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

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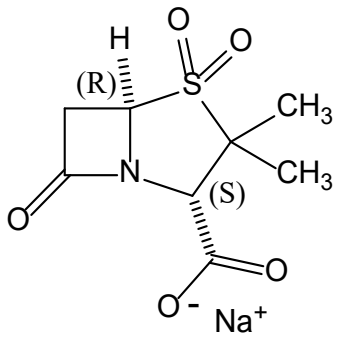
SUL-DUR: a β-lactam/β-lactamase Inhibitor Combination in Development for Treatment of *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Infections

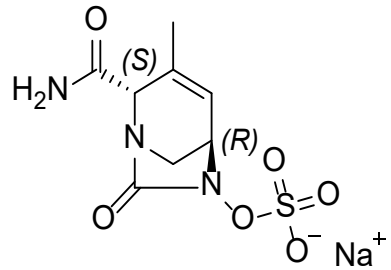
- ABC, identified by the WHO as a priority pathogen for the development of new antibiotics, is a group of closely related *Acinetobacter* species that cause serious infections associated with substantial mortality due to increasing resistance to existing therapies[1]
  - Carbapenem-resistant *A. baumannii*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

Sulbactam



- Penicillin derivative with intrinsic activity against ABC
- 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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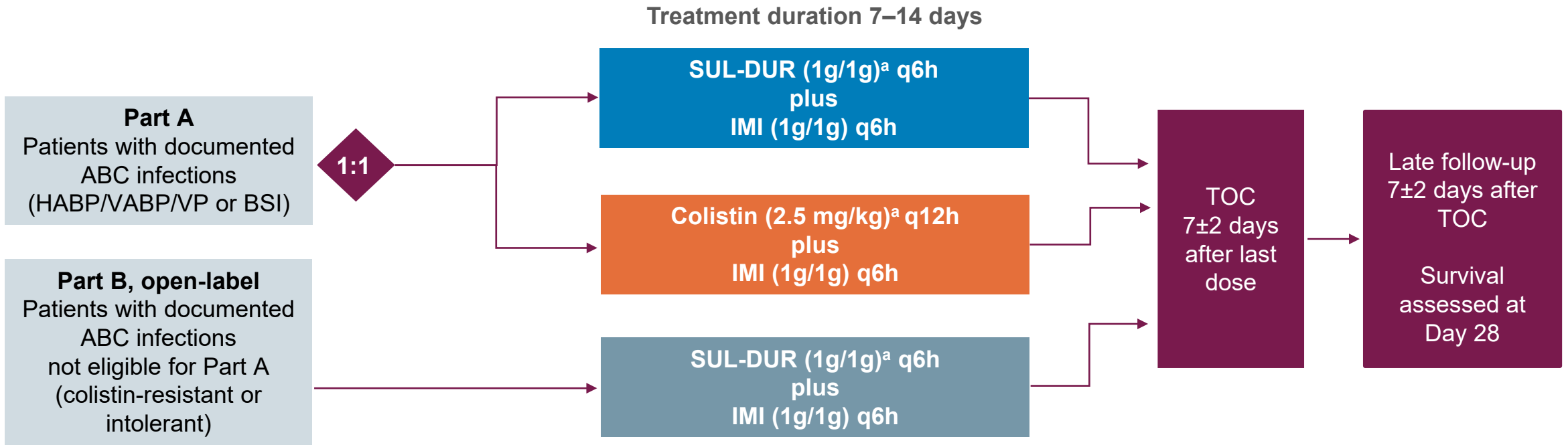
ATTACK Study Design

- ATTACK is a Phase 3, multinational, randomised, controlled, noninferiority 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 CRABC strains



This trial is registered at ClinicalTrials.gov: NCT03894046. Please see ECCMID abstract #02093 for Part B.
[a]SUL-DUR dosing was adjusted for renal function. Colistin dosing was adjusted to ideal body weight and renal function. A single colistin loading dose of 2.5 to 5 mg/kg given intravenously over 3 to 6 minutes (or according to standard of care) was administered on Day 1 for patients who had not received prior colistin therapy.
BSI, bloodstream infection; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem/cilastatin; q×h, every × hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia.

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ATTACK Key Methodology – Part A

Endpoints

Primary Efficacy: 28-day all-cause mortality in the CRABC m-MITT population (20% noninferiority margin)

Secondary Efficacy: Clinical Cure and Favorable Microbiological Outcome at TOC in the CRABC m-MITT population

Primary Safety: Nephrotoxicity, as measured by the RIFLE criteria, in the safety population

Inclusion Criteria

- Male or female adults (≥18 years old)
- APACHE II score 10–30 or SOFA score 1–11
- Diagnosed with HABP, VABP, VP, and/or BSI
- ABC in sputum/respiratory[a] or blood sample
- No more than 48 hours of potentially effective (ie, gram-negative) antimicrobial therapy before the first dose of study drug; OR
- Clinically failing prior treatment regimens (ie, clinical deterioration or failure to improve after at least 48 hours of antibiotic treatment)

Exclusion Criteria

- Infection known to be resistant to colistin or polymyxin B
- Hypersensitivity or allergic reaction to any β-lactam, any contraindication to the use of cilastatin
- Pulmonary disease that precludes evaluation of therapeutic response
- APACHE II score >30 and SOFA score >11 at diagnosis

The CRABC m-MITT population included patients who had a baseline ABC organism confirmed to be carbapenem-resistant by the central laboratory.
[a]Biofire® FilmArray® 2.0 Pneumonia Panel (BPP) technology was used to enable early identification of ABC pneumonia
APACHE, Acute Physiology and Chronic Health Evaluation; m-MITT, microbiologically modified intent-to-treat; RIFLE, risk, injury, failure, loss, end-stage renal disease; SOFA, sequential organ failure assessment.

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Key Baseline Demographics Comparable Across Treatment Groups

Balanced between Part A and Part B

	PART A SUL-DUR + IMI N = 64	PART A Colistin + IMI N= 64	PART B SUL-DUR + IMI N = 28
Age – Mean ± SD (Years)	61.6 ± 16.1	65.1 ± 17.0	56.2 ± 16.3
Age Group, n (%)			
<65 years	36 (56.3)	31 (48.4)	19 (67.9)
65 – 75 years	16 (25.0)	12 (18.8)	5 (17.9)
>75 years	12 (18.8)	21 (32.8)	4 (14.3)
Gender, Male, n (%)	46 (71.9)	49 (76.6)	21 (75.0)
Severity of Illness, n (%)			
APACHE II Score 10-19/SOFA Score 7-9/qSOFA Score 2	47 (73.4)	44 (68.8)	19 (67.9)
APACHE II Score 20-30/SOFA Score ≥10/qSOFA Score 3	16 (25.0)	20 (31.3)	9 (32.1)
Infection Type, n (%)			
Bacteremia	2 (3.1)	1 (1.6)	17 (60.7)
HABP	24 (37.5)	31 (48.4)	4 (14.3)
VABP	38 (59.4)	30 (46.9)	7 (25.0)
VP	0 (0.0)	2 (3.1)	0 (0.0)
Duration of ICU Stay at Baseline, n (%)			
No ICU Stay	21 (32.8)	19 (29.7)	5 (17.9)
<5	2 (3.1)	3 (4.7)	1 (3.6)
5-14	23 (35.9)	24 (37.5)	4 (14.3)
>14	18 (28.1)	18 (28.1)	18 (64.3)
Charlson Comorbidity Index – Mean ± SD	4.6 ± 3.2	4.8 ± 3.4	2.7 ± 2.6

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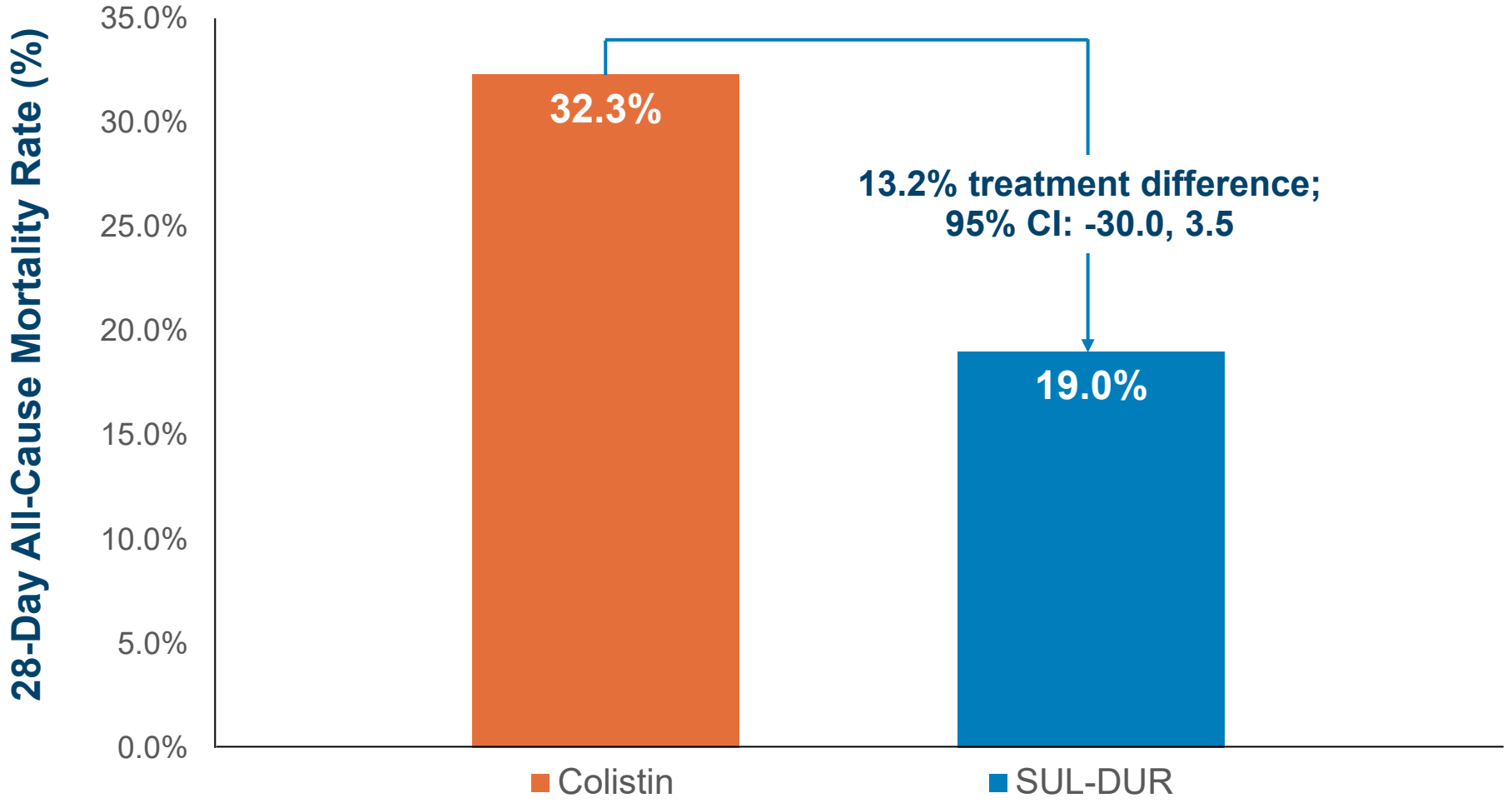
IMI: Imipenem; HABP: Hospital-acquired Bacterial Pneumonia; VABP: Ventilator-acquired Bacterial Pneumonia; VP: Ventilated pneumonia; ICU: Intensive Care Unit; SD: Standard Deviation
Note: APACHE II score was evaluated first, when not available SOFA or qSOFA were used

Achieved Primary Efficacy Endpoint

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

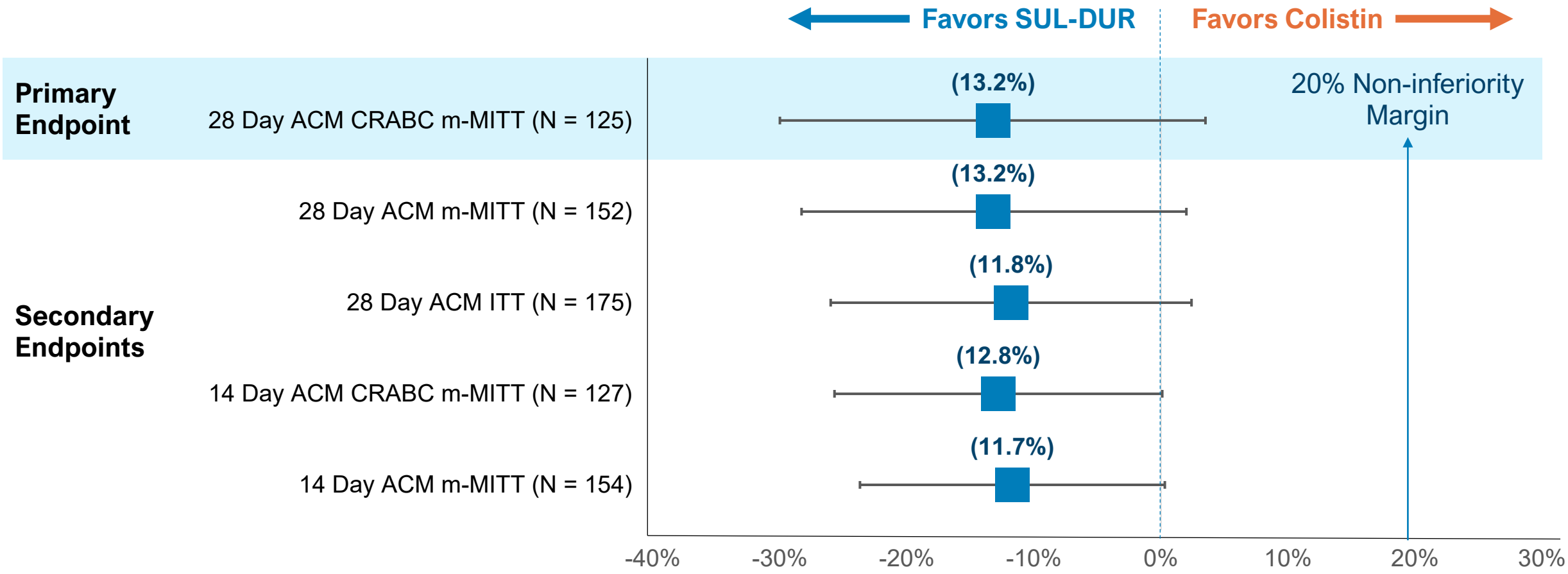


CI: Confidence Interval.

All-Cause Mortality Analyses Favor SUL-DUR

Favorable mortality difference for SUL-DUR vs. colistin across all study populations evaluated to date

Mortality Rate Treatment Difference and 95% Confidence Interval



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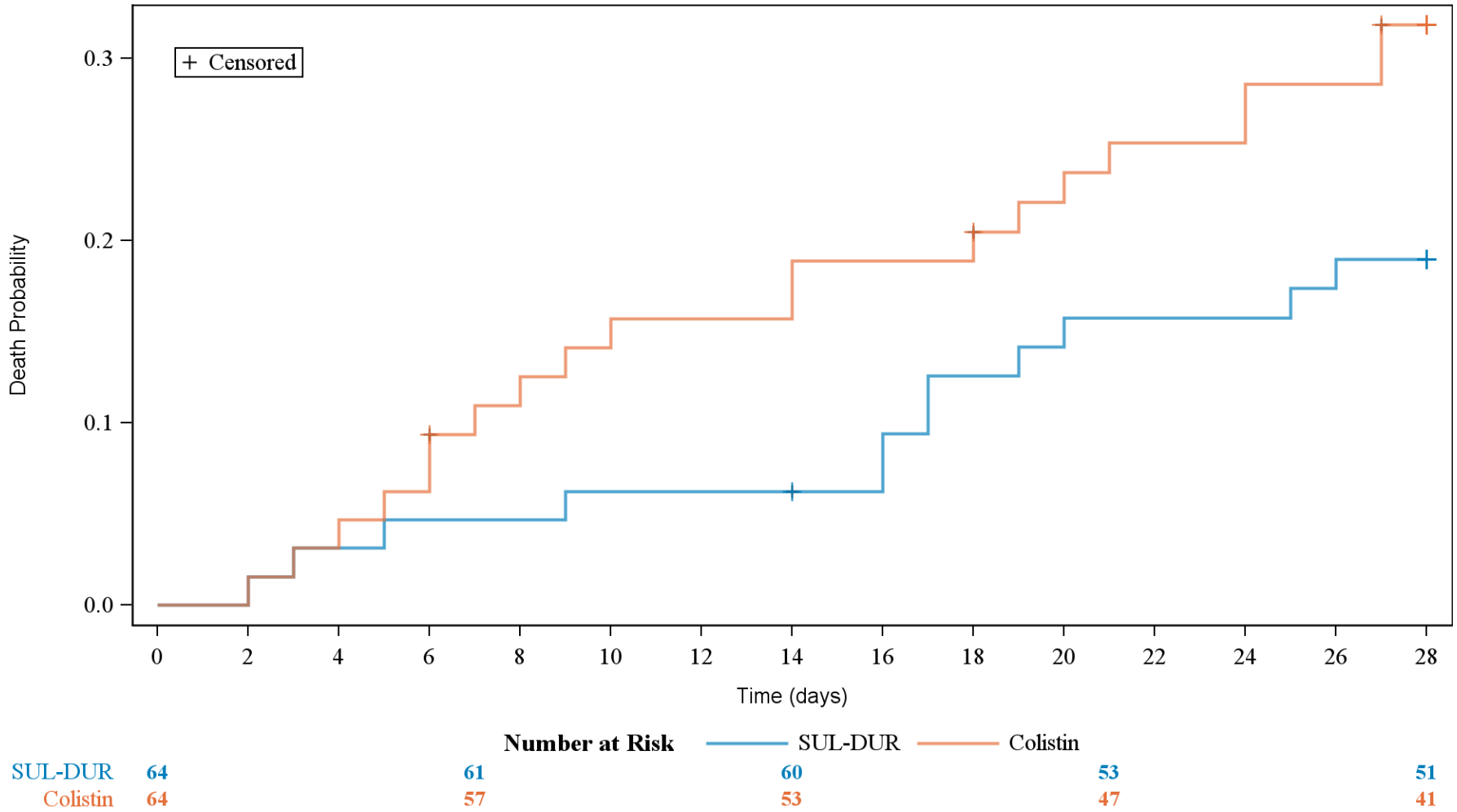
All-Cause Mortality Consistently Lower with SUL-DUR

Reduced mortality over time with SUL-DUR treatment in the CRABC m-MITT population



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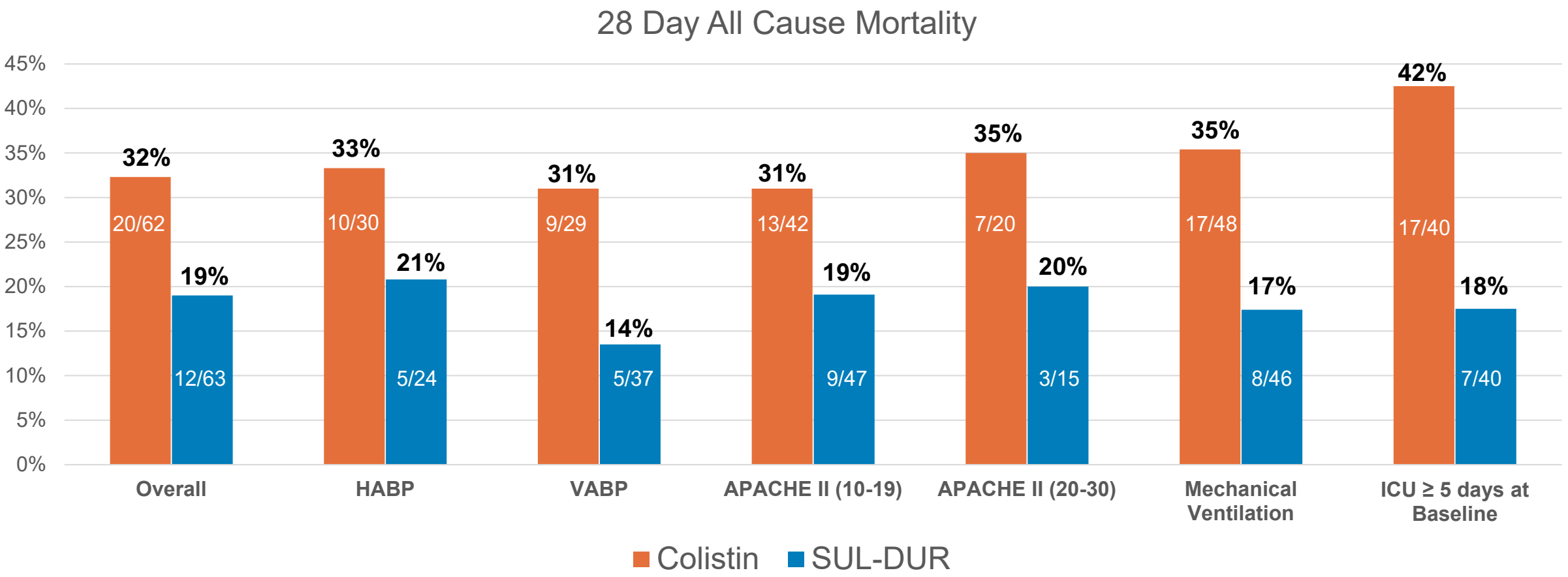
SUL-DUR was Non-Inferior Across Subgroup Analyses

28 Day All Cause Mortality in subgroups of the CRABC m-MITT population



HABP = Hospital-acquired bacterial pneumonia; VABP = Ventilator-associated bacterial pneumonia. Note: APACHE II score was evaluated first, when not available SOFA or qSOFA were used

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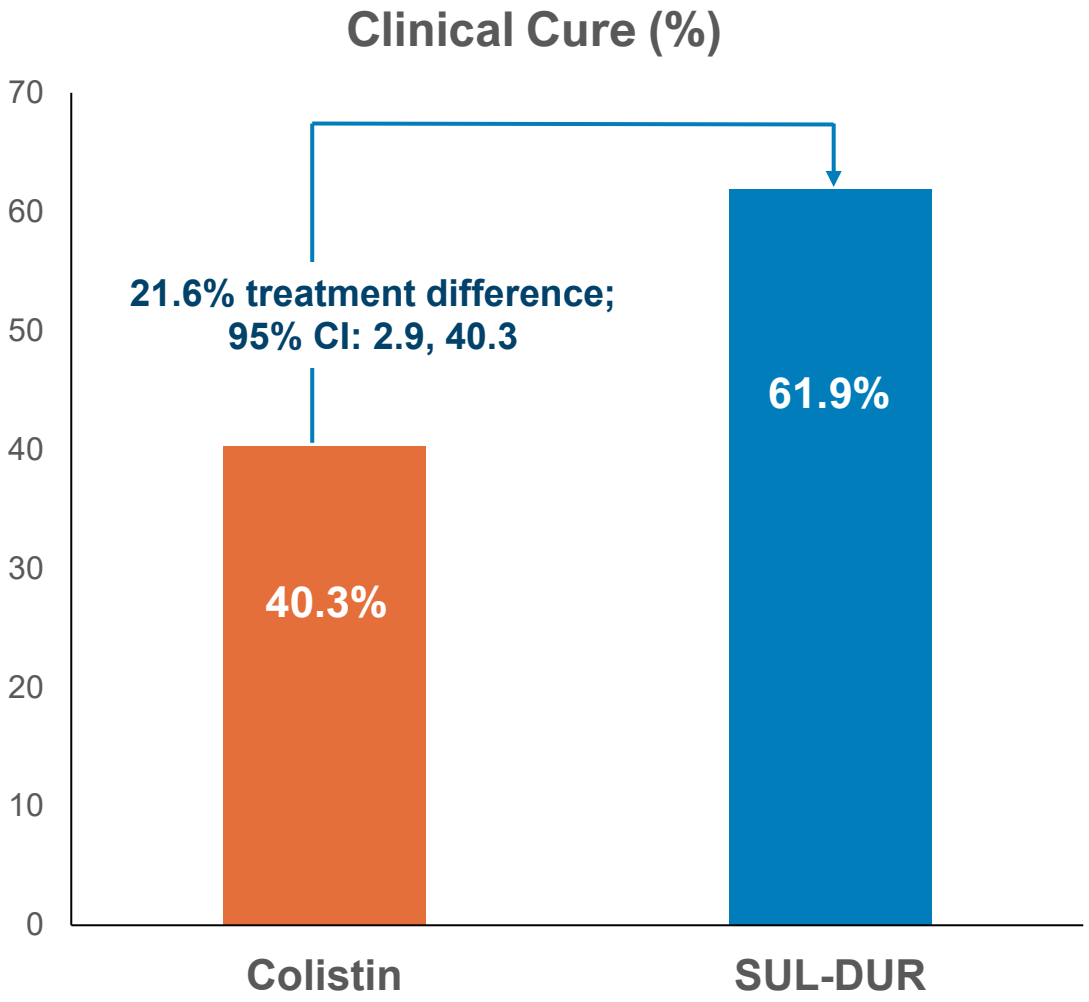
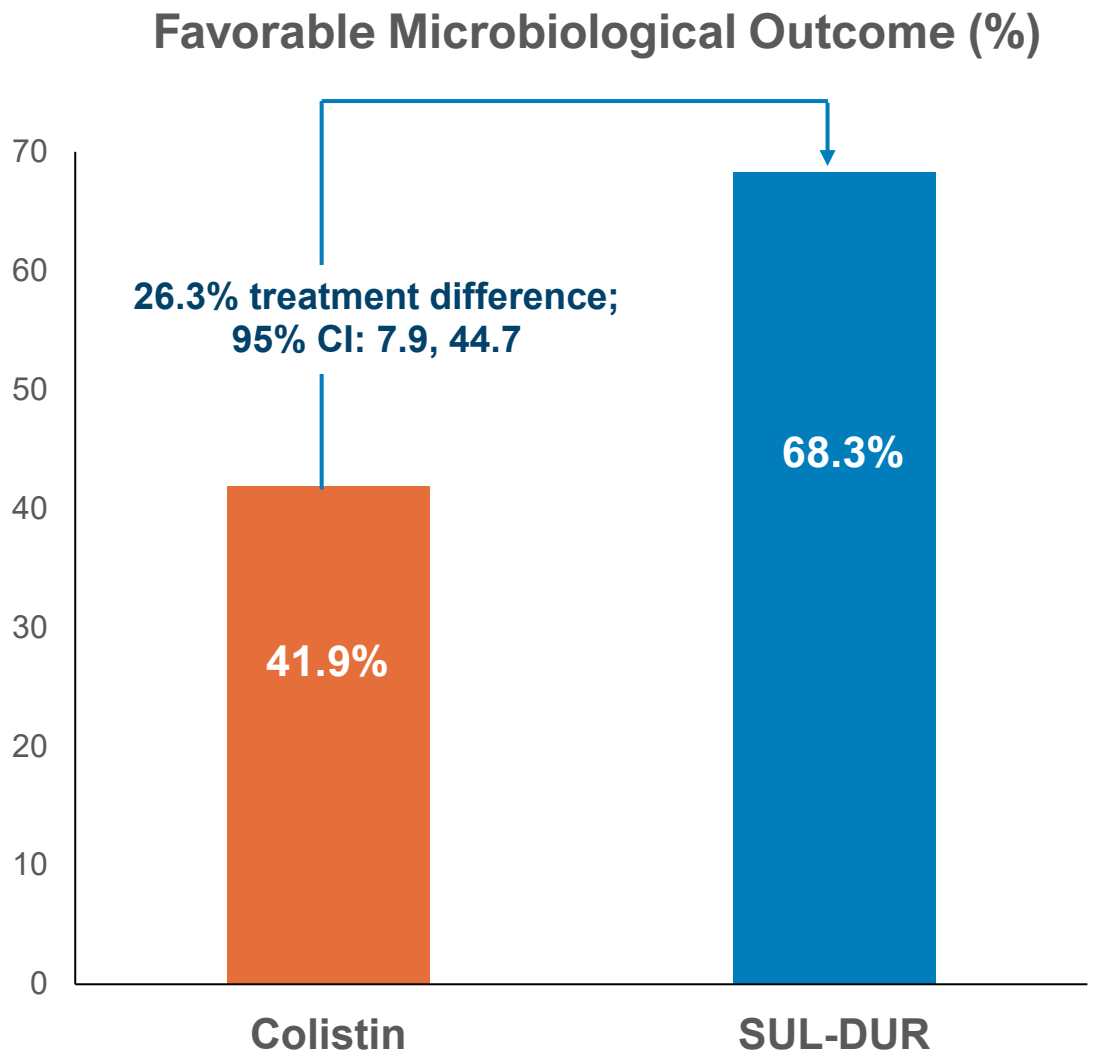
Significant Difference in Clinical Cure and Microbiological Outcome

SUL-DUR compared to colistin at Test of Cure





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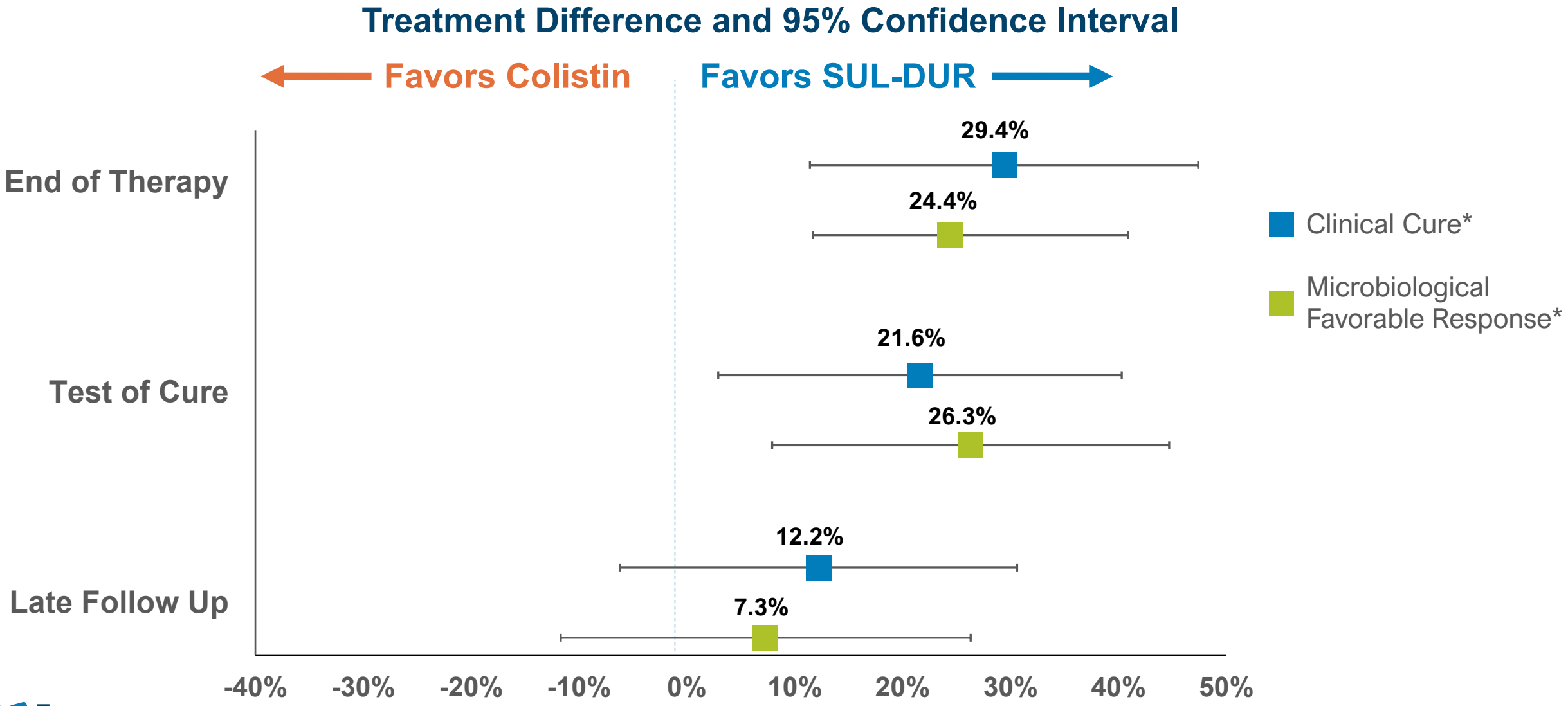
Clinical Cure Rates and Microbiological Response Favors SUL-DUR

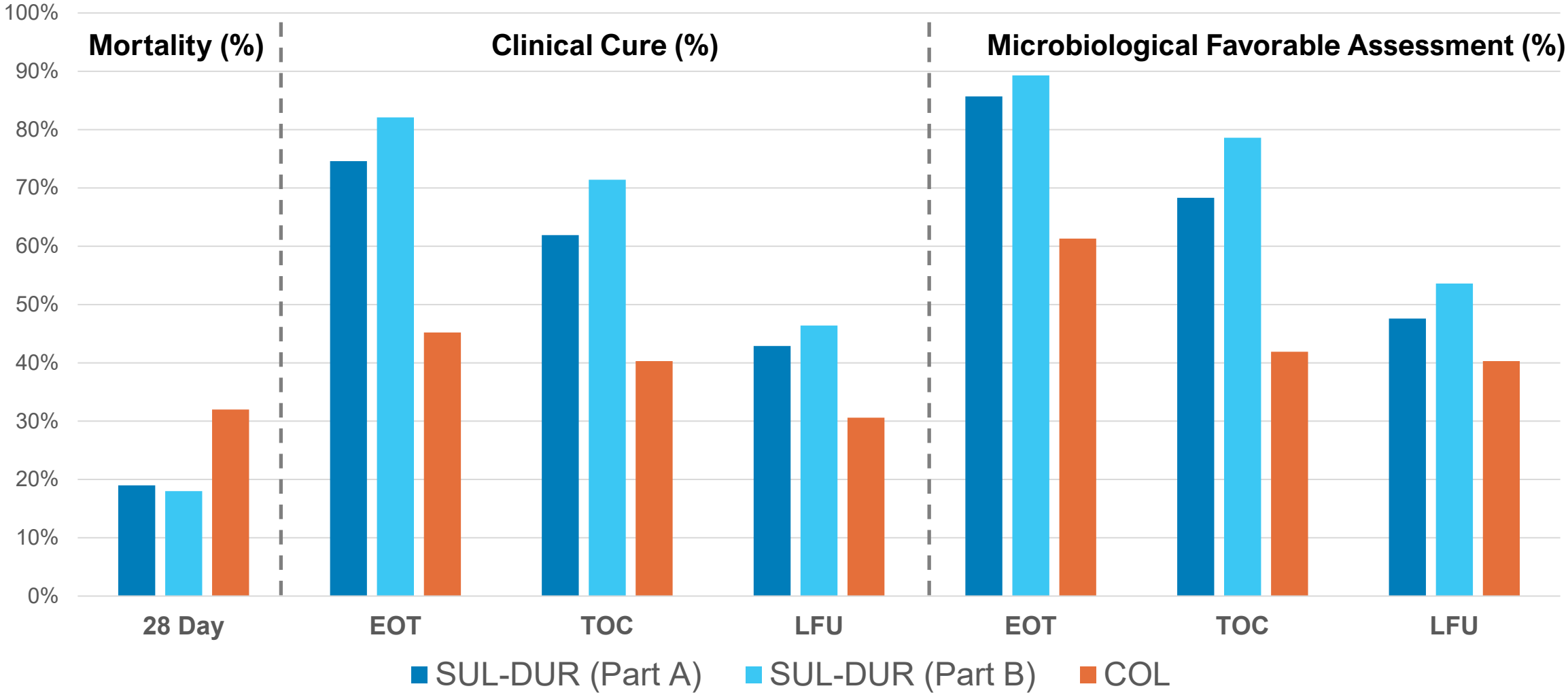
Significant differences at all timepoints for CRABC m-MITT population



*excluding withdrawn patients

Results from Part B were Consistent with Part A SUL-DUR Results

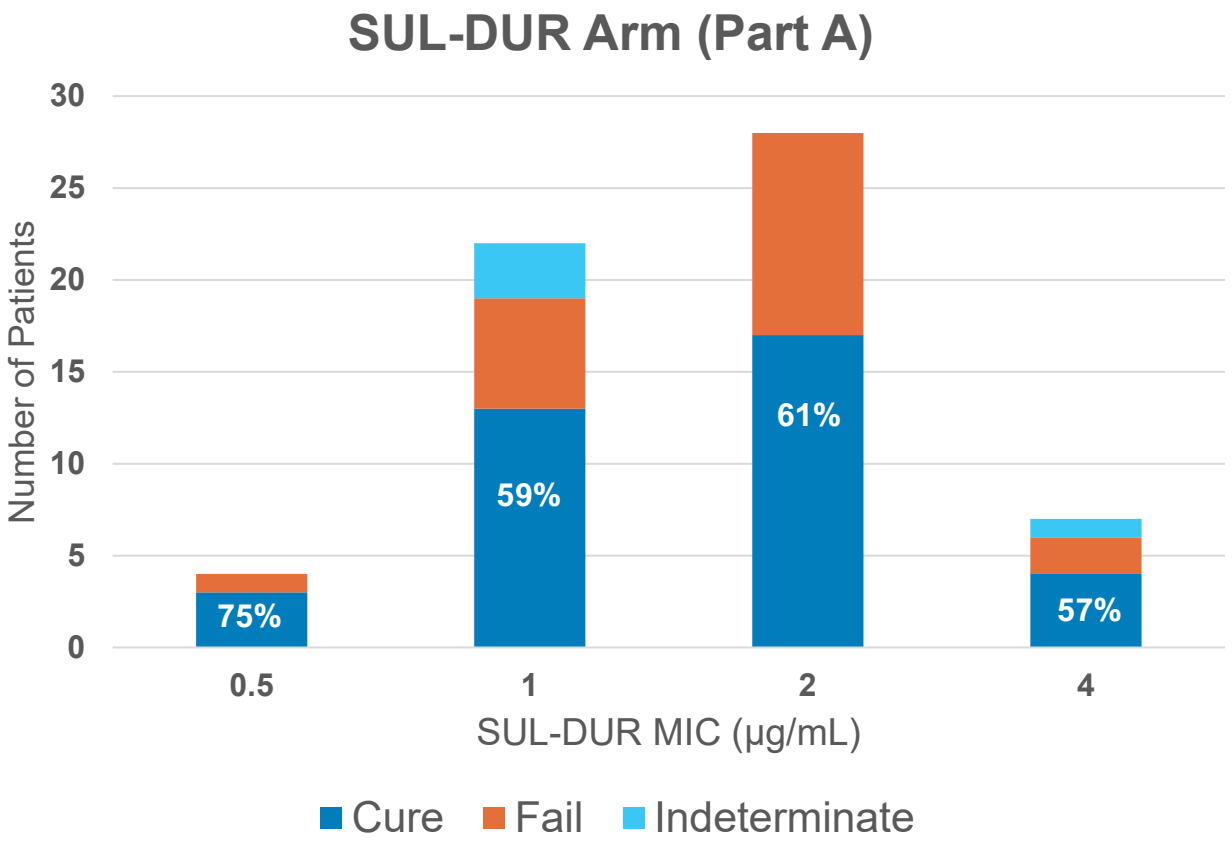
CRABC m-MITT population

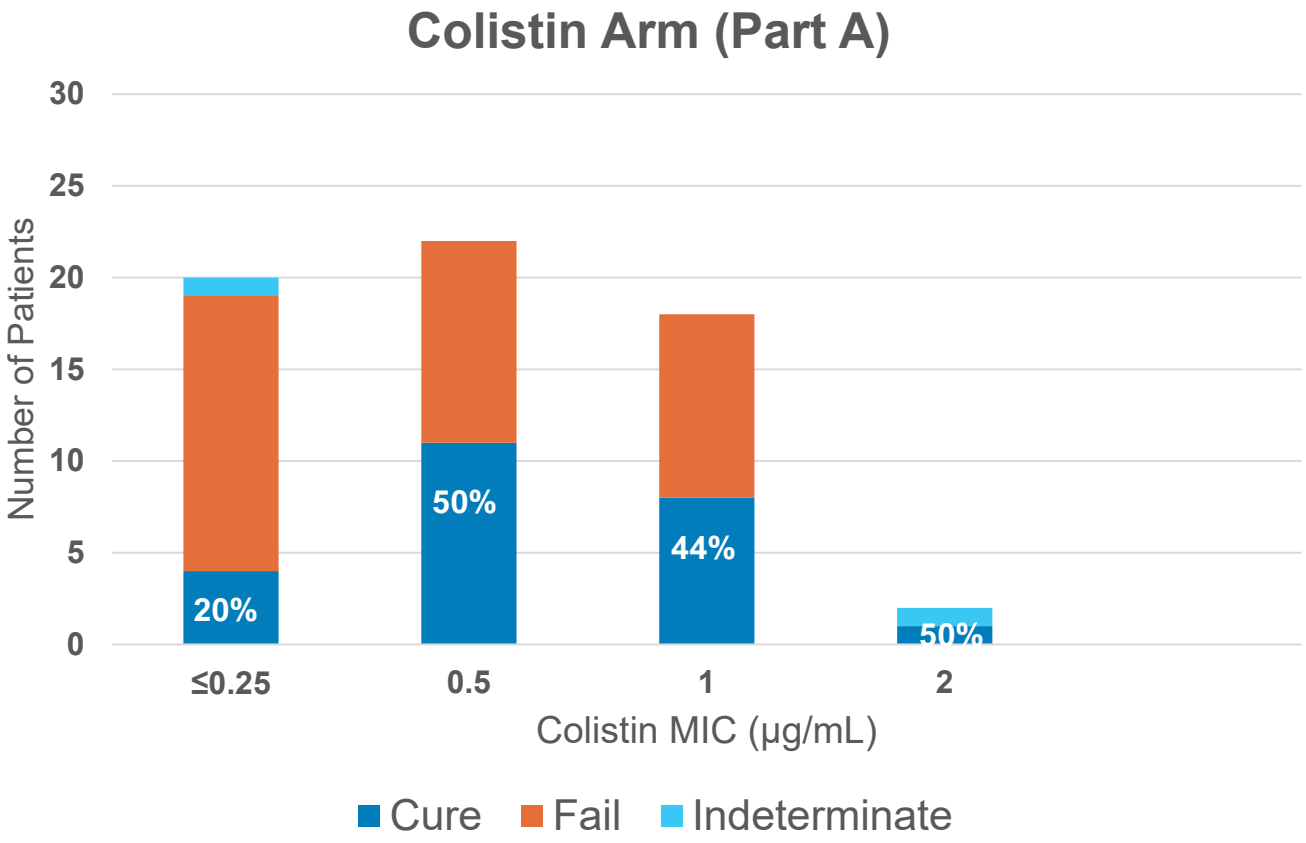


EOT = End of Treatment; TOC = Test of Cure; LFU = Late Follow Up

Clinical Outcome by MIC for ABC Baseline Pathogens

SUL-DUR compared to colistin for CRABC m-MITT at Test of Cure





Similar results were observed for End of Therapy and Late Follow Up visits

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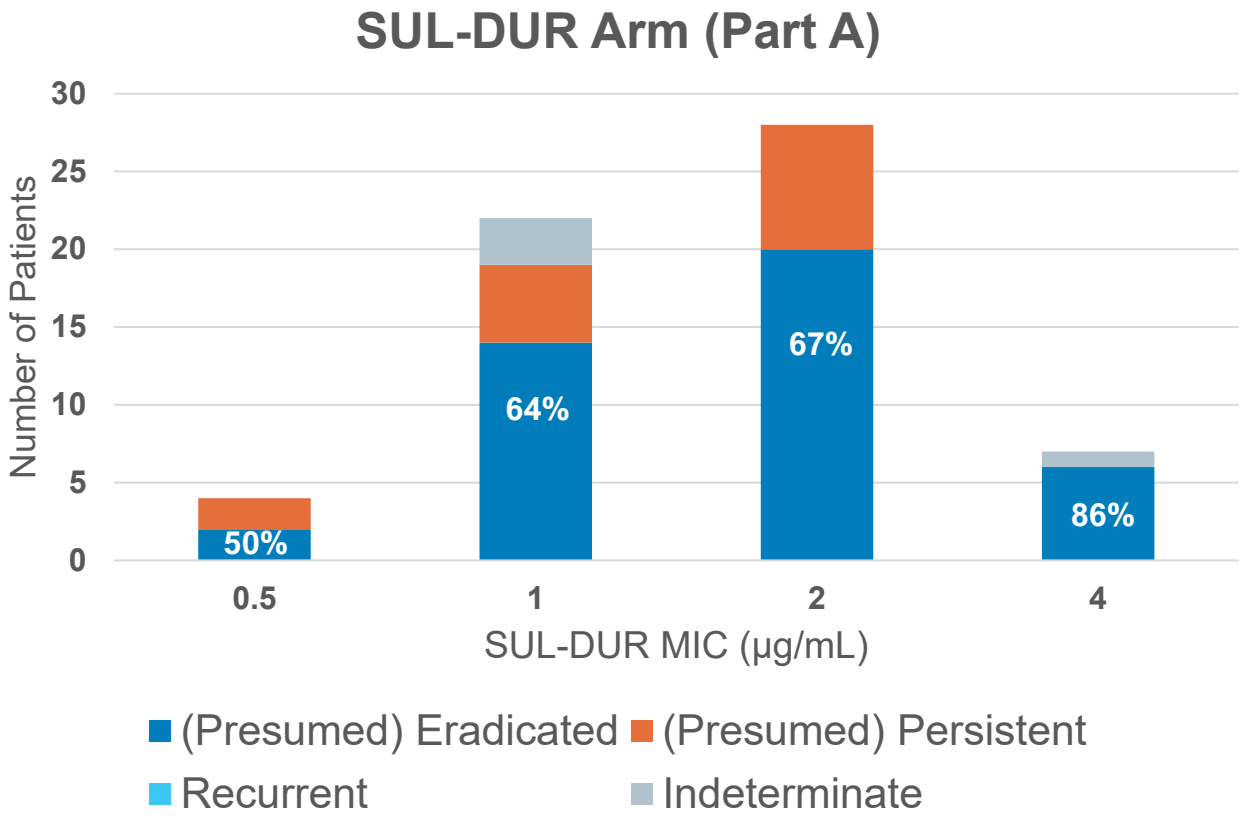
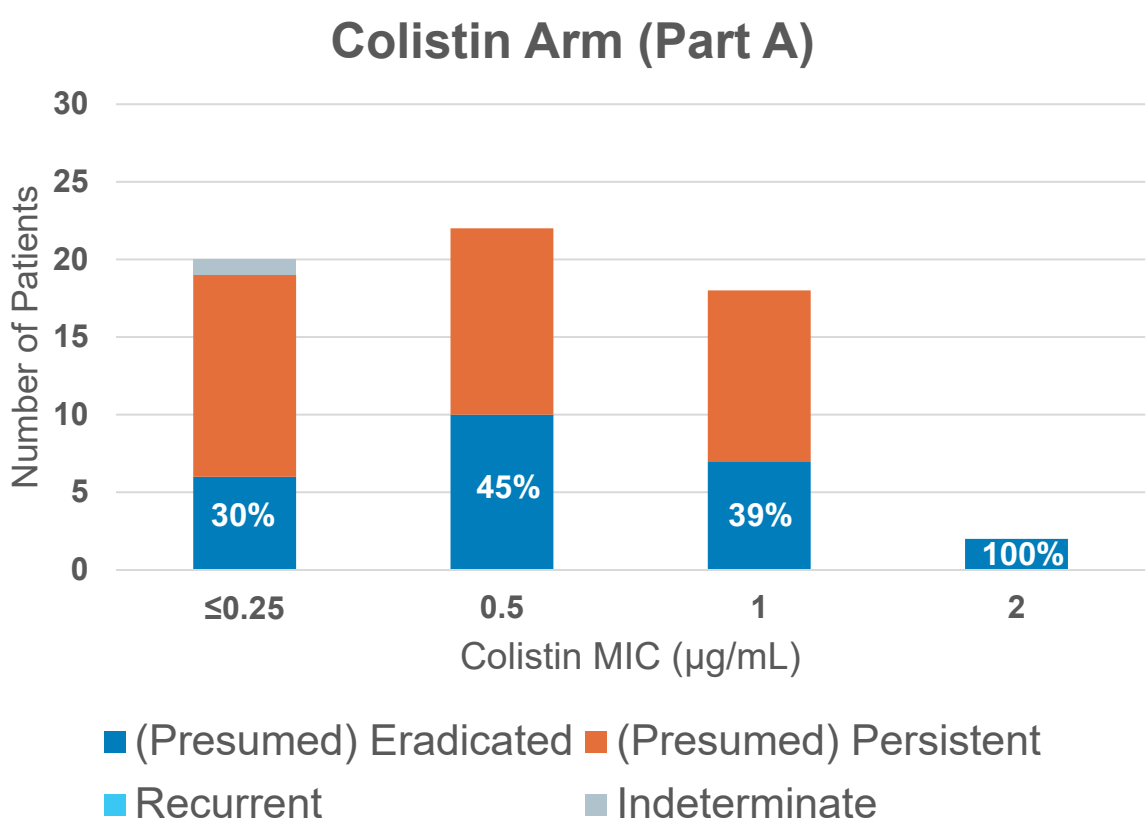
Microbiological Outcome by MIC for ABC Baseline Pathogens

SUL-DUR compared to colistin for CRABC m-MITT





Similar results were observed for End of Therapy and Late Follow Up visits

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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.

ATTACK Demonstrated Concordance in Clinical and Microbiologic Outcomes

SUL-DUR versus colistin therapy in patients with ABC infections

- Treatment with SUL-DUR demonstrated lower mortality, higher clinical cure rates and greater microbiologically favorable outcomes in patients with carbapenem-resistant ABC infections
- Non-inferiority in 28-day all-cause mortality and overall trends favoring SUL-DUR
- Higher clinical cure rate at Test of Cure
- Greater microbiologic favorable response for SUL-DUR at Test of Cure
- Similar clinical and microbiologic outcomes maintained for baseline ABC pathogens with SUL-DUR MICs of 0.5-4 µg/mL
- Part B results were consistent with Part A
- If approved, SUL-DUR could be an important therapeutic option for infections caused by multi-drug and carbapenem resistant ABC

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Sulbactam-Durlobactam Presentations at IDWeek 2022

Entasis Therapeutics

- Efficacy of sulbactam-durlobactam (SUL-DUR) versus colistin in patients with extensively drug-resistant (XDR) and pan-drug resistant (PDR) *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections
  - Oral Presentation #732 10/20/2022 1:45 - 3:00
- Population pharmacokinetic (PPK), pharmacokinetic/pharmacodynamic attainment (PTA), and clinical pharmacokinetic/pharmacodynamic (PK/PD) analyses for sulbactam-durlobactam (SUL-DUR) to support dose selection for the treatment of *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections
  - Oral Presentation #LB2306 10/222/2022 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

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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