Sulbactam-Durlobactam for the Treatment of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia Caused by Susceptible Strains of *Acinetobacter baumannii-calcoaceticus* Complex

Antimicrobial Drugs Advisory Committee

Entasis Therapeutics, A Wholly Owned Subsidiary of Innoviva, Inc.

April 17, 2023

Introduction

Shruta Rege, PhD

Senior Vice President

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Acinetobacter baumannii: Gram-Negative Opportunistic Bacterial Pathogen and Major Global Public Health Concern

- Predominant member of the *A. baumannii-calcoaceticus* complex[1]
- Associated with infections of lungs, bloodstream, urinary tract, skin, and other soft tissues[2]
- Infections associated with high morbidity and mortality
  - Estimates range from 30% - 70% globally for hospital-acquired and ventilator-associated pneumonia[3]
- Increasingly difficult to treat as multidrug resistant (MDR) and carbapenem-resistant (CR) strains have emerged[4]

1. Moubareck and Halat., 2020; 2. Alsan and Klompas, 2010; 3. Lim et al., 2019; 4. Gales et al., 2019

Carbapenem-resistant *Acinetobacter* Considered Urgent Public Health Threat by CDC[1]

- "Priority 1, critical" by WHO[2]
- 5th leading cause of death associated with antimicrobial resistance globally[3]
- Recent IDSA guidance states there is no clear standard of care antibiotic regimen for infections due to CR-*Acinetobacter*[4]

Significant unmet need for a safe and effective treatment option that provides clinically meaningful benefit over existing therapies

IDSA = Infectious Diseases Society of America

1. CDC, 2019; 2. WHO, 2017; 3. Antimicrobial Resistance Collaborators, Lancet 2022; 4. Tamma et al., 2021

Sulbactam-Durlobactam (SUL-DUR) Targeted Antibiotic for Treatment of Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex

Sulbactam (SUL)

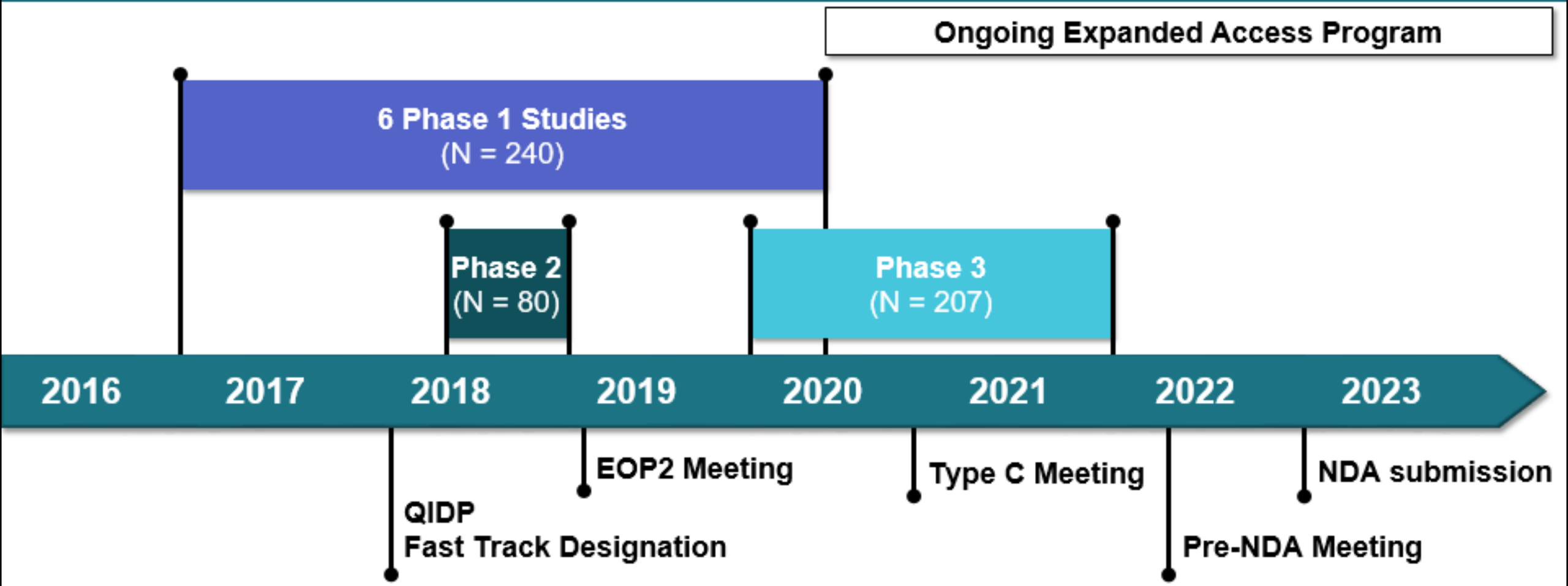
- Common β-lactamase inhibitor
- β-lactam with antibacterial activity against *Acinetobacter*
- Inhibits penicillin-binding proteins, required for bacterial cell wall synthesis
- β-lactamase-mediated resistance is common

+

Durlobactam (DUR)

- Diazabicyclooctane (DBO) class β-lactamase inhibitor
- Potent inhibitor of Ambler class A, C, and D β-lactamases
- Restores *in vitro* and *in vivo* activity of sulbactam against resistant *Acinetobacter*

SUL-DUR Pathogen-Focused Clinical Development Program



QIDP = Qualified Infectious Disease Product; EOP2 = End of Phase 2

Totality of Data Demonstrates Positive SUL-DUR Benefit-Risk Over Existing Treatment Options

Unmet Need

- Infections caused by carbapenem-resistant *Acinetobacter* are major public health concern
- Increased morbidity and mortality due to limited treatment options

Microbiology and Pharmacology

- Confirmatory evidence from microbiology and nonclinical data
- Robust population PK and PK/PD target attainment analyses

Efficacy

- Prespecified primary noninferiority endpoint for 28-day all-cause mortality achieved
- All secondary analyses, clinical and microbiological responses consistently showed benefit

Safety

- Favorable safety profile
- Statistically significant lower incidence in nephrotoxicity vs colistin

Proposed Indication and Dose

Indicated in adults (≥ 18 years) for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex

- Dose: 1.0 g sulbactam / 1.0 g durlobactam
- Schedule: q6h administered as 3-hour IV infusion
  - Dose adjustments recommended in patients with CL_{CR} < 45 mL/min or ≥ 130 mL/min

CL_{CR} = creatinine clearance

Agenda

Unmet Need	**David Paterson, MBBS, PhD, FRACP** Saw Swee Hock School of Public Health National University of Singapore
Microbiology & Pharmacology	**Alita Miller, PhD** Senior Vice President, Head of Research Entasis Therapeutics, A Wholly Owned Subsidiary of Innoviva, Inc.
Efficacy	**David Altarac, MD, MPA** Chief Medical Officer Entasis Therapeutics, A Wholly Owned Subsidiary of Innoviva, Inc.
Safety	**Drew Lewis, MD, MTM&H, FACP** Vice President, Clinical Development Entasis Therapeutics, A Wholly Owned Subsidiary of Innoviva, Inc.
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Unmet Need

David Paterson, MBBS, PhD, FRACP, FRCPA

Professor

Saw Swee Hock School of Public Health

National University of Singapore

Multidrug Resistant *Acinetobacter*: A Growing, Global Threat

- Carbapenem-resistant *Acinetobacter* is a priority pathogen for new antibiotic development (WHO)[1]
  - Associated with ~326,000 deaths worldwide in 2019[2]
- CR-*Acinetobacter* deemed urgent US public health threat (CDC)[3]
- Coinciding with COVID pandemic, CR-*Acinetobacter* cases in US hospitals increased by 78% in 2020 compared with 2019[4]

	CR-*Acinetobacter*	CR-*Enterobacterales*	Extended-Spectrum β-Lactamase Producers	MDR *P. aeruginosa*
Overall	35% increase	Stable	10% increase	Stable
Hospital-Onset	78% increase	35% increase	32% increase	32% increase

1. WHO, 2017; 2. Antimicrobial Resistance Collaborators. Lancet, 2022; 3. CDC, 2019; 4. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022

Acinetobacter is a Major Cause of Hospital-Acquired Infection

- Threat to hospitalized patients
  - Critically ill patients susceptible to infections due to *Acinetobacter*
  - Survives on variety of surfaces
  - Spreads within healthcare facilities[1]
- Pneumonia and bacteremia most common infections
- *Acinetobacter* can also cause urinary tract, skin and soft tissue, wound infections, osteomyelitis, and meningitis[2]

1. CDC, 2019; 2. Alsan and Klompas, 2010

Infections Caused by *Acinetobacter* Can Be Difficult to Treat Due to Antimicrobial Resistance

- *Acinetobacter* intrinsically resistant to most penicillins
- Encodes genes that confer resistance to common antibiotics used to treat infections caused by Gram-negative bacteria
  - Fluoroquinolones
  - Aminoglycosides
  - Cephalosporins
  - Carbapenems
- Decreasing susceptibility among *Acinetobacter* isolates for all antimicrobial agents, including carbapenems, in all regions[1]

1. SENTRY Antimicrobial Surveillance Program (1997 – 2016)

Acinetobacter Associated with High Morbidity, Mortality, Length of Hospitalization, and Costs

- Incidence and prevalence of infections due to resistant *Acinetobacter* increasing in
  - Patients with prolonged hospitalizations
  - Immunocompromised (transplants, burns, or cancer-treated)
  - Long-term care facilities[1]
- Global mortality rates range from 30% - 70%[2]
- Infections due to resistant *Acinetobacter* have highest attributable costs among hospital-onset invasive infections[3]
  - Ranging from $20K - $128K[3]

1. CDC, 2019; 2. Lim et al., 2019; 3. Nelson et al., 2021

No Clear "Standard of Care" for Infections Caused by Carbapenem-Resistant *Acinetobacter*[1]

- Developing clinical practice guidelines are a top IDSA initiative
- β-lactam, fluoroquinolone, and aminoglycoside resistance has resulted in reliance on carbapenems
- Increased carbapenem use has led to the global emergence of carbapenem-resistant *Acinetobacter*
- In recent years, up to 69% of carbapenem-resistant *Acinetobacter* infections in the US have been treated with last resort colistin/polymyxin-based therapies[2]

1. Tamma et al., 2022; 2. IQVIA market analysis for IST, 2022
IDSA = Infectious Diseases Society of America

Limited Data Available to Make Evidence-Based Treatment Recommendations

- No randomized-controlled trials comparing effectiveness of commonly used agents
- Physicians rely on combinations because no antibiotic regimen has clear efficacy
- Complete data needed to
  - Prioritize specific agents active against carbapenem-resistant *Acinetobacter*
  - Understand additive benefit of commonly used combination regimens[1]

1. Tamma et al., 2022

Infections Due to Resistant *Acinetobacter* are a Major US and Global Public Health Concern

- Associated with increased morbidity and mortality due to limited therapeutic options
- Serious, life-threatening, and more difficult to treat as resistance rates rise
- Carbapenem resistance is an urgent health threat worldwide

Patients and physicians need a safe and effective treatment option for serious infections caused by resistant *Acinetobacter* strains

Microbiology & Pharmacology

Alita Miller, PhD

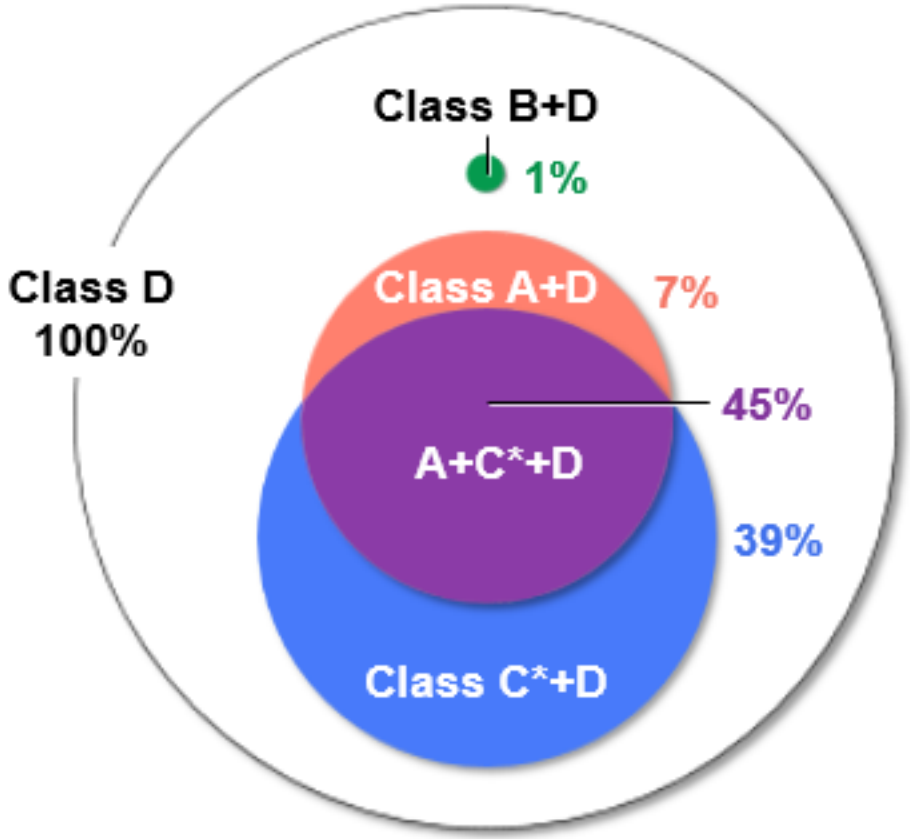
Senior Vice President, Head of Research

Entasis Therapeutics, A Wholly Owned Subsidiary of Innoviva, Inc.

Multidrug Resistant *Acinetobacter* Isolates Express Multiple Serine β-lactamases

- Sulbactam has unique *Acinetobacter*-targeting antibacterial activity
- Multidrug resistant (MDR) *Acinetobacter* express multiple Class A, C and D β-lactamases that confer sulbactam resistance
- β-lactamase inhibitors must be able to inactivate Class A, C and D enzymes in order to effectively restore sulbactam activity in *Acinetobacter*

Genomic analysis of β-lactamase genes in 84 representative MDR *Acinetobacter* clinical isolates[1]



1. Durand-Réville, et al., 2017; *extended spectrum Class C

Durlobactam

- Durlobactam is a non-β-lactam diazabicyclooctane (DBO) β-lactamase inhibitor
  - Predecessor DBOs include marketed agents such as avibactam
- Unlike predecessors, durlobactam inhibits a broad spectrum of Ambler class A, C, and D serine β-lactamases[1]
  - Durlobactam and other DBOs are not active against class B metallo-β-lactamases
- In studies with purified serine β-lactamases, durlobactam was more potent than avibactam against all enzymes tested[2]

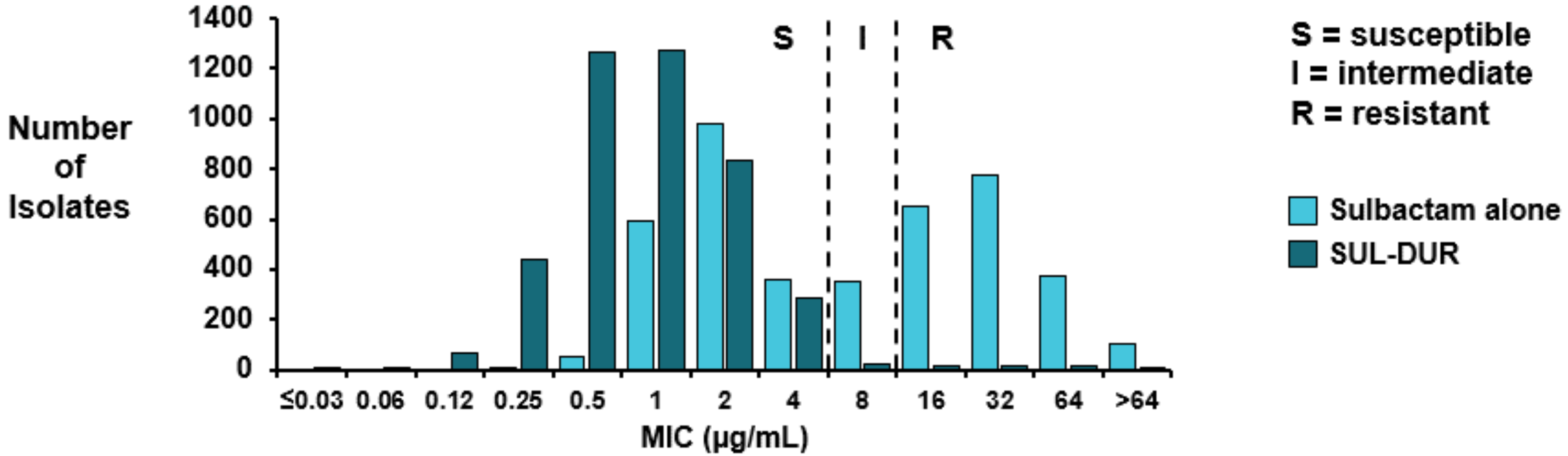
IC_{50} after 5 min incubation (in μM)

Compound	Class A			Class C		Class D		
	TEM-1	CTX-M-15	KPC-2	P99	AmpC	OXA-10	OXA-24/40	OXA-48
Avibactam (AVI)	0.010	0.0045	0.18	0.18	0.54	23	18	0.70
Durlobactam (DUR)	0.0012	0.00083	0.0043	0.0013	0.014	0.23	0.19	0.0063
Fold increase in potency (DUR vs AVI)	8.3X	5.4X	41.9X	138X	38.6X	100X	94.7X	111X

1. Durand-Réville, *et al. Nat Microbiol.* 2017;2:17104. 2. Shapiro AB, *et al. ACS Infect Dis.* 2017;3(11):833-844.

Durlobactam Restores Sulbactam Activity Against Global Clinical *Acinetobacter* Isolates

4,252 Global Clinical Isolates of *Acinetobacter* Collected in 2016-2020



- Sulbactam alone MIC_{90} = 64 µg/mL
- SUL-DUR MIC_{90} = 2 µg/mL
- 98.2% of isolates had SUL-DUR MIC ≤ 4 µg/mL

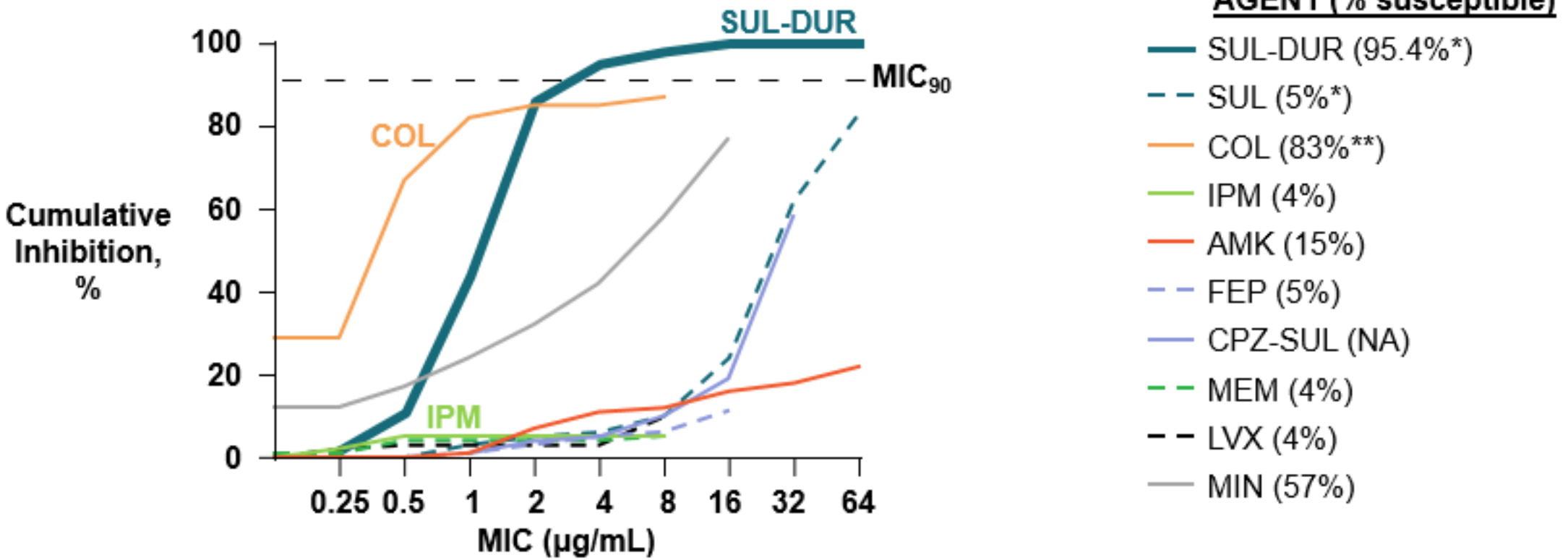
MIC = Minimum Inhibitory Concentration

Low Rates of SUL-DUR Resistance Observed to Date

- Laboratory studies
  - Low frequency of spontaneous resistance (~10^{-10} at 4X MIC)
  - Bactericidal activity in static time kill studies
- Global surveillance studies
  - < 2% of isolates with SUL-DUR MIC values > 4 µg/mL
- Phase 3 results
  - 8 of 175 (4.6%) baseline isolates had SUL-DUR MIC values > 4 µg/mL
    - 5 had MIC = 8 µg/mL; 3 had MIC = 16 µg/mL

Activity of Sulbactam-Durlobactam Against 175 Baseline *Acinetobacter* Isolates from Phase 3

- 96% MDR[1], 85% XDR[1], 15% PDR[2]
- 4.6% non-susceptible to sulbactam-durlobactam based on preliminary breakpoint of 4 µg/mL*



AMK, amikacin; FEP, cefepime; CPZ-SUL, cefoperazone-sulbactam (2:1); COL, colistin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; SUL, sulbactam; DUR, durlobactam, [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; **although no susceptibility breakpoints are recognized for colistin, for the purposes of the Phase 3 trial, COL-S was ≤ 2 ug/mL; NA = no breakpoints available

Durlobactam was Well Tolerated in Nonclinical Toxicology Studies

	14-Day GLP			
Species	NOAEL (mg/kg/day)	Human Equiv. Dose[1] (mg/kg/day)	Human Dose[2] (mg/kg/day)	Safety Margin
Rat	2000	323	67	4.8X
Dog	2000	1111	67	16.6X

	28-Day GLP			
Species	NOAEL (mg/kg/day)	Human Equiv. Dose[1] (mg/kg/day)	Human Dose[2] (mg/kg/day)	Safety Margin
Rat	600[3]	97	67	1.4X
Dog	1000	556	67	8.3X

- No genotoxicity, reproductive toxicity, or safety pharmacology findings (cardiovascular, CNS, or pulmonary)

1. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharma 2016;7:27-31
2. Assuming a 60 kg human body weight; based on proposed clinical dose of 4 g / day of durlobactam
3. Top dose evaluated based on tolerance of sulbactam-durlobactam combination, driven by sulbactam toxicity

NOAEL = No Observed Adverse Effect Level; GLP = Good Laboratory Practice

Key Clinical Pharmacology Results

- Linear, dose proportional pharmacokinetics (PK)
- Low protein binding
- Relatively low volume of distribution, exceeding plasma volume, indicating distribution to extravascular space
- Good intrapulmonary penetration
- Renal elimination as unchanged drug
- Low potential for drug-drug interaction

Key Clinical Pharmacology Results, Continued

- Population PK analyses incorporated clinical data from Phase 1, 2, and 3 trials and showed
  - Dose adjustments needed for patients with creatinine clearance < 45 mL/min or ≥ 130 mL/min
  - No dose adjustments needed for other covariates, including age, sex, race, weight, and site of infection
- Population PK models considered robust for probability of target attainment (PTA) analyses

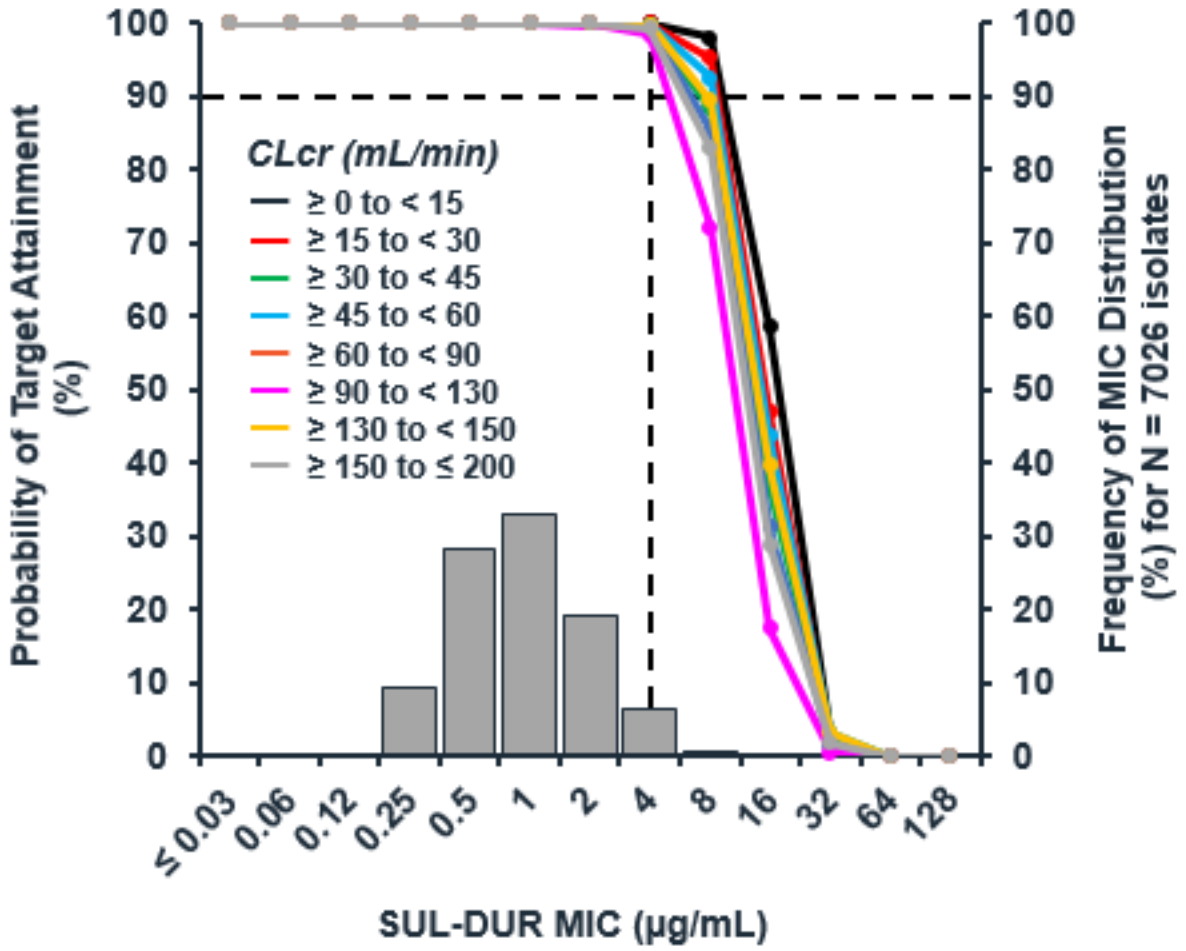
Sulbactam-Durlobactam PK / PD Summary

- SUL-DUR was efficacious in murine neutropenic thigh and lung models of *Acinetobacter* infection
- PK / PD targets were derived from in vitro dynamic model systems and in vivo thigh and lung studies with unbound plasma and total ELF:
  - Sulbactam: 50% *f*T>MIC (1-$\log_{10}$ CFU reduction)
  - Durlobactam: *f*$AUC_{0\text{-}24}$/MIC = 10 (1-$\log_{10}$ CFU reduction)

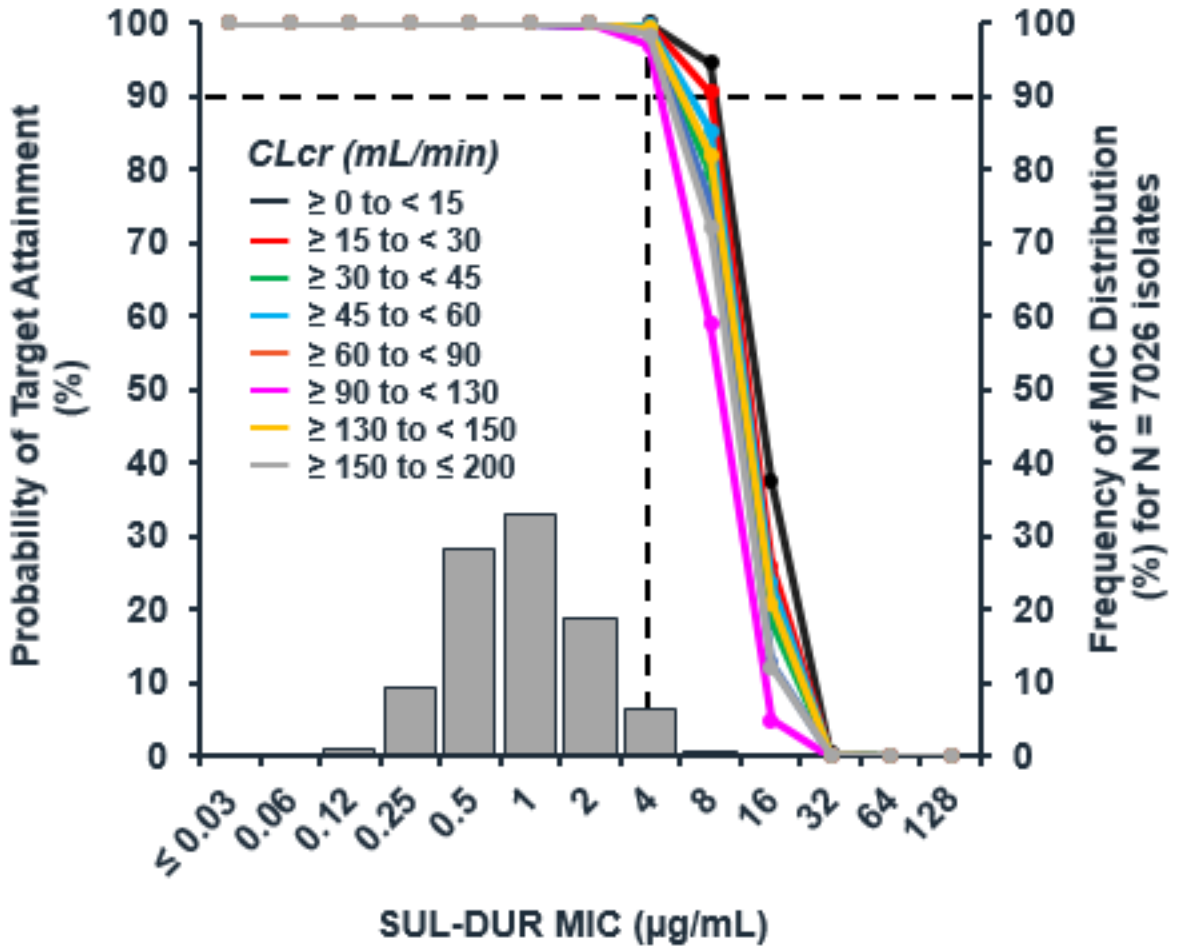
CFU = Colony Forming Unit; ELF = Epithelial Lining Fluid; $AUC_{0\text{-}24}$= Area Under the Curve from 0 to 24 hours after dose

High Probability of Target Attainment (PTA) for *Acinetobacter* at Proposed MIC of ≤ 4 µg/mL

PTA assessment in plasma*



PTA assessment in epithelial lining fluid (ELF)*



*Based on unbound drug concentration in plasma and total drug concentration in ELF; CLcr = creatinine clearance; MIC = minimum inhibitory concentration

Robust Non-clinical Package Supports SUL-DUR Clinical Development Program

- Durlobactam restores sulbactam activity against *Acinetobacter* isolates
- Low potential for resistance development
- Non-clinical safety supports clinical package
- Well characterized PK properties and PK/PD drivers
- High PTA in plasma and ELF

Efficacy

David Altarac, MD, MPA

Chief Medical Officer

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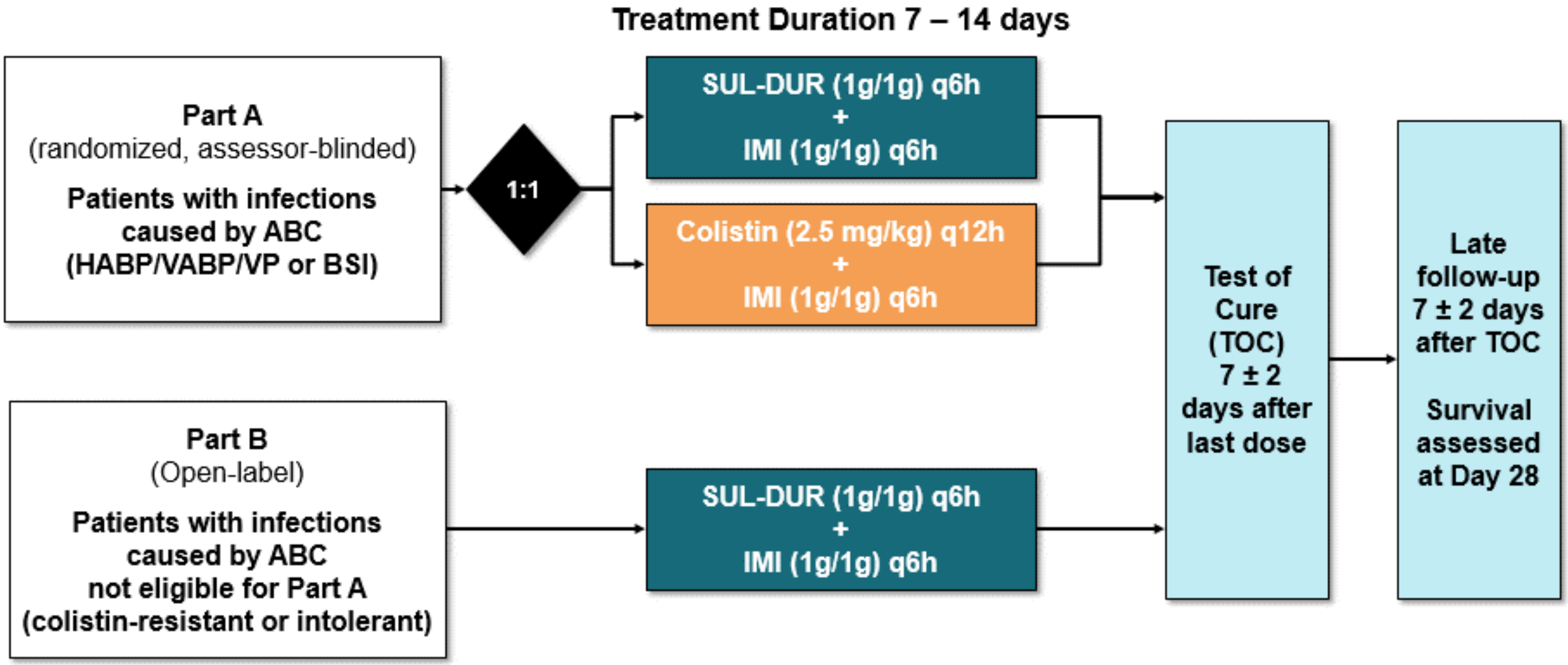
Global Pivotal Phase 3 Trial



ABC = *Acinetobacter baumannii-calcoaceticus complex*, HABP = Hospital-acquired bacterial pneumonia, VABP = ventilator-associated bacterial pneumonia, VP = ventilated pneumonia, BSI = bacteremia, IMI = imipenem

Global Pivotal Phase 3 Trial: Key Inclusion and Exclusion Criteria

Inclusion

- Adults (≥ 18 years old)
- Known infection caused by *Acinetobacter* based on culture
  - Rapid diagnostic used to facilitate enrollment
- ≤ 48 hours of potentially effective antimicrobial therapy before first dose of study drug; OR
- Clinically failing prior treatment (i.e., clinical deterioration or failure to improve after ≥ 48 hours of antibiotics)
- APACHE II score 10 – 30 or SOFA score 1 – 11

Exclusion

- Infection known to be resistant to colistin or polymyxin B (Part A)
- Hypersensitivity or allergic reaction to β-lactam, contraindication to use of imipenem / cilastatin
- Pulmonary disease that precludes evaluation of therapeutic response
- Presence of suspected or confirmed deep-seated infection

Primary Efficacy Endpoint Assessed in Part A

- Primary endpoint
  - 28-day all-cause mortality (ACM)
- Primary efficacy analysis population
  - CR *Acinetobacter* m-MITT population
- Primary analysis
  - Non-inferiority (NI) for 28-day ACM (SUL-DUR vs colistin)
  - NI concluded if upper limit of 2-sided 95% CI < 20%

CR = carbapenem-resistant; m-MITT = microbiologically modified intent-to-treat

Sample Size and 20% Non-inferiority (NI) Margin

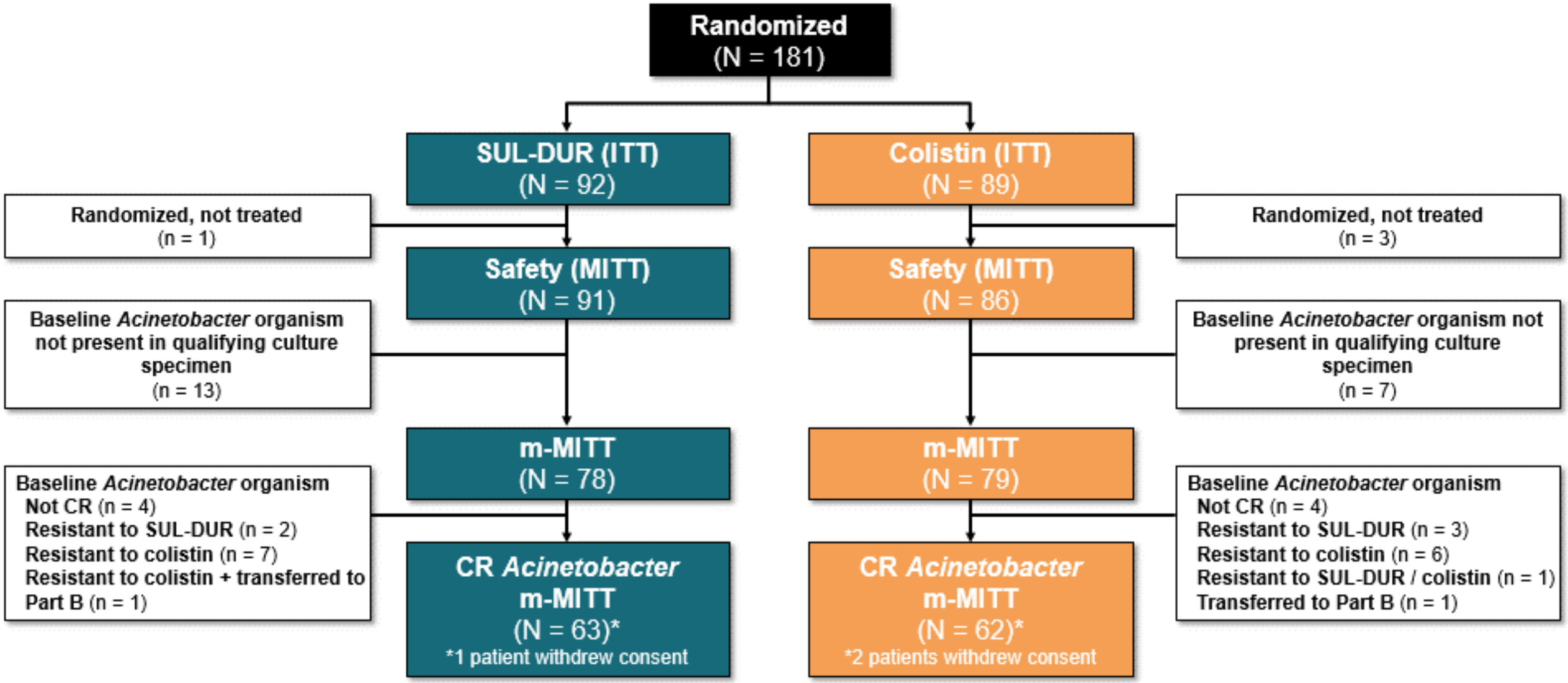
- Assumptions for sample size included
  - 41% mortality rate in the colistin arm
  - 36% mortality rate in the SUL-DUR arm
  - 1:1 randomization
  - 80% power
  - 2-sided alpha = 0.05
- 20% NI margin
  - Based on comprehensive literature reviews of HABP / VABP trials in patients with serious *Acinetobacter* infections treated with colistin or delayed / no therapy

Pre-specified Secondary Efficacy Endpoints

- 14-day ACM and 28-day ACM in ITT and m-MITT
- Clinical cure at TOC
- Clinical cure at EOT and LFU
- Microbiologic favorable assessment at EOT, TOC, and LFU

ITT = intent-to-treat; m-MITT = microbiologically modified intent-to-treat; TOC = test of cure; EOT = end of treatment; LFU = late follow-up; ACM = all-cause mortality

Part A: Patient Disposition



CR = carbapenem-resistant; m-MITT = microbiologically modified intent-to-treat

Demographics and Baseline Characteristics Reflective of Patients in Real World

Characteristics	Part A		Part B
	SUL-DUR (N = 64)	Colistin (N = 64)	SUL-DUR (N = 28)
Age (years), Median (Min, Max)	**62** (25, 91)	**66** (19, 98)	**59** (18, 80)
Male, %	**72%**	**77%**	**75%**
Region			
United States	**2%**	**0%**	**0%**
Rest of World	**98%**	**100%**	**100%**
APACHE II score, Mean (SD)	**16.4** (5.11)	**17.2** (5.21)	**18.0** (5.03)
10 – 19	**67%**	**58%**	**65%**
20 – 30	**23%**	**30%**	**32%**
Creatinine clearance (mL/min), %			
< 90	**39%**	**40%**	**25%**
≥ 90	**61%**	**59%**	**75%**
Infection type, %			
Bacteremia	**3%**	**2%**	**61%**
HABP	**38%**	**48%**	**14%**
VABP	**59%**	**47%**	**25%**
Mechanical ventilation at baseline, %	**73%**	**78%**	**29%**
Monomicrobial infection, %	**58%**	**70%**	**82%**
Polymicrobial infection, %	**42%**	**30%**	**18%**

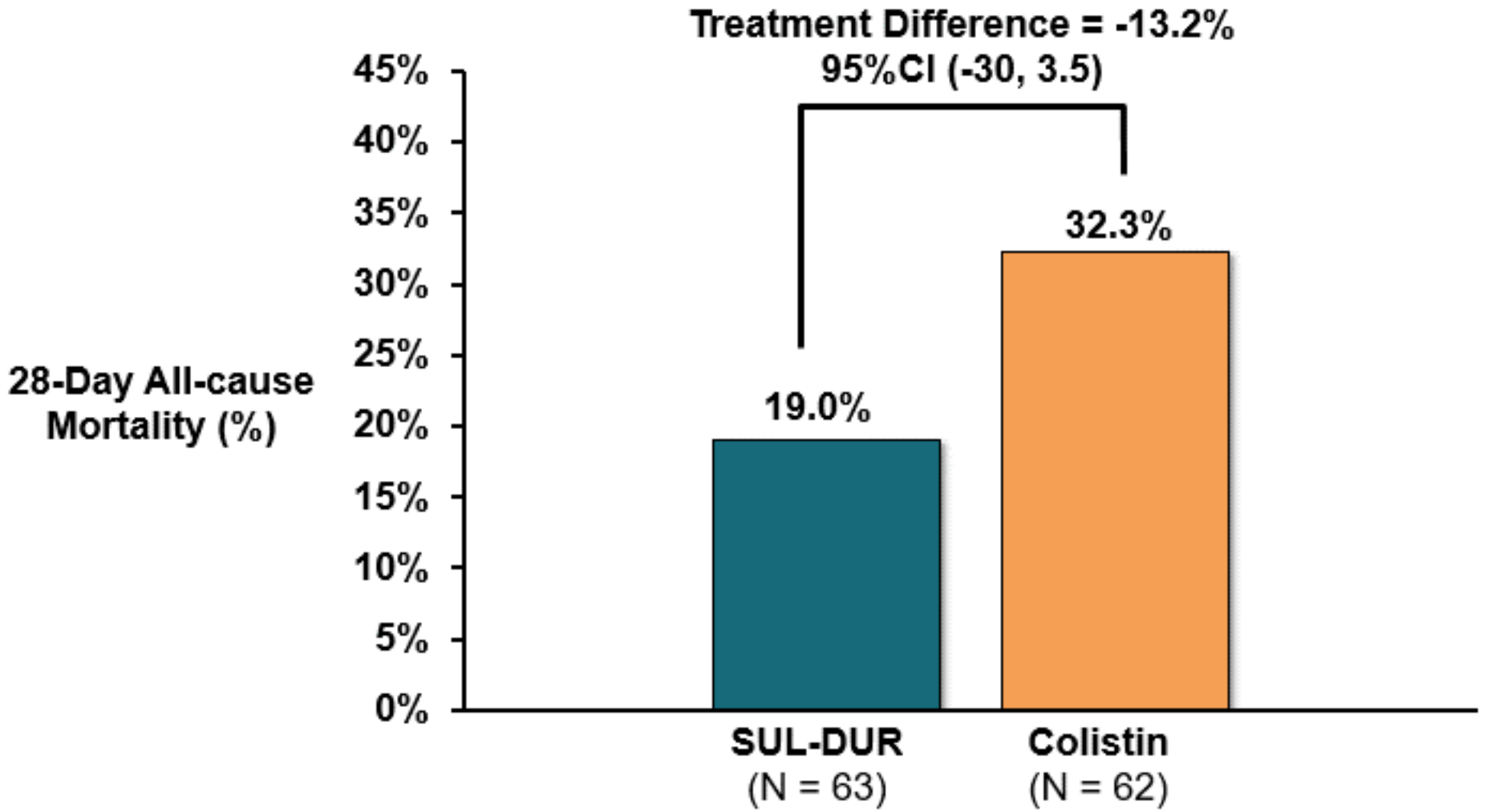
Antibiotic Susceptibility of Baseline *Acinetobacter* Isolates (m-MITT Population, Parts A & B)

Category	*Acinetobacter* baseline isolates, N (%)	SUL-DUR MIC (µg/mL)		
		Range	MIC_{50}	MIC_{90}
All	175 (100%)	0.25 - 16	2	4
Carbapenem resistant	168 (96%)	0.5 - 16	2	4
Colistin-non-susceptible	30 (17%)	1 - 8	2	4
Multidrug resistant*	168 (96%)	0.5 - 16	2	4
Extensively drug resistant*	148 (85%)	0.5 - 16	2	4
Pan drug resistant	26 (15%)	1 - 8	2	4

175 baseline *Acinetobacter* isolates from m-MITT patients were available for testing at the central laboratory
*As defined by Magiorakos *et al.*, *Clin. Microb. Infect.* 2012 18:268-81

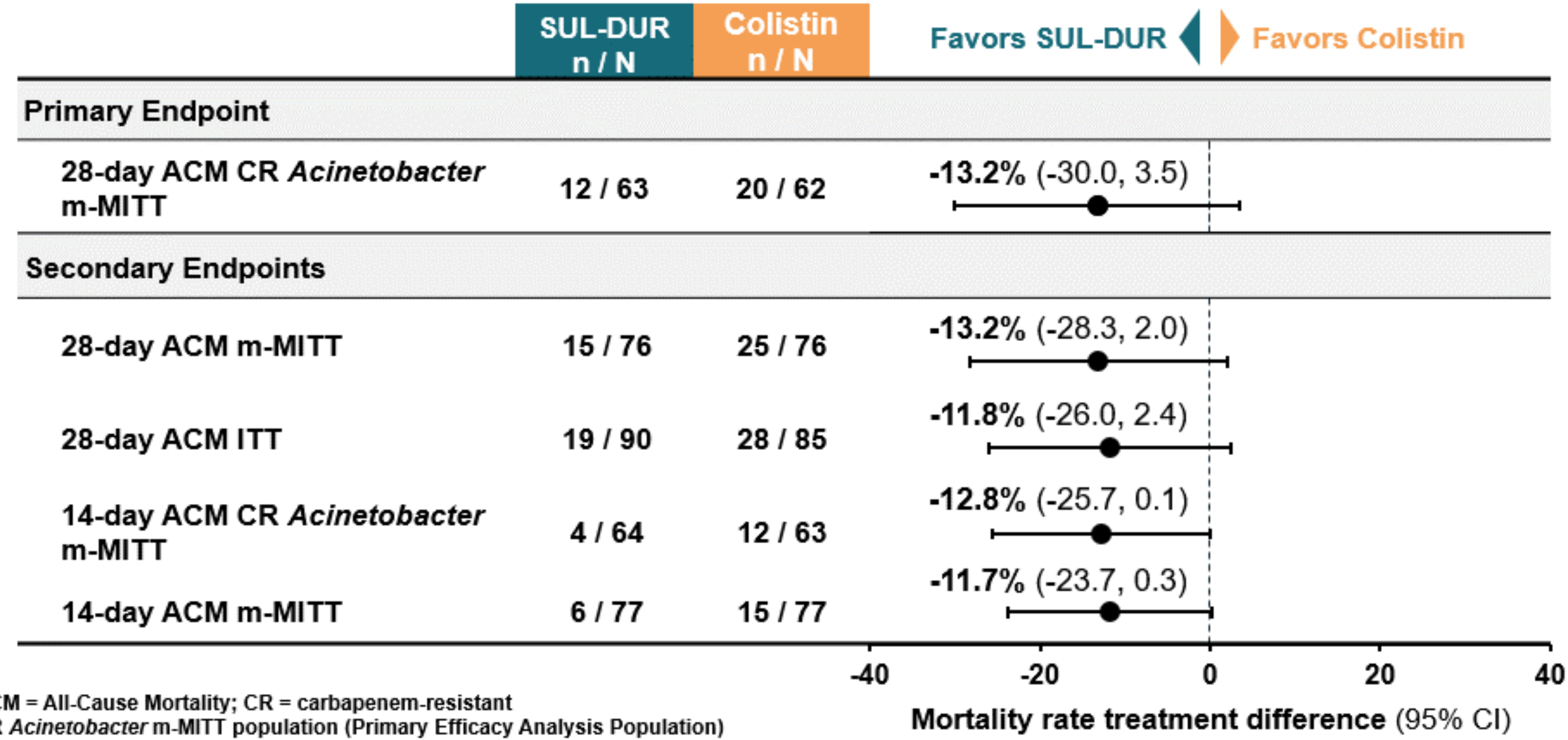
Primary Endpoint Achieved

SUL-DUR Non-inferior to Colistin for 28-Day All-Cause Mortality (ACM)



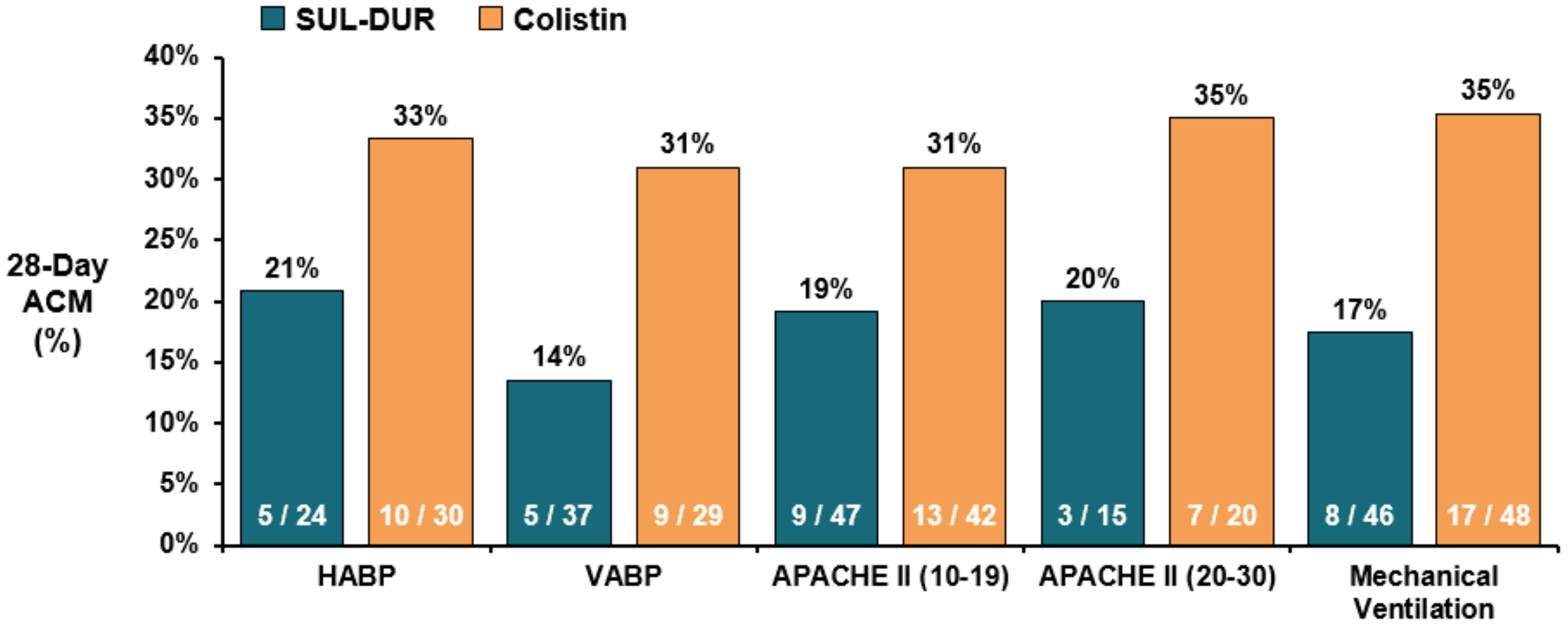
Participants with missing survival status treated as a death
Non-inferiority concluded if upper limit of 2-sided 95% CI < 20%
Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

ACM Consistently Lower with SUL-DUR in All Prespecified Secondary Endpoints



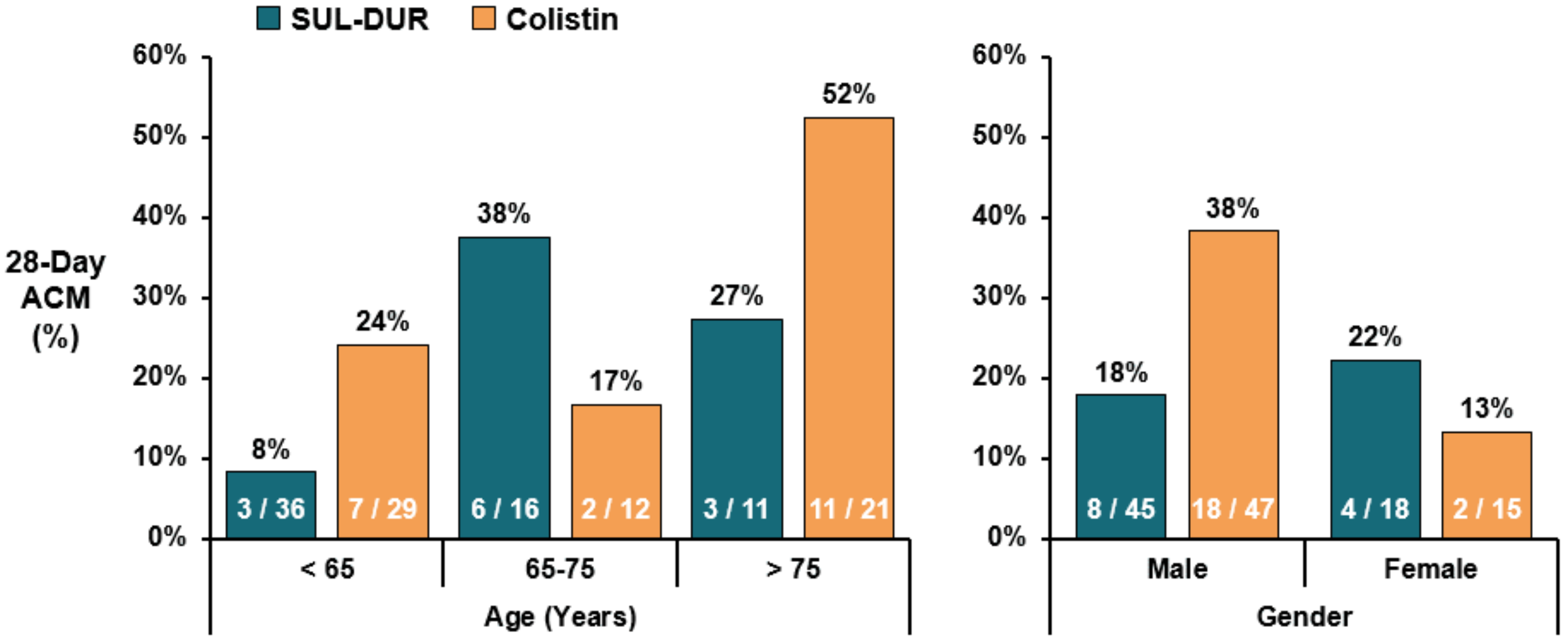
ACM = All-Cause Mortality; CR = carbapenem-resistant
CR *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

28-Day All-Cause Mortality Lower for SUL-DUR in Subgroup Analyses (Part A)



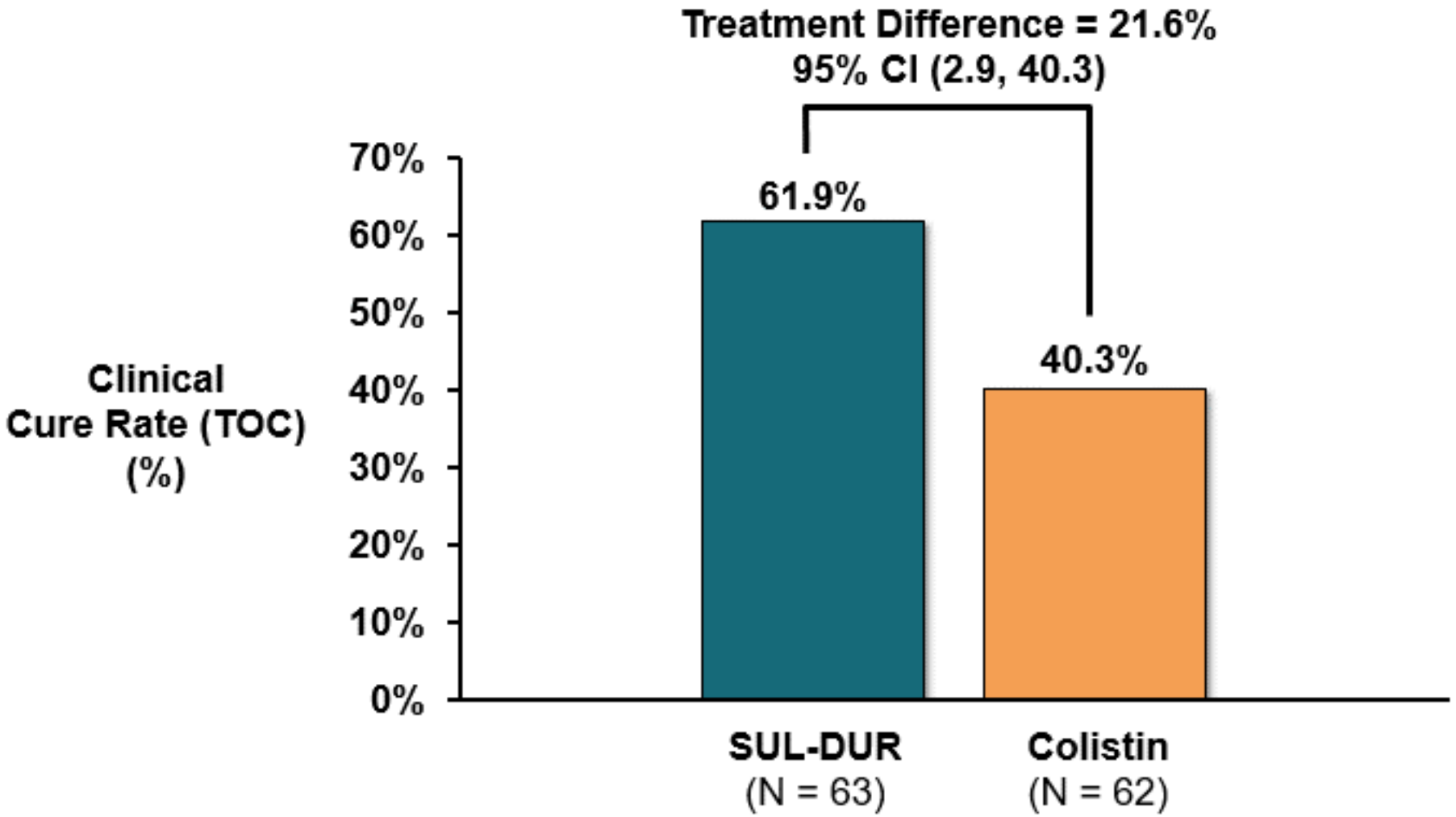
HABP = Hospital-acquired bacterial pneumonia; VABP = Ventilator-associated bacterial pneumonia
Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)
Note: APACHE II score was used first and when not available SOFA or qSOFA were used

Subgroup Analyses for 28-Day All-Cause Mortality – Age and Gender (Part A)



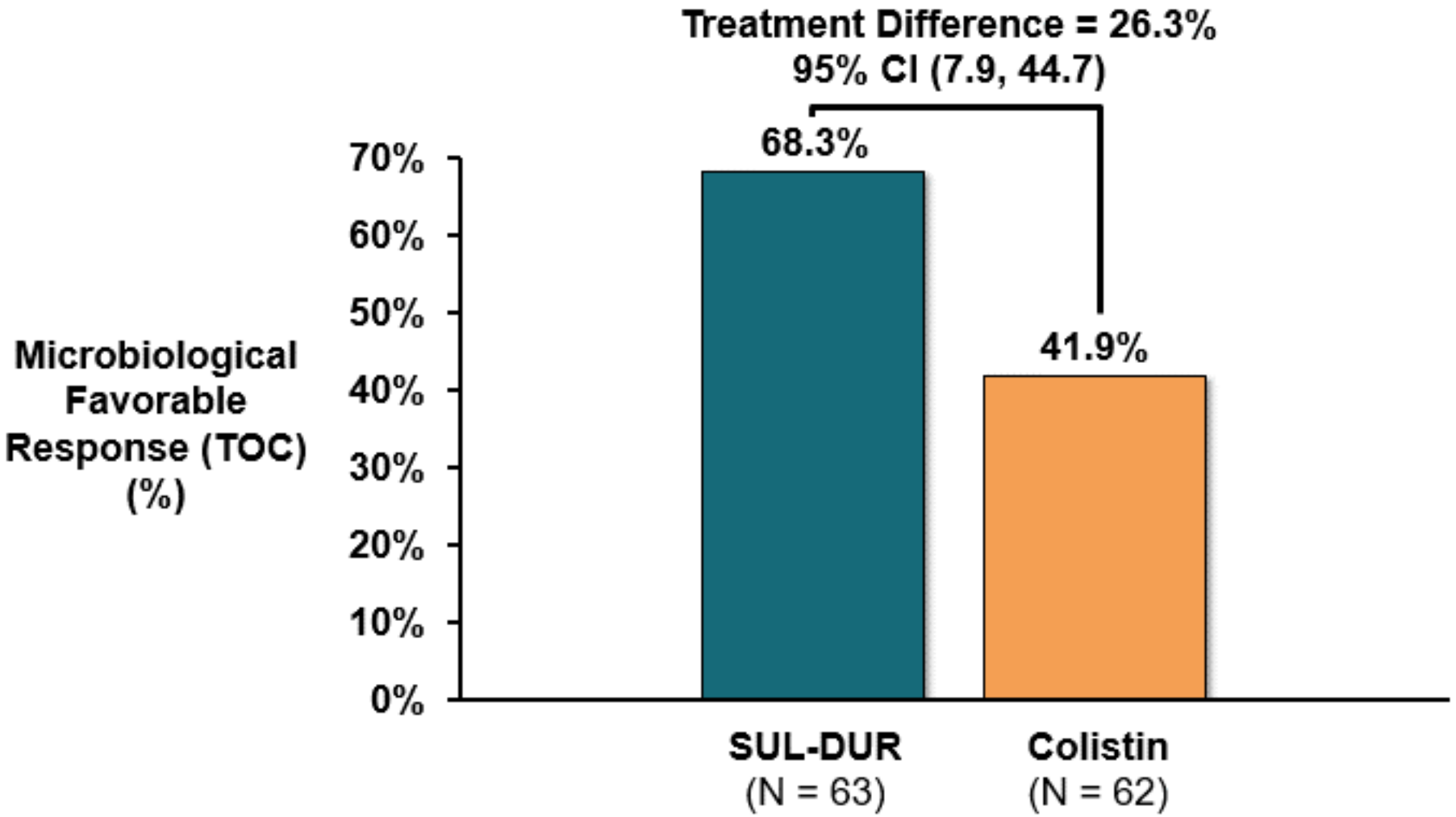
Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

Higher Clinical Cure Rates with SUL-DUR



Clinical cure = Complete resolution/significant improvement of baseline signs and symptoms and no new symptoms, such that no additional Gram-negative antimicrobial therapy warranted; Test of cure was 7 ± 2 days after end of treatment
Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

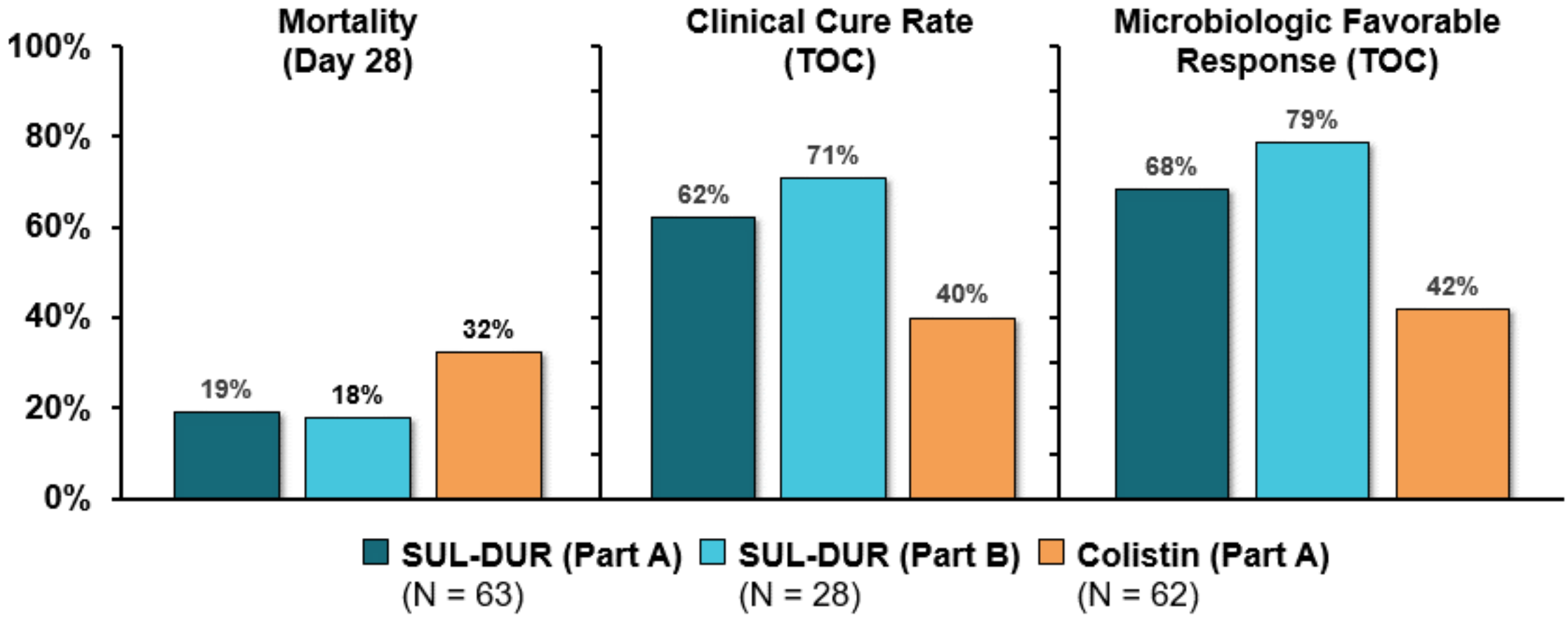
Higher Microbiologic Favorable Assessment with SUL-DUR



Microbiologic Favorable Assessment = microbiologic eradication or presumed eradication; Test of cure was 7 ± 2 days after end of treatment
Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

Part B (N = 28) Results Consistent with Part A

Part B: colistin-resistant or intolerant to colistin (61% with blood-stream infections)



Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

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

SUL-DUR Demonstrated Efficacy in Patients with Serious Infections Caused by Resistant *Acinetobacter*

- SUL-DUR met primary endpoint of noninferiority for 28-day ACM in primary analysis population
- Prespecified secondary endpoints of clinical cure and microbiologic favorable assessment
  - Consistently greater in SUL-DUR group vs comparator at all timepoints and in all assessed populations

Safety

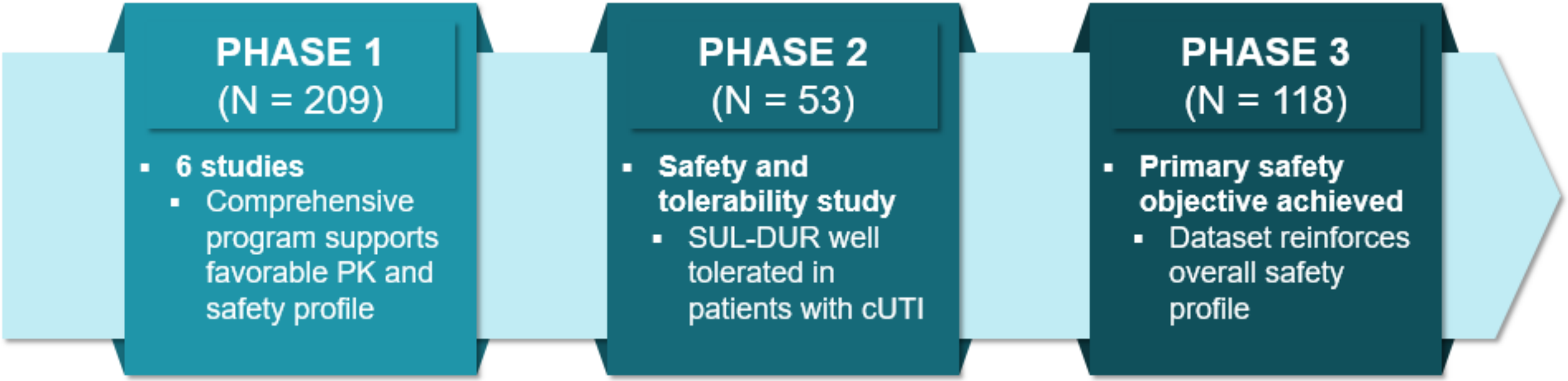
Drew Lewis, MD, MTM&H, FACP

Vice President of Clinical Development

Entasis Therapeutics, A Wholly Owned Subsidiary of Innoviva, Inc.

Safety Profile Characterized in 8 Clinical Studies

- 380 patients exposed to durlobactam alone or in combination with sulbactam
- 181 patients received SUL-DUR at proposed dose
- 158 patients at proposed dose and duration



cUTI = complicated urinary tract infection

Incidence of Adverse Events with SUL-DUR vs Colistin Treatment Groups

	Part A		Part B
	SUL-DUR (N = 91)	**Colistin** (N = 86)	**SUL-DUR** (N = 28)
Any AEs	80 **(88%)**	81 **(94%)**	24 **(86%)**
Treatment-related AEs	12 **(13%)**	26 **(30%)**	3 **(11%)**
SAE	36 **(40%)**	42 **(49%)**	9 **(32%)**
Treatment-related SAEs	1 **(1%)**	2 **(2%)**	1 **(4%)**
AEs leading to study drug discontinuation	10 **(11%)**	14 **(16%)**	4 **(14%)**
AE leading to death	24 **(26%)**	30 **(35%)**	4 **(14%)**
Treatment-related deaths	**0**	**1 (1%)**	**0**

Common Adverse Events Consistent with Patient Population and Pharmacologic Class

Preferred Term	Part A		Part B
	SUL-DUR (N = 91)	Colistin (N = 86)	SUL-DUR (N = 28)
Any AE	80 (88%)	81 (94%)	24 (86%)
Diarrhea	15 (17%)	9 (11%)	2 (7%)
Anemia	12 (13%)	12 (14%)	3 (11%)
Hypokalemia	11 (12%)	9 (11%)	0
Pyrexia	9 (10%)	8 (9%)	1 (4%)
Septic shock	9 (10%)	8 (9%)	0
Urinary tract infection	7 (8%)	7 (8%)	1 (4%)
Acute kidney injury	4 (4%)	11 (13%)	0
Blood creatinine increased	1 (1%)	7 (8%)	3 (11%)
Seizure	1 (1%)	6 (7%)	0
Renal impairment	0	6 (7%)	1 (4%)

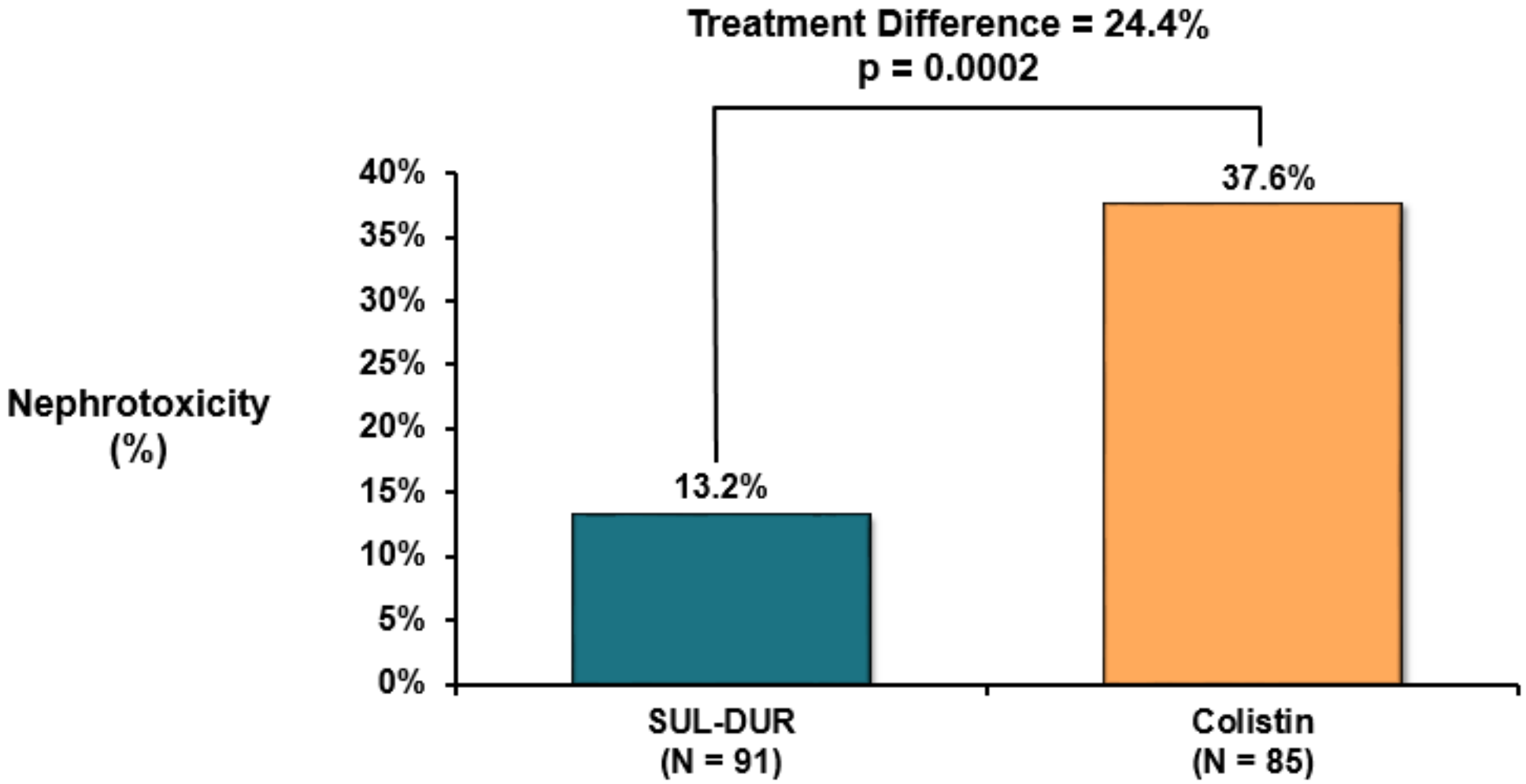
Adverse events in > 5 patients in any group without regard to causality

Incidence of Serious Adverse Events in SUL-DUR vs Colistin Treatment Groups

Preferred Term	Part A		Part B
	SUL-DUR (N = 91)	Colistin (N = 86)	SUL-DUR (N = 28)
Any Serious AE	36 (40%)	42 (49%)	9 (32%)
Septic shock	7 (8%)	7 (8%)	0
Cardiac arrest	2 (2%)	4 (5%)	1 (4%)
Sepsis	2 (2%)	3 (4%)	0
Acute respiratory distress syndrome	2 (2%)	2 (2%)	0
Brain edema	2 (2%)	1 (1%)	0
Gastrointestinal hemorrhage	2 (2%)	1 (1%)	0
Respiratory failure	2 (2%)	1 (1%)	1 (4%)
Tracheo-esophageal fistula	2 (2%)	0	0
Pneumonia	1 (1%)	5 (6%)	0
Multiple organ dysfunction syndrome	1 (1%)	4 (5%)	2 (7%)
Acute kidney injury	1 (1%)	2 (2%)	0
Pulmonary embolism	1 (1%)	2 (2%)	0
Seizure	0	3 (4%)	0
Anemia	0	2 (2%)	0

≥ 2 patients in any group without regard to causality

SUL-DUR Achieved the Primary Safety Objective of Lower Nephrotoxicity than Colistin



Phase 3 Trial Part A
Based on modified RIFLE criteria
RIFLE = Risk, Injury, Failure, Loss, End Stage Kidney Disease

Most Renal and Urinary Disorder AEs Mild or Moderate

System Organ Class Severity	Part A		Part B
	SUL-DUR (N = 91)	Colistin (N = 86)	SUL-DUR (N = 28)
Renal and urinary disorders	9 **(10%)**	27 **(31%)**	3 **(11%)**
Mild	4 **(4%)**	12 **(14%)**	1 **(4%)**
Moderate	4 **(4%)**	8 **(9%)**	1 **(4%)**
Severe	1 **(1%)**	7 **(8%)**	1 **(4%)**

Summary: SUL-DUR Safety Profile Similar to Established Class of β-lactam / β-lactamase Inhibitor Combinations

- SUL-DUR generally well tolerated in severely ill patients with no new safety signals identified
- Phase 3 primary safety objective achieved with significantly lower incidence of nephrotoxicity vs colistin
- Phase 1 and 2 safety data provide supportive evidence of SUL-DUR tolerability

SUL-DUR could provide an important treatment option for infections due to susceptible strains of *Acinetobacter*

Clinical Perspective

J. Patrik Hornak, MD

Assistant Professor of Medicine

Division of Infectious Diseases

Assistant Clinical Director, AIDS Education & Training Center

The University of Texas Medical Branch at Galveston

Urgent, Unmet Need for New Treatments for Serious Infections Caused by Resistant *Acinetobacter*

- Infections caused by *Acinetobacter*
  - Difficult to treat
  - Consume vast healthcare resources
  - Inflict excess morbidity & mortality on vulnerable patients
- Treatment options are limited and lack clinical efficacy evidence needed to inform treatment decisions

Real-World Case Report

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CHALLENGING CLINICAL CASE IN ANTIMICROBIAL RESISTANCE

Extensively Drug-Resistant *Acinetobacter baumannii* Nosocomial Pneumonia Successfully Treated with a Novel Antibiotic Combination

Noor Zaidan,[a] J. Patrik Hornak,[b] David Reynoso[b]

[a]Department of Pharmacy, University of Texas Medical Branch at Galveston, Galveston, Texas, USA

[b]Division of Infectious Diseases, Department of Internal Medicine, University of Texas Medical Branch at Galveston, Galveston, Texas, USA

This Journal section presents a real, challenging case involving a multidrug-resistant organism. The case authors present the rationale for their therapeutic strategy and discuss the impact of mechanisms of resistance on clinical outcome. Expert clinicians then provide a commentary on the case.

Zaidan et al., 2021

Patient with Serious *Acinetobacter* VABP Successfully Treated with Sulbactam-Durlobactam: a Real-World Case

DAYS 1-15

- Patient admitted for respiratory failure (COVID)
- Surveillance sputum & blood cultures negative
- Improves, extubated on day 13
- Condition deteriorates, re-intubated on day 14
- Syndrome compatible with VABP, septic shock
- Empiric antibiotics started: vancomycin, meropenem

Patient with Serious *Acinetobacter* VABP Successfully Treated with Sulbactam-Durlobactam: a Real-World Case

DAYS 16-21

- Repeat sputum cultures: pan-resistant *Acinetobacter*
- Antibiotics adjusted to AMP-SUL, MEM, PMX B
- Continues to worsen, eravacycline added on day 19
- No improvement

Patient with Serious *Acinetobacter* VABP Successfully Treated with Sulbactam-Durlobactam: a Real-World Case

DAYS 22-37

- SUL-DUR requested via Expanded Access Program
- Day 23, stopped AMP-SUL, MEM, eravacycline, PMX B. Started cefiderocol.
- No improvement, remains intubated with shock
- Day 24, started SUL-DUR
- Fevers, leukocytosis, shock resolve within 72 hrs
- Ventilator support weaned

Patient with Serious *Acinetobacter* VABP Successfully Treated with Sulbactam-Durlobactam: a Real-World Case

DAY 38

- Completes 14 days of SUL-DUR
- No adverse events
- Discharged on day 38
- Ultimately makes full recovery

Concluding Remarks

Shruta Rege, PhD

Senior Vice President

Head of Regulatory Affairs and Development Operations

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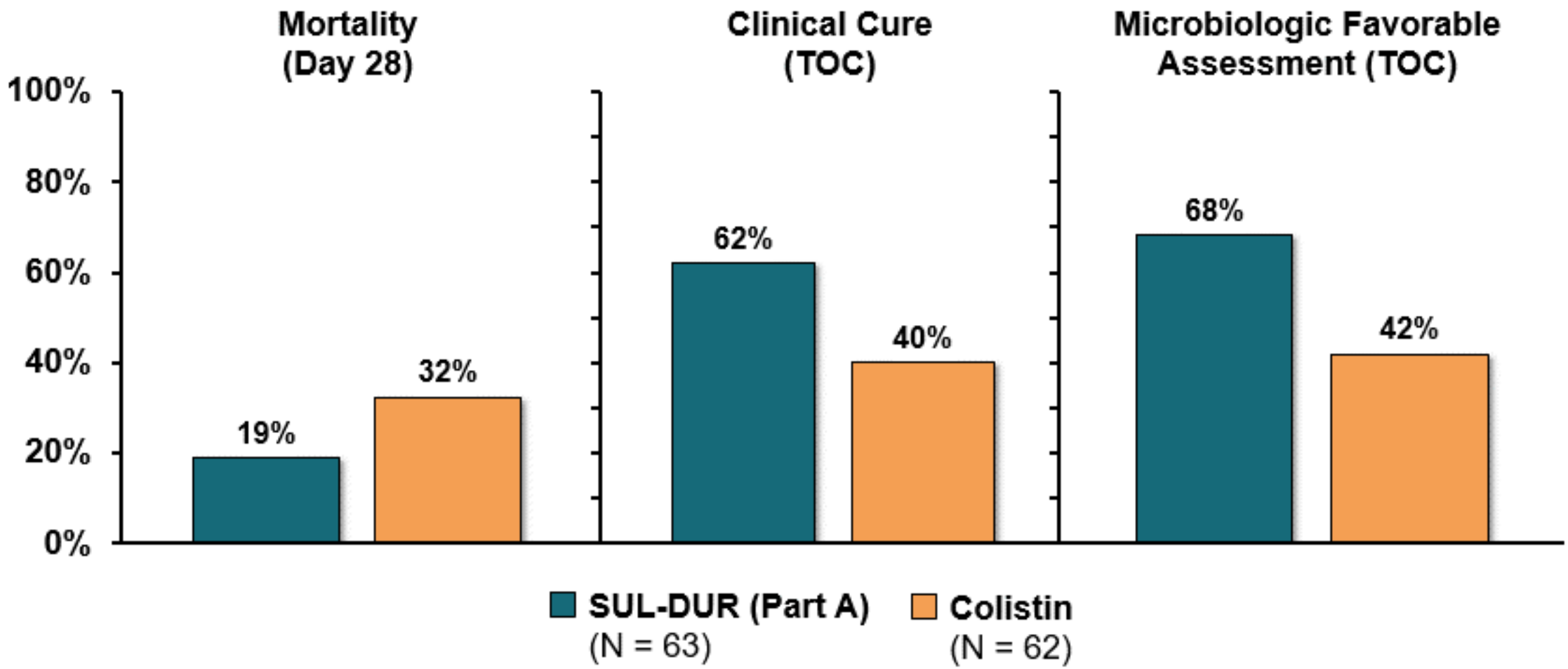
SUL-DUR Demonstrated Robust Efficacy in Patients With *Acinetobacter* Infections



Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)
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

SUL-DUR Was Well Tolerated in Clinical Trials

- SUL-DUR provides benefit over existing options
  - Polymyxin toxicity is well-known risk
- SUL-DUR had significantly lower incidence of nephrotoxicity compared to colistin
- SUL-DUR safety profile supportive of use in severely ill patients who often have many comorbidities

Totality of Data Support Positive Benefit-Risk Profile for SUL-DUR

- Increasing multidrug resistance creates urgent unmet need
- Durlobactam restores efficacy of sulbactam against resistant *Acinetobacter*
- Efficacy data from Phase 3 trial with confirmatory evidence from in vitro and animal data
- Safety profile consistent with β-lactam / β-lactamase inhibitor class

Sulbactam-durlobactam will address the unmet and urgent need for a safe and efficacious treatment for patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex.

Sulbactam-Durlobactam for the Treatment of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia Caused by Susceptible Strains of *Acinetobacter baumannii-calcoaceticus* Complex

Antimicrobial Drugs Advisory Committee

Entasis Therapeutics, A Wholly Owned Subsidiary of Innoviva, Inc.

April 17, 2023

ADDITIONAL SLIDES SHOWN

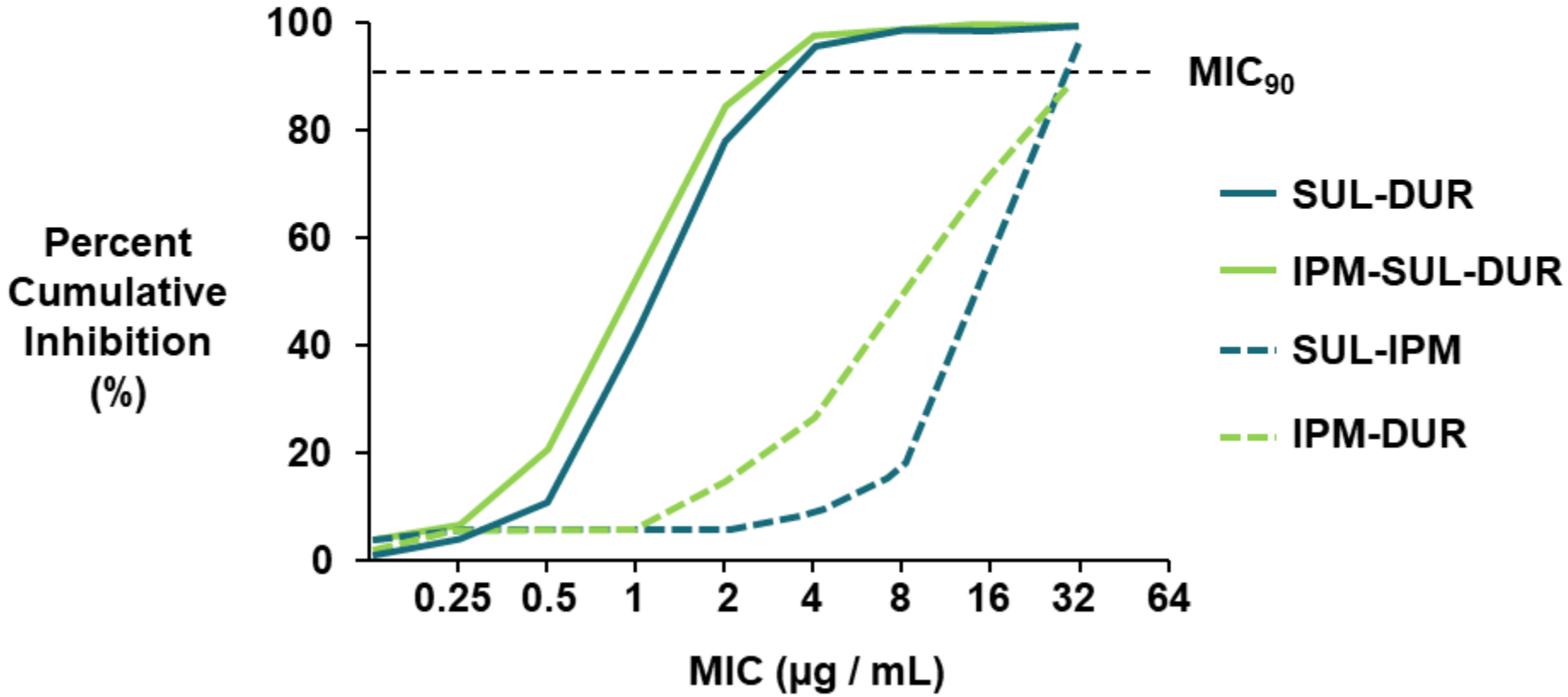
Phase 3: 1 Patient had ABC that Developed Decreased Susceptibility on SUL-DUR

- MLST and genomic analyses showed same strain throughout infection
- Only genetic difference between baseline isolate and subsequent isolates was a G288S mutation in AdeJ, a gene associated with efflux
- No difference in efflux potential between baseline and longitudinal isolates was observed in phenotypic assay.

		Patient 1
MIC at Screening (µg/mL)		4
Subsequent MIC (µg/mL) (Visit)		32 (Day 7), 8 (TOC)
In CRABC m-MITT population (Yes / No)		No
Completed Treatment (Yes / No)		Yes
Completed Study (Yes / No)		Yes
Survived to Day 28 (Day of death) (Yes / No)		Yes
Response Type	Visit	Individual Response Outcome
Clinical Outcome	EOT	Cure
	TOC	Cure
	LFU	Fail
Microbiological Outcome	EOT	Persistence
	TOC	Persistence
	LFU	Eradicated

Sulbactam + Durlobactam Was More Active Than Combinations of Imipenem With Sulbactam or Durlobactam

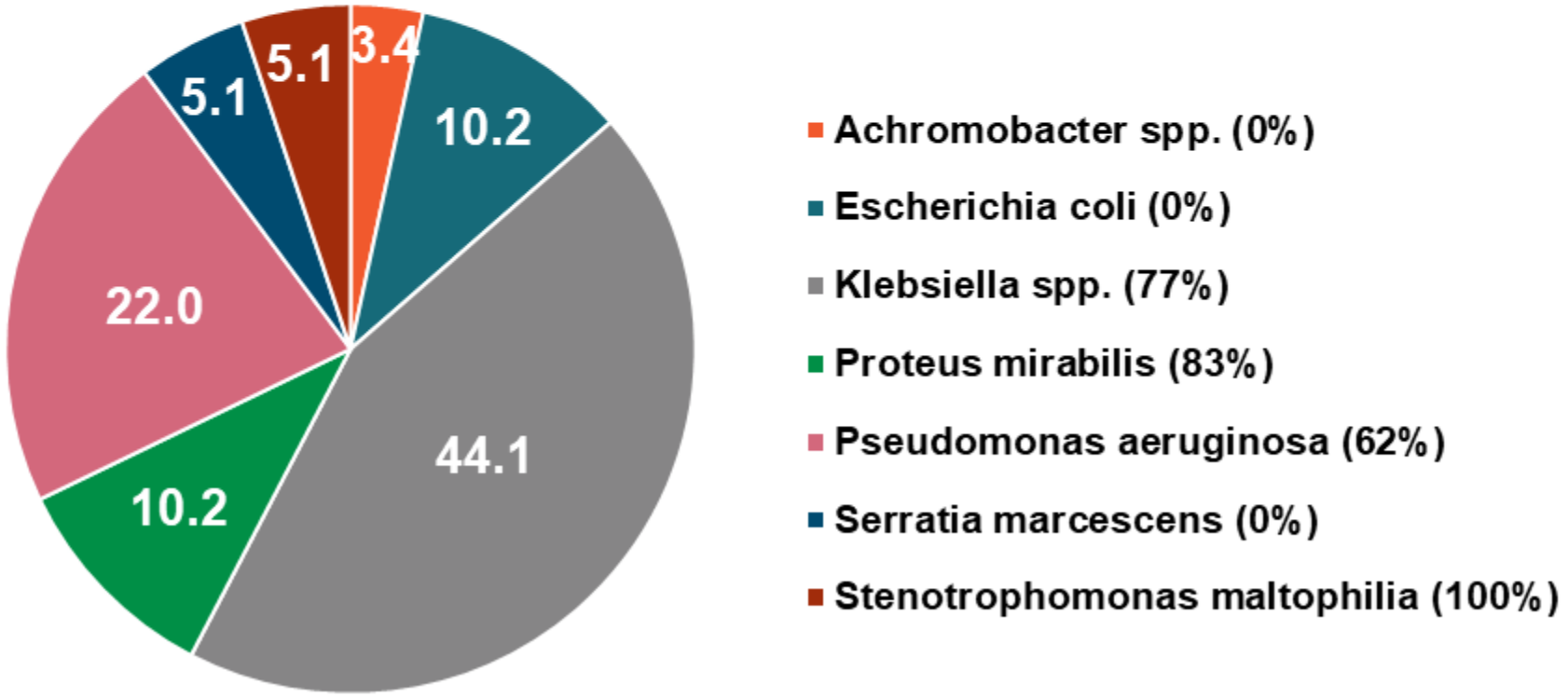
In vitro studies show that sulbactam in combination with durlobactam was more active than combinations of imipenem with sulbactam or durlobactam



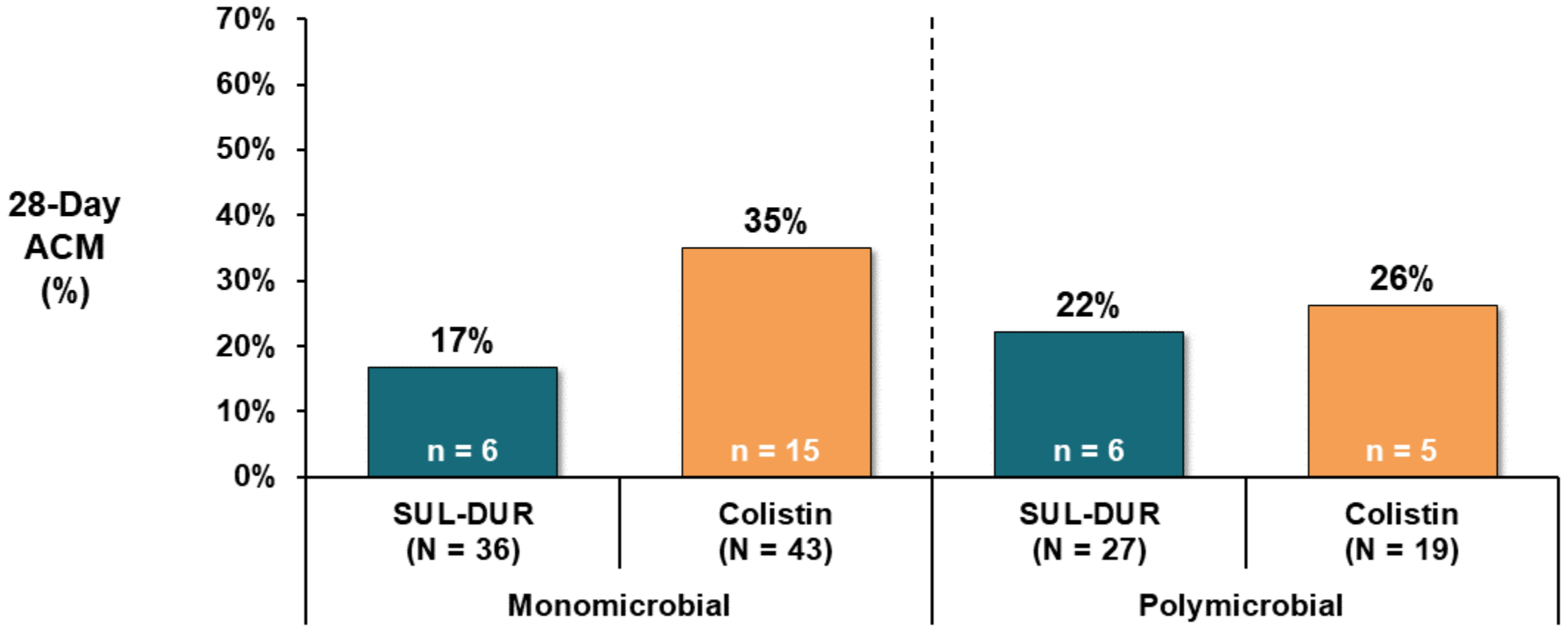
Most Common Co-Infecting Gram-Negative Pathogens Were *Klebsiella* spp. and *P. aeruginosa*

- ~30% of baseline Acinetobacter-positive cultures contained other Gram-negative bacterial pathogens
- 61% of co-infecting baseline Gram-negative pathogens were carbapenem-resistant

Breakdown by % Species of Co-infecting Gram-negative Pathogens (%IPM-NS)
CRABC m-MITT population



28-day ACM Lower With SUL-DUR Than Colistin Regardless of Monomicrobial or Polymicrobial Infections at Baseline



Outcomes For CRABC M-Primary Efficacy Population For Monomicrobial ABC Vs Polymicrobial ABC Infections

Type of Infection, n (%)	SUL-DUR	Colistin
All ABC infections, N	63	62
28 Day All Cause Mortality	12 (19%)	20 (32.2%)
Clinical Cure at TOC	39 (61.9%)	25 (40.3%)
Favorable Microbiological Assessment at TOC	43 (68.2%)	26 (41.9%)
Monomicrobial ABC infections, N	36	43
28 Day All Cause Mortality	6 (16.7%)	15 (34.9%)
Clinical Cure at TOC	23 (63.9%)	15 (34.9%)
Favorable Microbiological Assessment at TOC	24 (66.7)	14 (32.6)
Polymicrobial ABC infections, N	27	19
28 Day All Cause Mortality	6 (22.2%)	5 (26.3%)
Clinical Cure at TOC	16 (59.3%)	10 (52.6%)
Favorable Microbiological Assessment at TOC	19 (70.4%)	12 (63.2%)

ABC = *Acinetobacter baumannii-calcoaceticus* complex; CRABC m-MITT = carbapenem-resistant ABC microbiologically modified Intent-to-Treat; SUL-DUR = sulbactam-durlobactam; COL = colistin; IMI = imipenem / cilastatin; TOC = test of cure

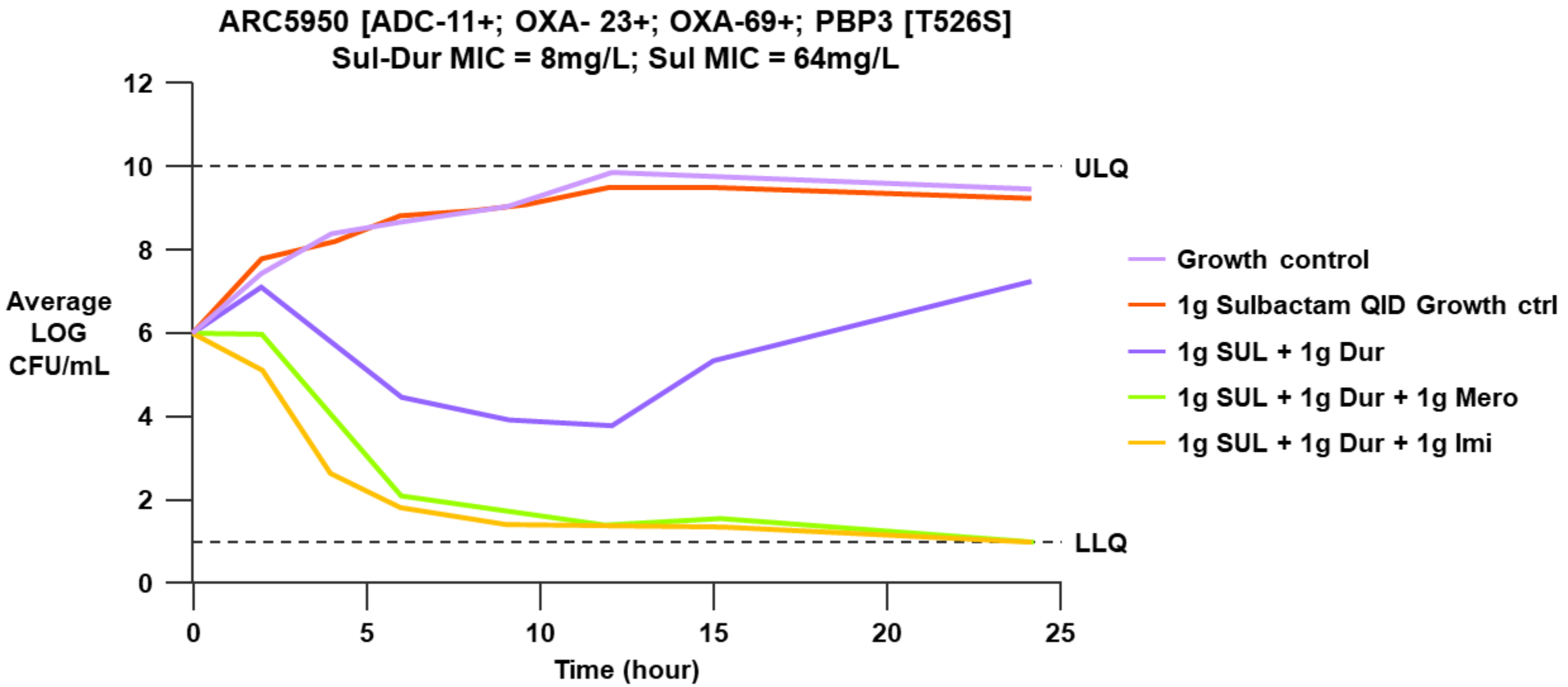
Colistin Selection as an Active Comparator

- Colistin remains frequently used for drug-resistant *Acinetobacter* infections despite known toxicities
- At time of study design, there was no clear standard-of-care for treatment of CRAB infections and no new treatment options were approved
- Overall mortality rates reported in the literature:

	Mortality Rates
Colistin-Based Therapies	**25 - 57%[a]**
No / Delay Treatment	**65 - 87%[b]**

a. Alvarez-Marin et al 2016; Sirijatuphat and Thamlikikul 2014; b. Erbay et al 2009; Lee et al 2014

Sulbactam-Durlobactam Hollow Fiber Infection Model



Source: Study Report PC2514-2020-0023 SUL: Sulbactam; Dur: Durlobactam; Mer: Meropenem; Imi: Imipenem; QID: Q6h; every 6hrs

Relevant Classes of Antibiotics Tested in Combination With SUL-DUR Against ABC Showed No Antagonism

- The checkerboard assay was used to determine whether there were examples of antagonism, synergy or indifferent effects between sulbactam-durlobactam and major classes of other antimicrobial agents
  - Gram negative agents tested: Imipenem, meropenem, ceftazidime-avibactam, ciprofloxacin, amikacin, colistin, cefepime and minocycline
  - Gram positive agents tested: oritavancin, rifaximin, rifampicin, tedizolid, vancomycin, dalbavancin, daptomycin, fidaxomicin, linezolid
  - Antifungal agent tested: fluconazole
  - Anaerobic species agent: metronidazole
- The prevailing observation was an indifferent or additive interaction
  - No examples of antagonism were observed
  - A few instances of synergy were observed but these were strain- and drug-dependent

Clinical and Microbiological Outcomes at Different Visits for 3 Recent VAP Trials

Outcome		SUL-DUR (ATTACK)			REPROVE[1]			CREDIBLE-CR[2]		
		Sulbactam-Durlobactam	Colistin	Difference	Ceftazidime-Avibactam	Meropenem	Difference	Cefiderocol	Best available therapy	Difference
Clinical Cure (%)	EOT	74.6	45.2	29.4	82	83.5	-1.5	66	58	8.0
	TOC	61.9	40.3	21.6	68.8	73	-4.2	53	50	3.0
	LFU	42.9	30.6	12.3	-	-		48	34	14.0
Favorable Microbiologic Response (%)	EOT	85.7	61.3	24.4	79.4	80.4	-1.0	48	26	22.0
	TOC	68.3	41.9	26.4	55.6	64.1	-8.5	31	24	7.0
	LFU	47.6	40.3	7.3	-	-	-	26	18	8.0

1. Torres et al., 2018. 2. Bassetti et al., 2021

For ATTACK, source is from CRABC microbiologically modified intent-to-treat population. For REPROVE, source is from clinically or microbiologically modified intent-to-treat. For CREDIBLE-CR, source is from carbapenem-resistant microbiological intention-to-treat population

Comorbidities

Preferred Term, n (%)	ETX2514SUL + IMI (Part A) (N = 64)	Colistin + IMI (Part A) (N = 64)	Total (Part A) (N = 128)	ETX2514SUL + IMI (Part B) (N = 28)
Patients with any comorbidities	48 (75%)	48 (75%)	96 (75%)	13 (46%)
Cerebrovascular disease	21 (33%)	18 (28%)	39 (31%)	1 (4%)
Diabetes without end-organ damage	13 (20%)	15 (23%)	28 (22%)	5 (8%)
Congestive heart failure	15 (23%)	11 (17%)	26 (20%)	2 (7%)
Chronic pulmonary disease	9 (14%)	15 (23%)	24 (19%)	3 (11%)
Hemiplegia	12 (19%)	7 (11%)	19 (15%)	1 (4%)
Moderate or severe renal disease	7 (11%)	12 (19%)	19 (15%)	6 (21%)
Mild liver disease	7 (11%)	7 (11%)	14 (11%)	0
Peripheral vascular disease	8 (13%)	4 (6%)	12 (9%)	1 (4%)
Diabetes with end-organ damage	6 (9%)	4 (6%)	10 (8%)	2 (7%)
Metastatic solid tumor	5 (8%)	5 (8%)	10 (8%)	0
Tumor without metastases	3 (5%)	7 (11%)	10 (8%)	1 (4%)
Peptic ulcer disease	4 (6%)	4 (6%)	8 (6%)	2 (7%)
Myocardial infarction	3 (5%)	4 (6%)	7 (6%)	1 (4%)
Moderate or severe liver disease	2 (3%)	3 (5%)	5 (4%)	0
Dementia	3 (5%)	1 (2%)	4 (3%)	1 (4%)
Leukemia	1 (2%)	0	1 (0.8%)	0
Lymphoma	1 (2%)	0	1 (0.8%)	0

Preclinical Infection Models Support Use of Sulbactam-Durlobactam Beyond Pneumonia

Clinical Indication (site)	Relevant Matrix	Non-Clinical Model	PK / PD Targets (Net 1-log_{10} CFU Reductions in 24 Hours)	PK / PD Targets (Net 2-log10 CFU Reductions in 24 Hours)
Nosocomial Pneumonia (lung)	Total Epithelial Lining Fluid and Unbound Plasma	Murine Lung	Sulbactam 50% Time > MIC and Durlobactam AUC_{0-24} / MIC = 10	Sulbactam 50% Time > MIC and Durlobactam AUC_{0-24} / MIC = 30
Bacteremia (bloodstream)	Unbound Plasma	Murine Thigh		
Intra-abdominal (tissue)	Unbound Plasma	Murine Thigh		
Pyelonephritis (tissue)	Unbound Plasma	Murine Thigh		
Urinary Tract Infection (urine)	Total Urine	Murine Thigh / In vitro HFIM		

AUC_{0-24} = area under the plasma concentration-time curve from time of dosing to 24 hours postdose; CFU = colony-forming units; HFIM = hollow-fiber infection model; MIC = minimum inhibitory concentration; PD = pharmacodynamics; PK = pharmacokinetics