasis Therapeutics when the study was conducted
- The ATTACK trial was funded by Entasis Therapeutics
- Zai Labs, China, provided financial and operational support for the ATTACK trial in China

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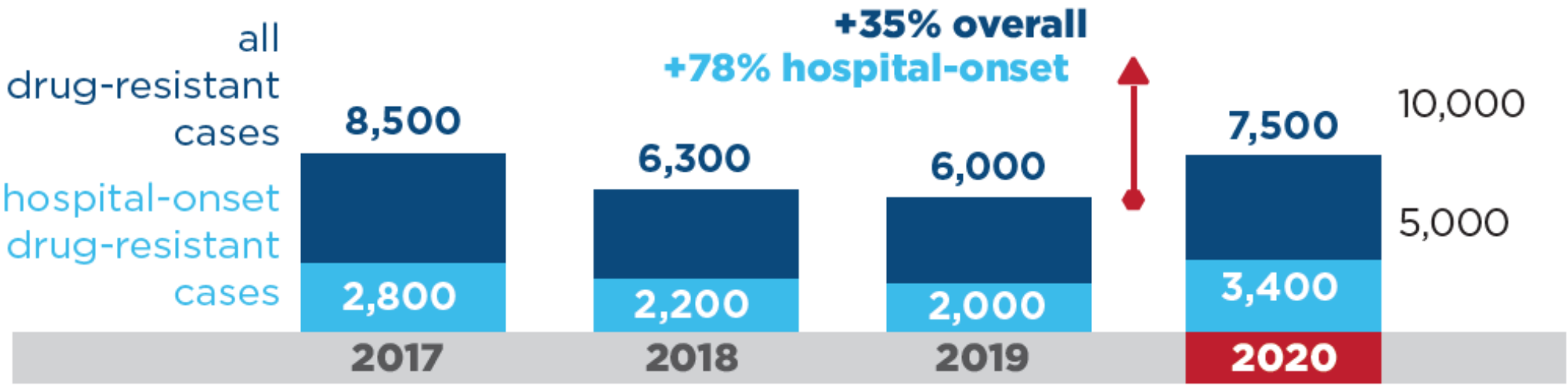
MDR *Acinetobacter* Infections: A Growing, Global Threat

- *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* (CRAB) is the fourth leading cause of death attributable to antimicrobial resistance globally[1]
  - The rate of CRAB cases in US hospitals increased by 78% in 2020 compared with 2019[2]



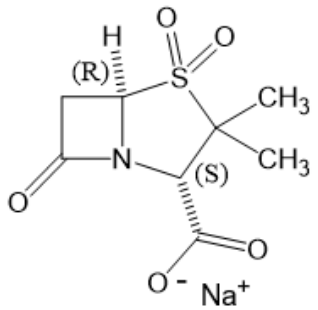
Data from 2018–2020 are preliminary.

1. Antimicrobial Resistance Collaborators. *Lancet.* 2022;399:629-655. 2. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022

SUL-DUR: a β-lactam/β-lactamase Inhibitor Combination in Development for Treatment of *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Infections

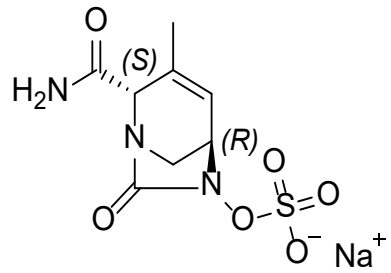
- ABC, identified by the WHO as a priority pathogen for the development of new antibiotics, is a group of closely related *Acinetobacter* species that cause serious infections associated with substantial mortality due to increasing resistance to existing therapies[1]

Sulbactam



- Penicillin derivative with intrinsic activity against ABC
- β-lactamase–mediated resistance is common[2] (MIC_{90} 64 µg/mL; N = 5,032 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, WHO, World Health Organization.

1. Antimicrobial Resistance Collaborators. *Lancet.* 2022;399:629-655. 2. Shapiro AB et al. *Front Microbiol*. 2021;12:709974. 3. Karlowsky JA et al. *Antimicrob Agents Chemother*. 2022 Aug 25:e0078122.

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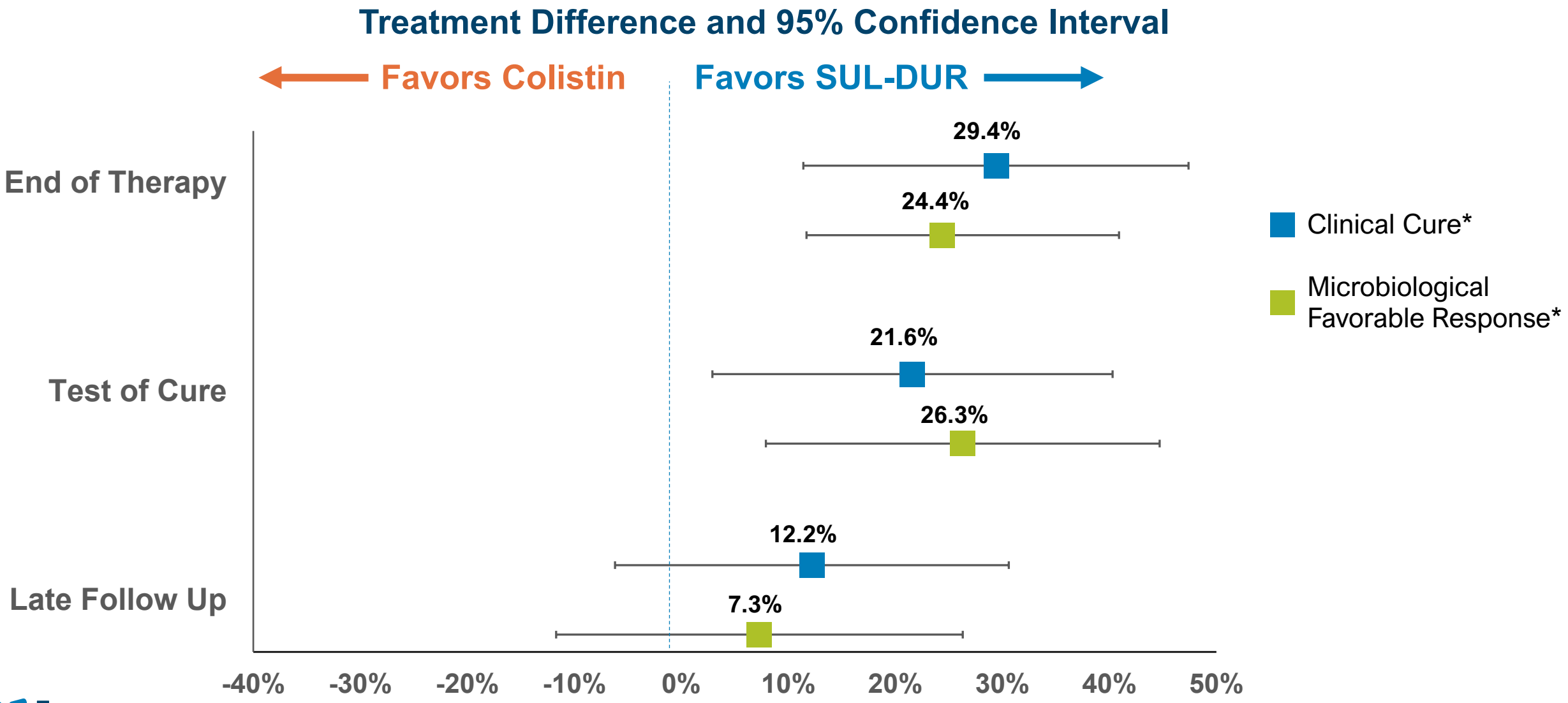
Clinical Cure Rates and Microbiological Response Favors SUL-DUR in ATTACK

Significant differences at all time points for CRABC m-MITT population

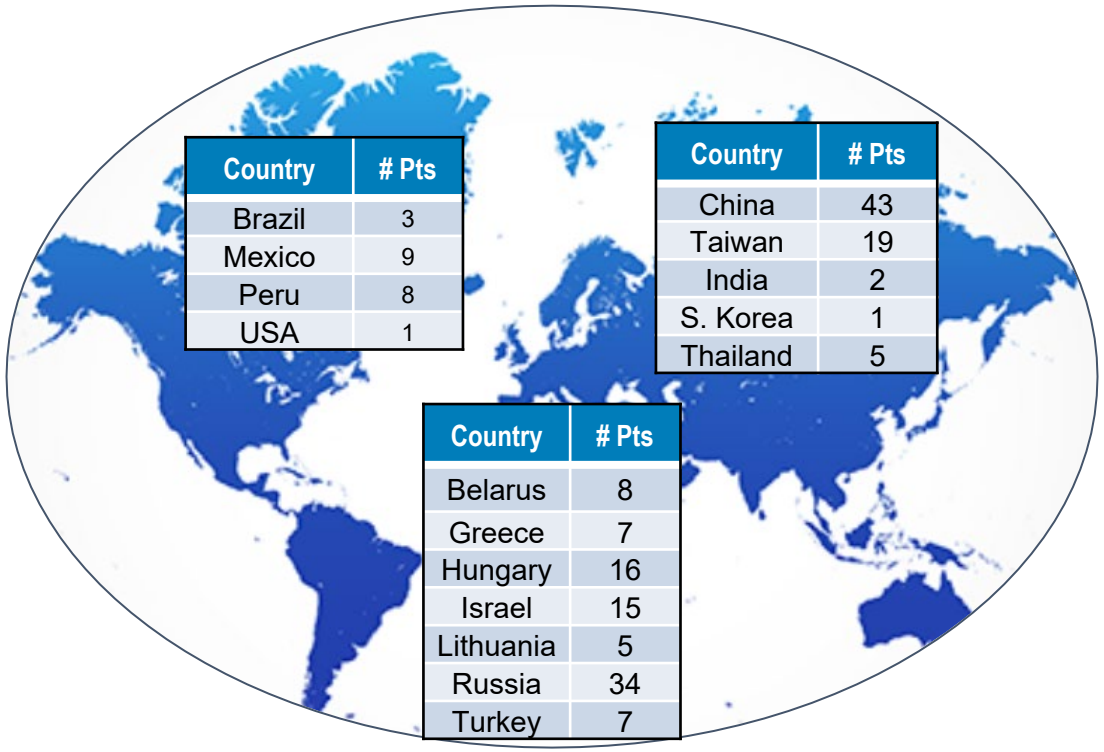


*excluding withdrawn patients

m-MITT Population (N = 183)

156 patients in the CRABC m-MITT population (128 in Part A, 28 in Part B)

183 patients from 16 countries enrolled in m-MITT population

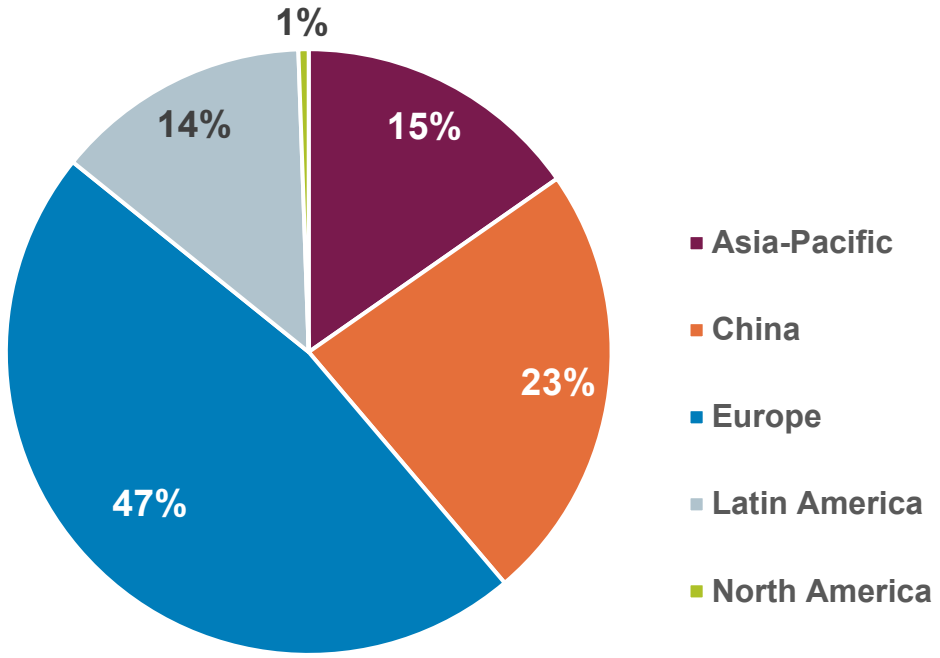


Country	# Pts
Brazil	3
Mexico	9
Peru	8
USA	1

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

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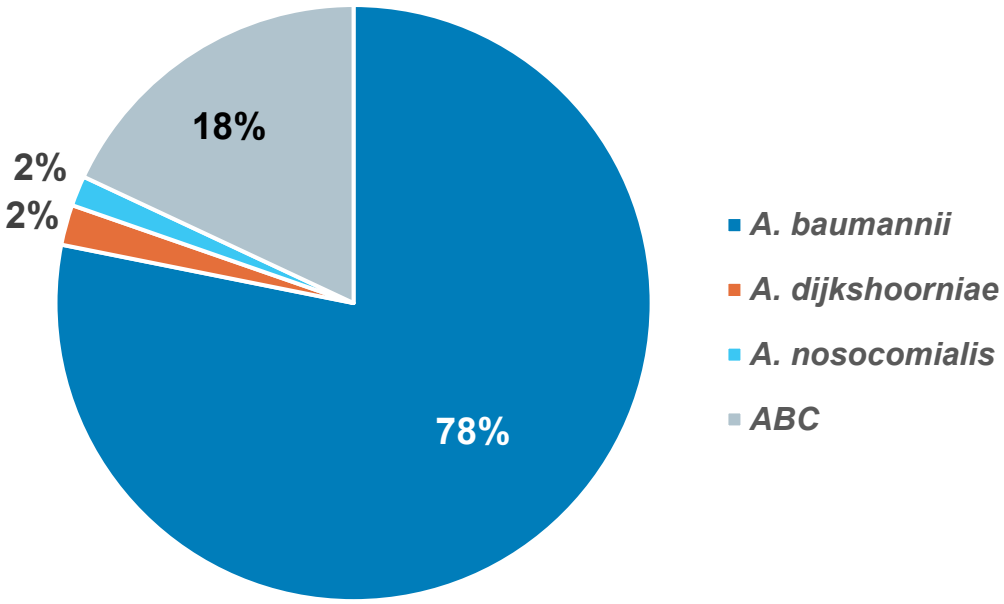
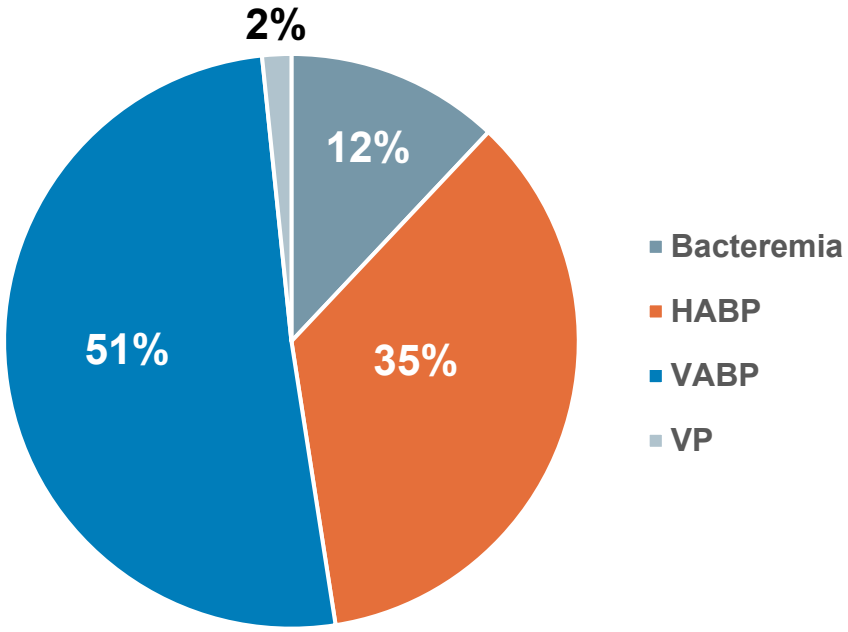
Demographics of Baseline ABC Isolates

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

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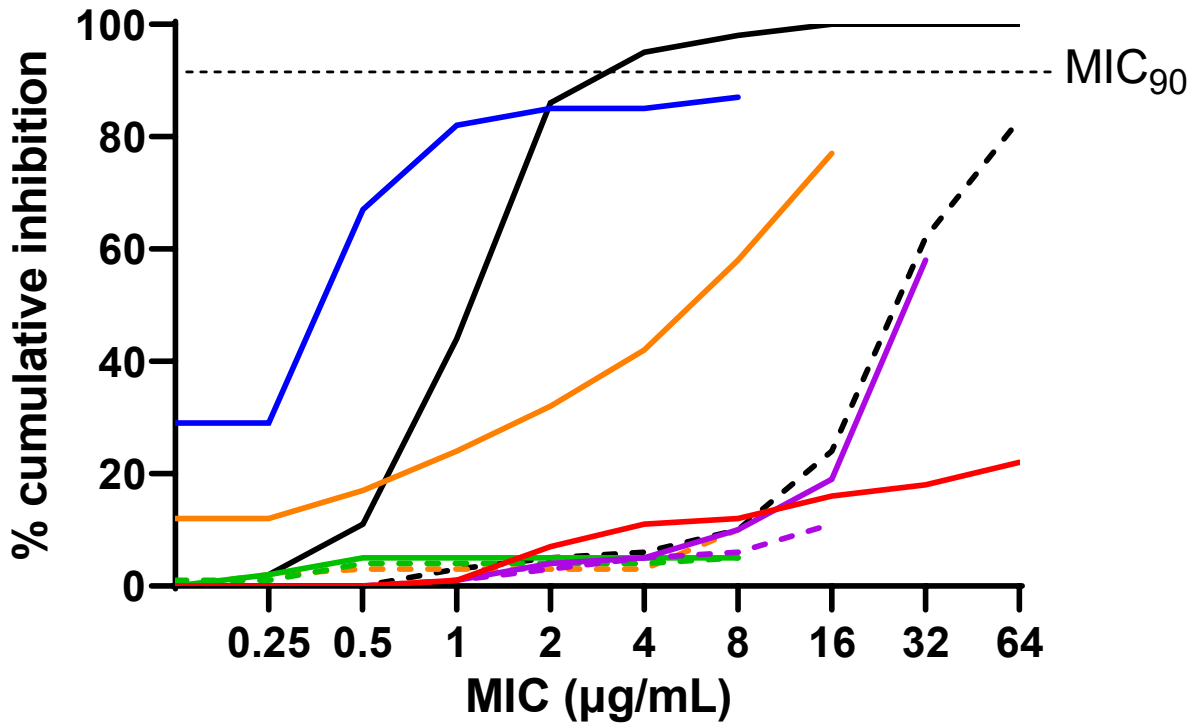
Antibiotic Susceptibility of Baseline ABC Isolates from m-MITT

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



AMK
FEP
CPZ-SUL
COL
IPM
MEM
LVX
MIN
SUL
SUL-DUR

	$MIC_{50/90}$	%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*

- 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*

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*preliminary susceptibility breakpoint for sulbactam-durlobactam is 4/4 µg/mL based on O'Donnell *et al*, 2019 ECCMID Poster P1953, Rodvold *et al.* AAC 2018; 62:e01089
[1]multi-drug and extensively drug resistant as defined by Magiorakos *et al* CMI, 2012; [2]pan-drug resistant (non-susceptible to all approved agents tested)

Activity of SUL-DUR against XDR and PDR ABC Isolates from ATTACK

CRABC m-MITT population (Parts A and B, N = 149 of 156 were available for testing)

Category	ABC baseline isolates, N (%)	SUL-DUR MIC range (µg/mL)	SUL-DUR $MIC_{50/90}$ (µg/mL)
ALL	149 (100%)	0.5 - 8	2/4
CARB-R	149 (100%)	0.5 - 8	2/4
MDR	149 (100%)	0.5 - 8	2/4
XDR[1]	129 (87%)	0.5 - 8	2/4
PDR[2]	14 (9.4%)	1 - 8	2/4

- 10 (71%) of PDR ABC infections were in patients with bacteremia
- All (N = 14) PDR ABC infections were in European patients

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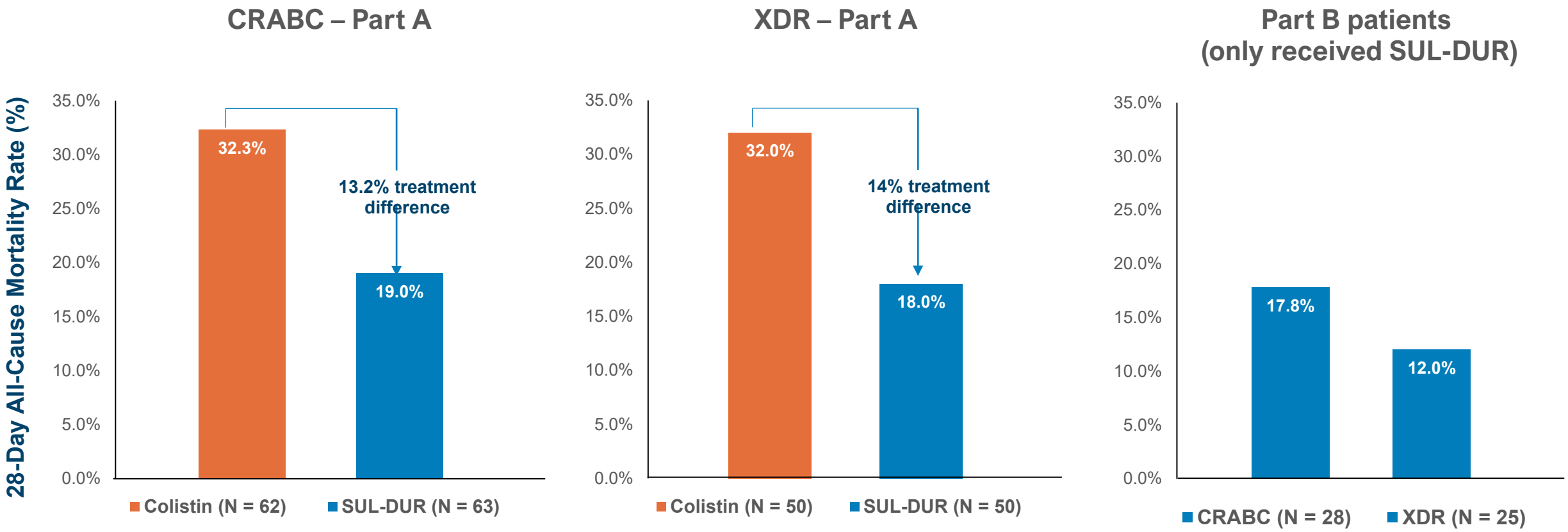
Clinical outcomes of patients infected with XDR ABC in ATTACK

All Cause Mortality Rates in CRABC m-MITT - Parts A and B



- All cause mortality rates favoring SUL-DUR over COL were nearly identical in patients with XDR ABC infections

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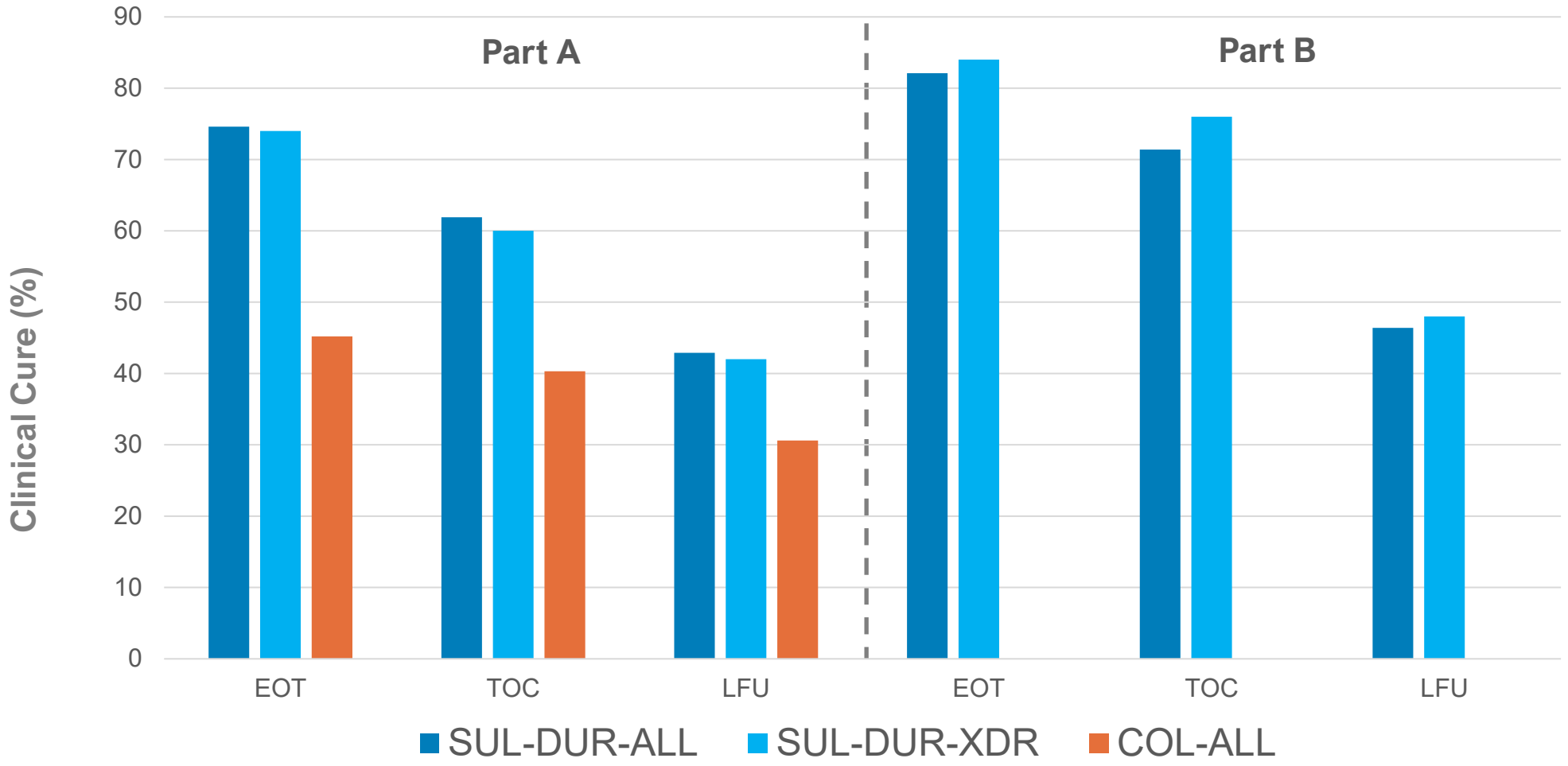
Clinical outcomes of patients infected with XDR ABC in ATTACK, con't.

Clinical cure - CRABC m-MITT in Parts A and B



- Clinical cure rates favoring SUL-DUR over COL were nearly identical in patients with XDR ABC infections

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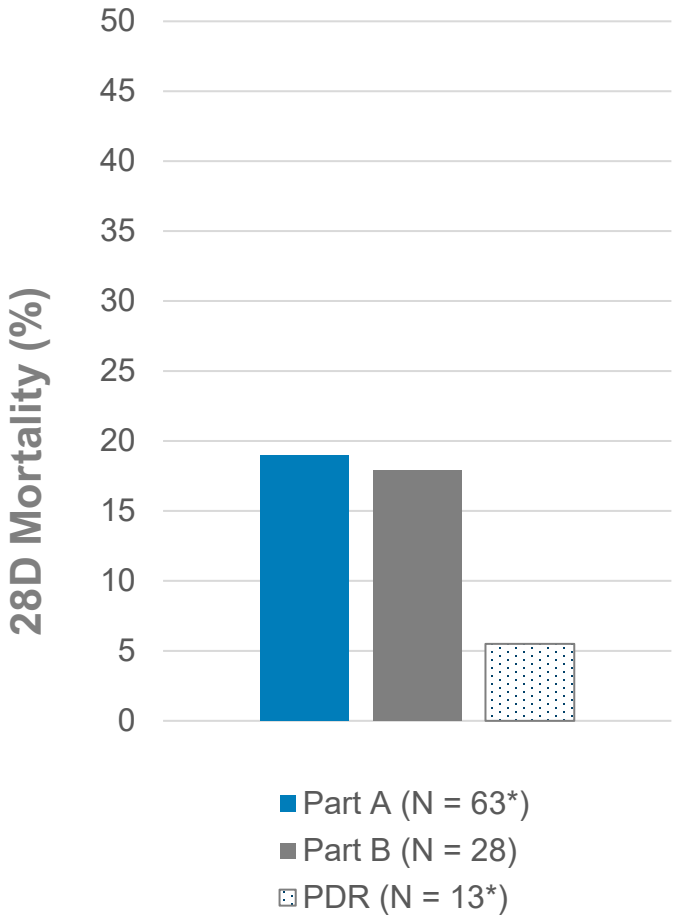
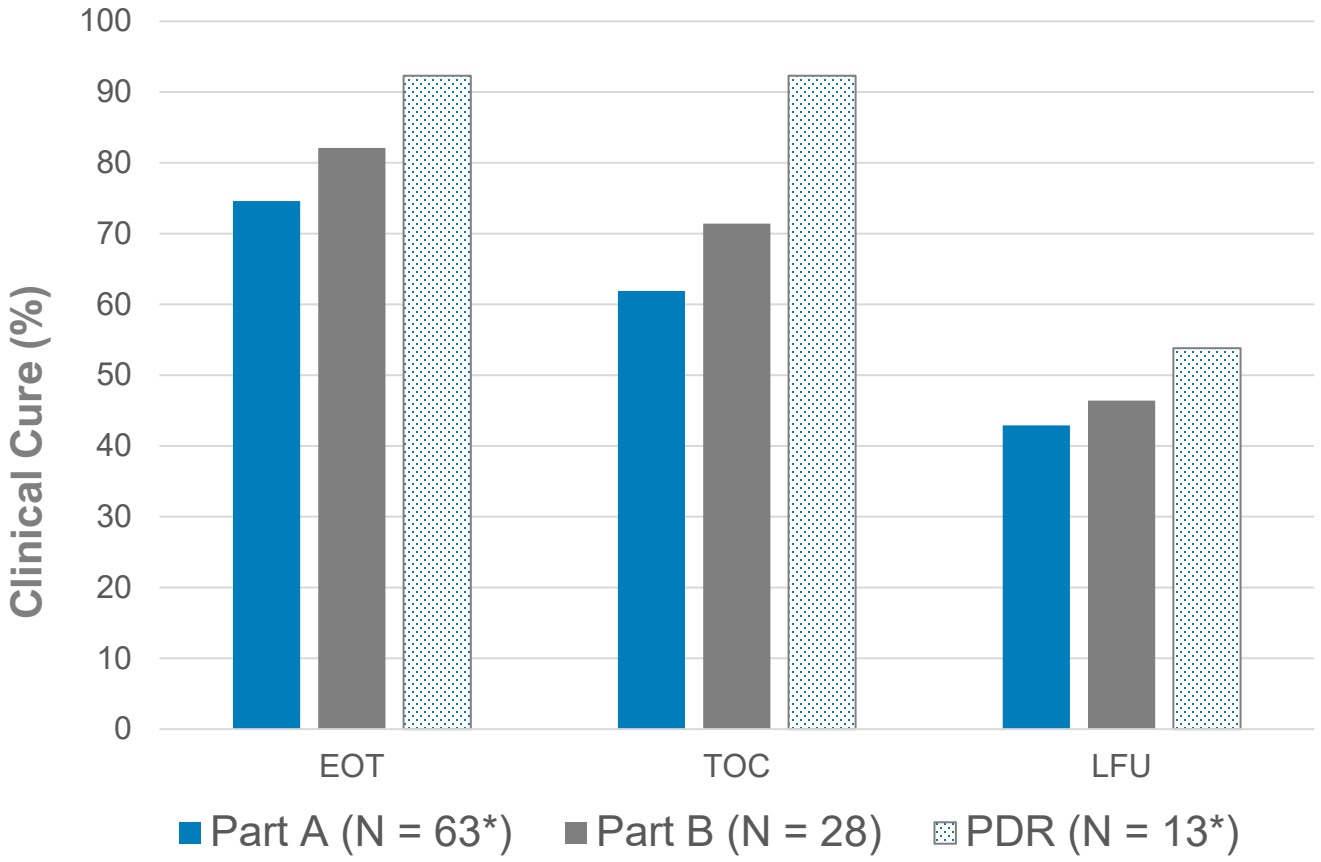
Clinical outcomes of patients infected with PDR ABC in ATTACK

All were in Part B





- Clinical outcomes for patients with PDR ABC infections treated with SUL-DUR were also quite favorable.

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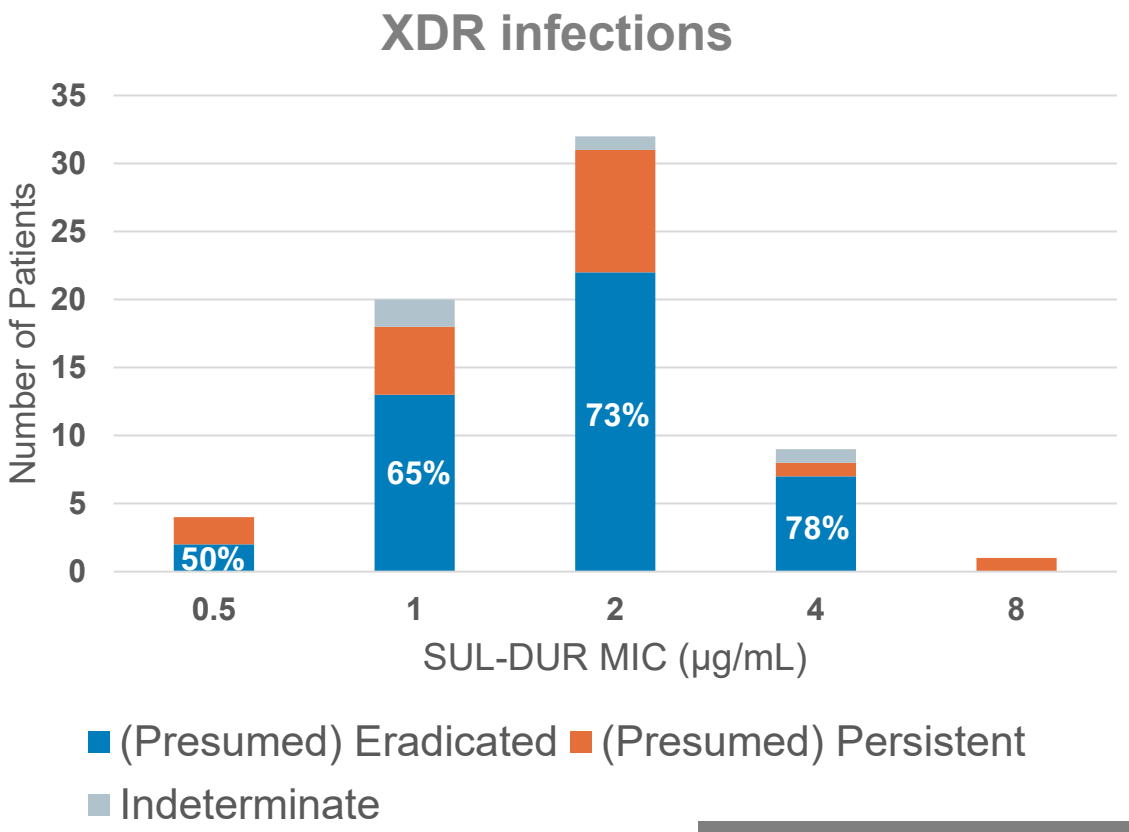
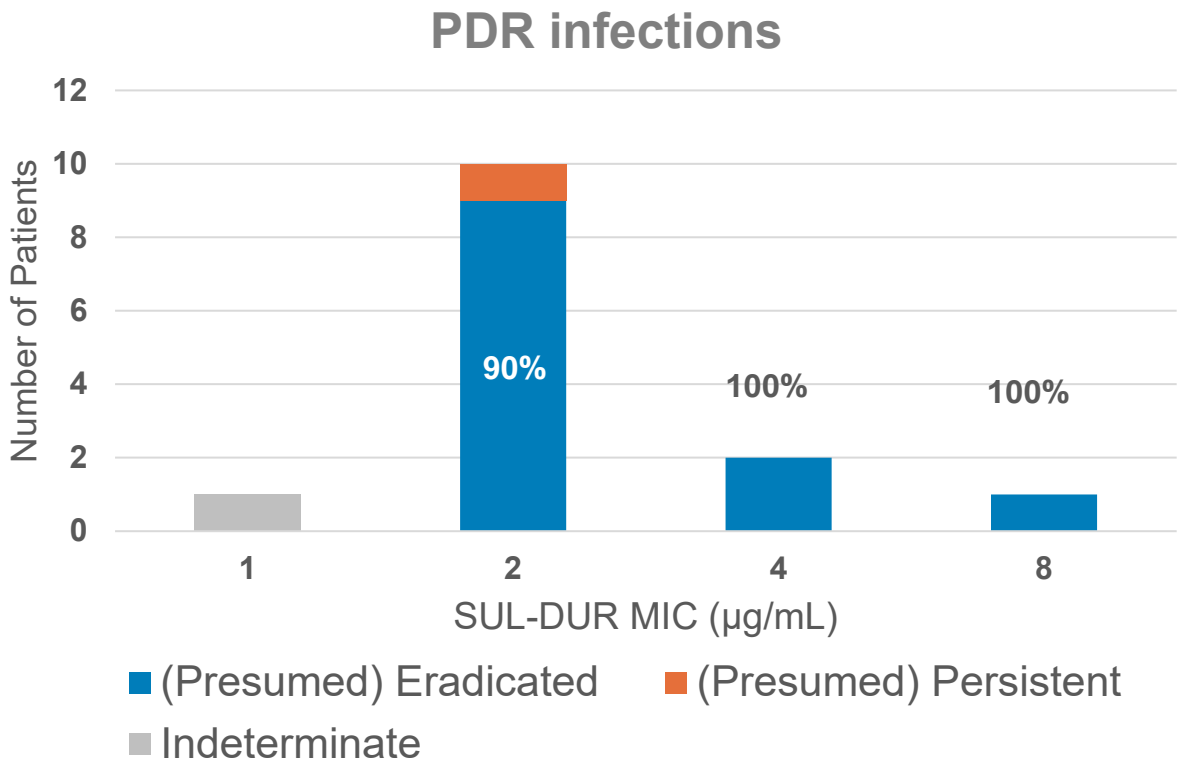
*patients who did not withdraw consent

Microbiological Outcome by SUL-DUR MIC for XDR and PDR ABC Baseline Pathogens

At TOC for CRABC m-MITT patients treated with SUL-DUR





- Microbiological outcomes for patients with XDR or PDR ABC infections treated with SUL-DUR were concordant with clinical outcomes.

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A microbiological outcome is presumed eradicated or persistent if the clinical outcome was Cure or Fail, respectively, and no culture sample was obtained at that time.

In Vitro Activity of SUL-DUR against 95 Pan-Drug Resistant ABC Isolates from Global Surveillance studies

- 4,252 geographically diverse, ABC clinical isolates from 2016 to 2020
- SUL-DUR $MIC_{50/90}$ values were 1/2 µg/mL; 98.2% were inhibited at ≤ 4 µg/mL
- 11% of isolates were XDR[1] and 2.2% (N = 95) were pan-drug resistant (PDR)[2]

Compound	PDR ABC isolates (N = 95)			
	MIC_{50}	MIC_{90}	Range	%S CLSI
SUL-DUR	2	4	0.5 - 4	100*
Sulbactam	32	64	8 - >64	0
Amikacin	>64	>64	32 - >64	0
Cefepime	>16	>16	16 - >16	0
Ciprofloxacin	>4	>4	>4	0
Colistin	>8	>8	4 - >8	0
Imipenem	64	>64	16- >64	0
Meropenem	64	>64	16- >64	0
Minocycline	16	16	8->16	0

- Nearly all PDR ABC were from Europe and increased in prevalence over time.
- SUL-DUR activity was consistent across time, geographic region, infection type and antibiotic-resistant subsets.
- All 95 PDR ABC were susceptible to SUL-DUR (MIC values ≤ 4 µg/mL).

[1]Magiorakos et al (2012) *CMI*: 18, 268-81
[2]defined as non-susceptibility to all approved antibiotics tested.
*based on a preliminary susceptibility breakpoint of 4/4 µg/mL

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2022 ASM Microbe Abstract # 3490 (AAR326)

Conclusions

- ABC isolates from patients in ATTACK were highly antibiotic-resistant, but >95% susceptible to SUL-DUR.
- Treatment with SUL-DUR demonstrated lower mortality, higher clinical cure rates and greater microbiologically favorable outcomes than colistin in patients with carbapenem-resistant ABC infections.
- Concordance between clinical and microbiological outcomes was observed.

- Patients with XDR or PDR ABC infections treated with SUL-DUR also had favorable clinical and microbiological outcomes.

- In global surveillance studies, 100% of PDR ABC isolates were susceptible to SUL-DUR.
- If approved, SUL-DUR could be an important therapeutic option for infections caused by multi-drug and carbapenem resistant ABC.

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

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Other Sulbactam-Durlobactam Presentations at IDWeek 2022

Entasis Therapeutics

- Microbiologic and clinical outcome concordance in the global phase 3 ATTACK trial: Sulbactam-Durlobactam versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex infections.
  - Oral Presentation Session 78 10/20/2022 1:45 - 3:00
- Sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections: A detailed safety review from the pivotal phase 3, global, randomized, active-controlled trial (ATTACK)
  - Poster Presentation #675 10/20/2022 12:15 - 1:30
- Efficacy and safety of sulbactam-durlobactam are consistent across regions in the global ATTACK phase 3 trial in the treatment of carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) infections
  - Poster Presentation #225 10/20/2022 12:15 - 1:30
- Characterization of colistin-resistant *Acinetobacter baumannii-calcoaceticus* complex (ABC) isolates from a recent global phase 3 trial (ATTACK)
  - Poster Presentation #518 10/20/2022 12:15 - 1:30