02060

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)

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Disclosures

- David Altarac, Sarah McLeod, and Khurram Rana are employees of, and own stock or have stock options in, Entasis Therapeutics
- Robin Isaacs, Subasree Srinivasan, and Gabrielle Poirier were employees of Entasis Therapeutics when the study was conducted, and have stock or stock options in Entasis Therapeutics
- Andrew Shorr is a member of the scientific and clinical board for Entasis Therapeutics and has received consulting fees
- Keith Kaye was the chair of the data and safety monitoring board of this study
- The ATTACK trial was funded by Entasis Therapeutics
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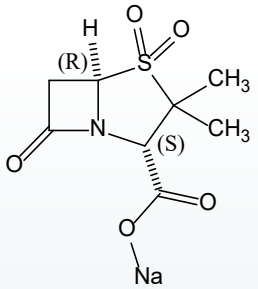
SUL-DUR: a ß-Lactam/ß-Lactamase Inhibitor Combination in Development For Treatment of *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Infections

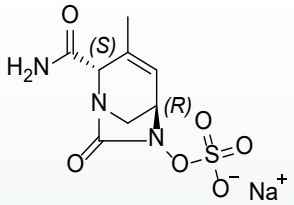
- ABC, identified by the WHO as a priority pathogen for the development of new antibiotics, is a group of closely related *Acinetobacter* species that cause serious infections associated with substantial mortality due to increasing resistance to existing therapies[1]
  - Carbapenem-resistant *A. baumannii* (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 mg/L; N = 4252 global clinical isolates)[3]

Durlobactam (ETX2514)



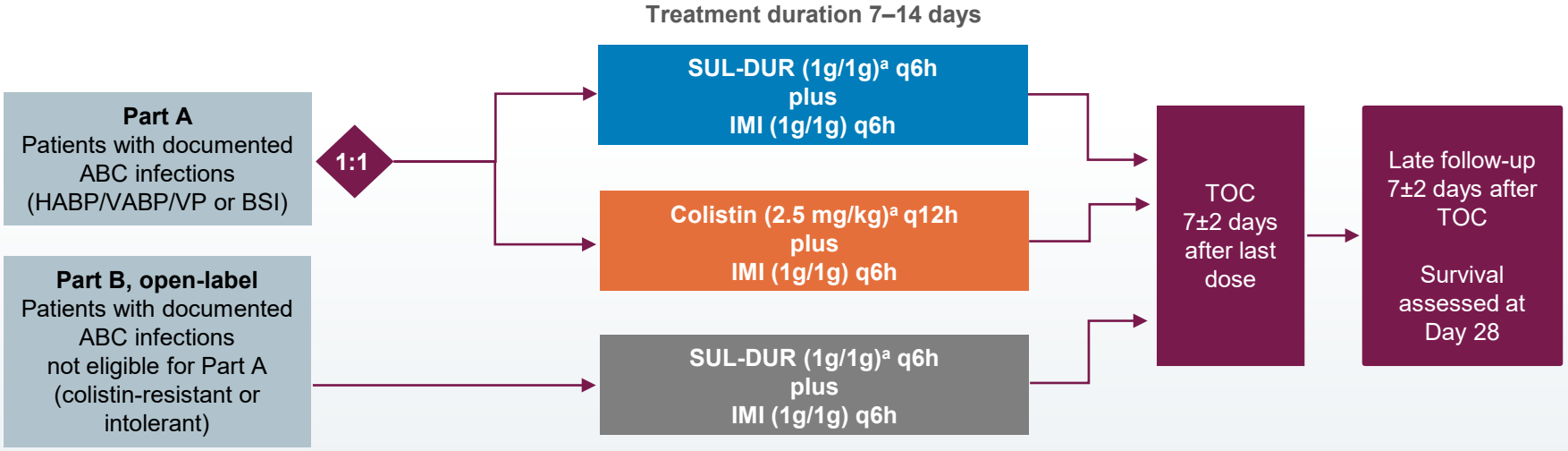
- Diazabicyclooctane β-lactamase inhibitor
- Potent inhibitor of class A, C, and D β-lactamases
- Restores sulbactam activity in vitro and in vivo

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

1. Antimicrobial Resistance Collaborators. *Lancet*. 2022;399:629-655. 2. Shapiro AB et al. *Front Microbiol*. 2021;12:709974. 3. Hackel M et al. Presented at ECCMID; April 23-26, 2022; Lisbon, Portugal. Abstract #01106.

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.

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 at TOC in the CRABC m-MITT population

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

Inclusion Criteria

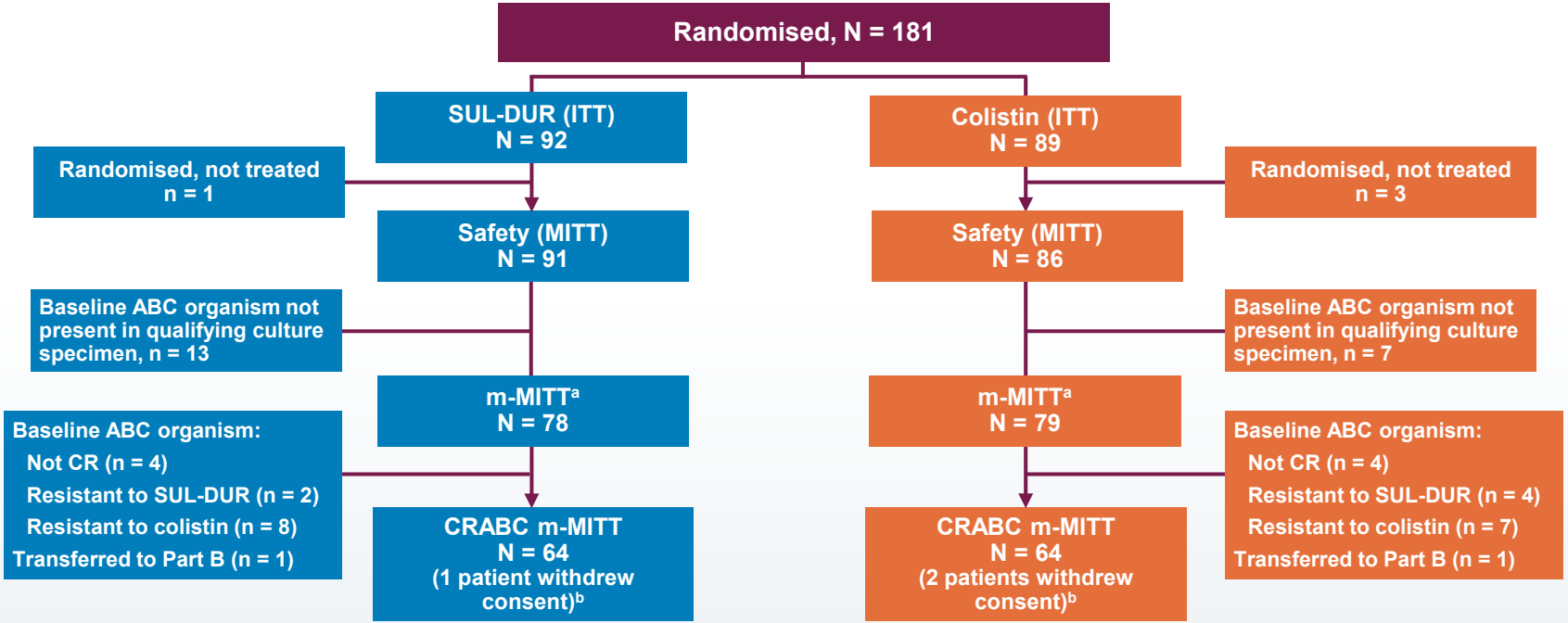
- Male or female adults (≥18 years old)
- APACHE II score 10–30 or SOFA score 1–11
- Diagnosed with HABP, VABP, VP, and/or BSI
- ABC in sputum/respiratory[a] or blood sample
- No more than 48 hours of potentially effective (ie, gram-negative) antimicrobial therapy before the first dose of study drug; 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.

Patient Disposition and Analysis Populations – Part A



Resistance rates for baseline ABC isolates (m-MITT) were 95% CR, 95% MDR [1], 84% XDR [1], and 15% PDR.

[a]The m-MITT population included patients with an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory.
[b]The primary efficacy analysis population (CRABC m-MITT) excluded patients who withdrew consent prior to obtaining survival status. Patients could have ≥1 reason for exclusion from the CRABC m-MITT population.
CR, carbapenem resistant; ITT, intent-to-treat; MDR, multidrug resistant; MITT, modified intent-to-treat; PDR, pan-drug resistant (defined as non-susceptible to all approved agents tested); XDR, extensively drug resistant.

1. Magiorakos A-P, et al. *Clin Microb Infect.* 2012;18:268-281.

Baseline Characteristics Generally Comparable Between Groups

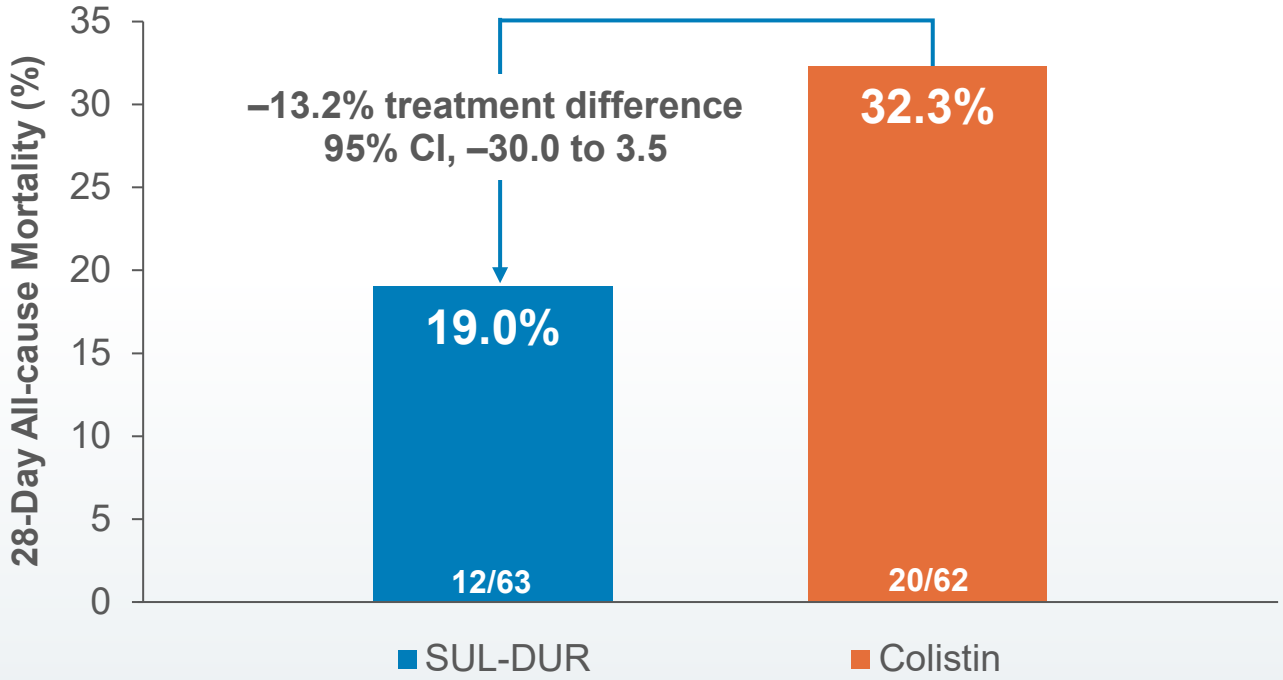
Most patients had HABP/VABP at baseline and severe illness

Baseline Demographic and Clinical Characteristics CRABC m-MITT Population	SUL-DUR N = 64	Colistin N = 64
Age, mean (SD), years	61.6 (16.1)	65.1 (17.0)
Age group, n (%)		
<65 years	36 (56.3)	31 (48.4)
65–75 years	16 (25.0)	12 (18.8)
>75 years	12 (18.8)	21 (32.8)
Male, n (%)	46 (71.9)	49 (76.6)
APACHE II score, mean (SD)[a]	16.4 (5.1)	17.2 (5.2)
Infection type, n (%)		
BSI	2 (3.1)	1 (1.6)
HABP	24 (37.5)	31 (48.4)
VABP	38 (59.4)	30 (46.9)
VP	0 (0)	2 (3.1)
Duration of ICU stay at randomisation, n (%)		
No ICU stay	21 (32.8)	19 (29.7)
<5 days	2 (3.1)	3 (4.7)
5–14 days	23 (35.9)	24 (37.5)
>14 days	18 (28.1)	18 (28.1)
Charlson Comorbidity Index, mean (SD)	4.6 (3.2)	4.8 (3.4)
Creatinine clearance <90 mL/min, n (%)	25 (39.1)	26 (40.6)

[a]Mean APACHE II scores were not available for all patients (SUL-DUR, n = 59; colistin, n = 57).
ICU, intensive care unit; SD, standard deviation.

Primary Efficacy Endpoint Achieved

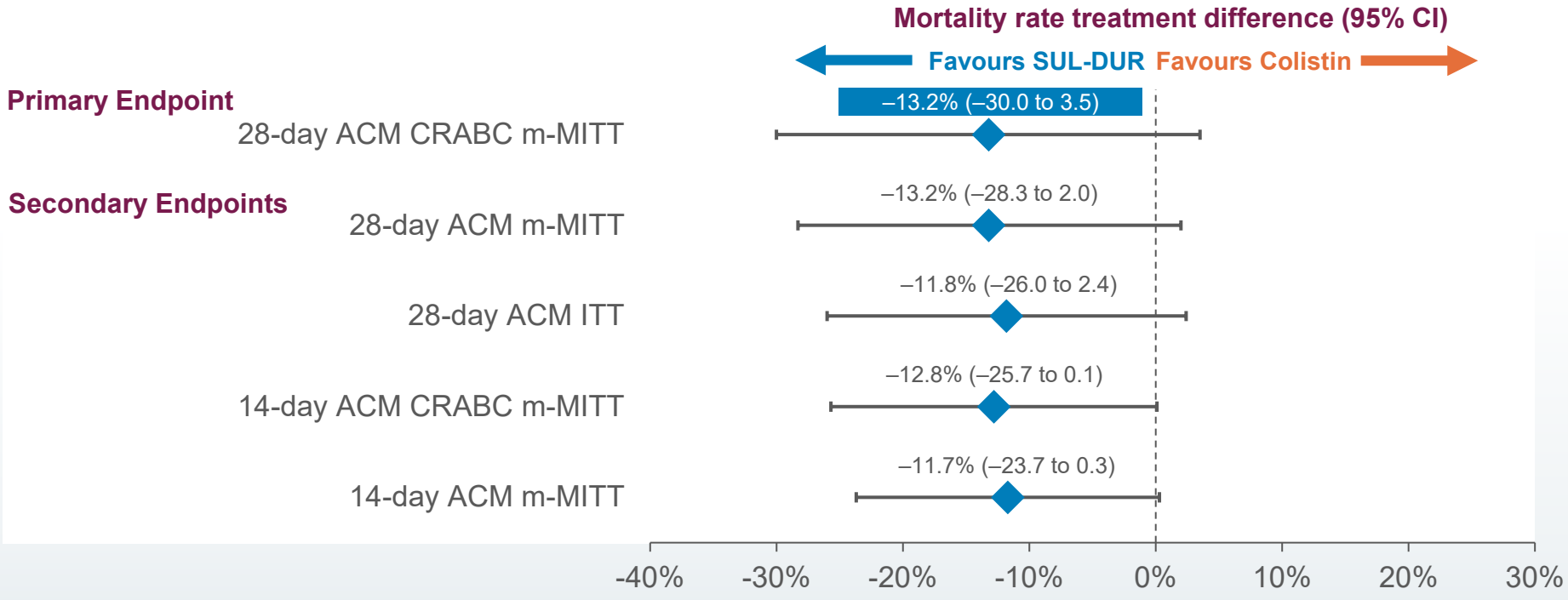
SUL-DUR noninferior on 28-day all-cause mortality vs colistin in the CRABC m-MITT population



Participants with missing survival status were treated as a death.
Noninferiority was concluded if the upper limit of the 2-sided 95% confidence interval (CI) was less than +20%.

All-cause Mortality Consistently Lower With SUL-DUR

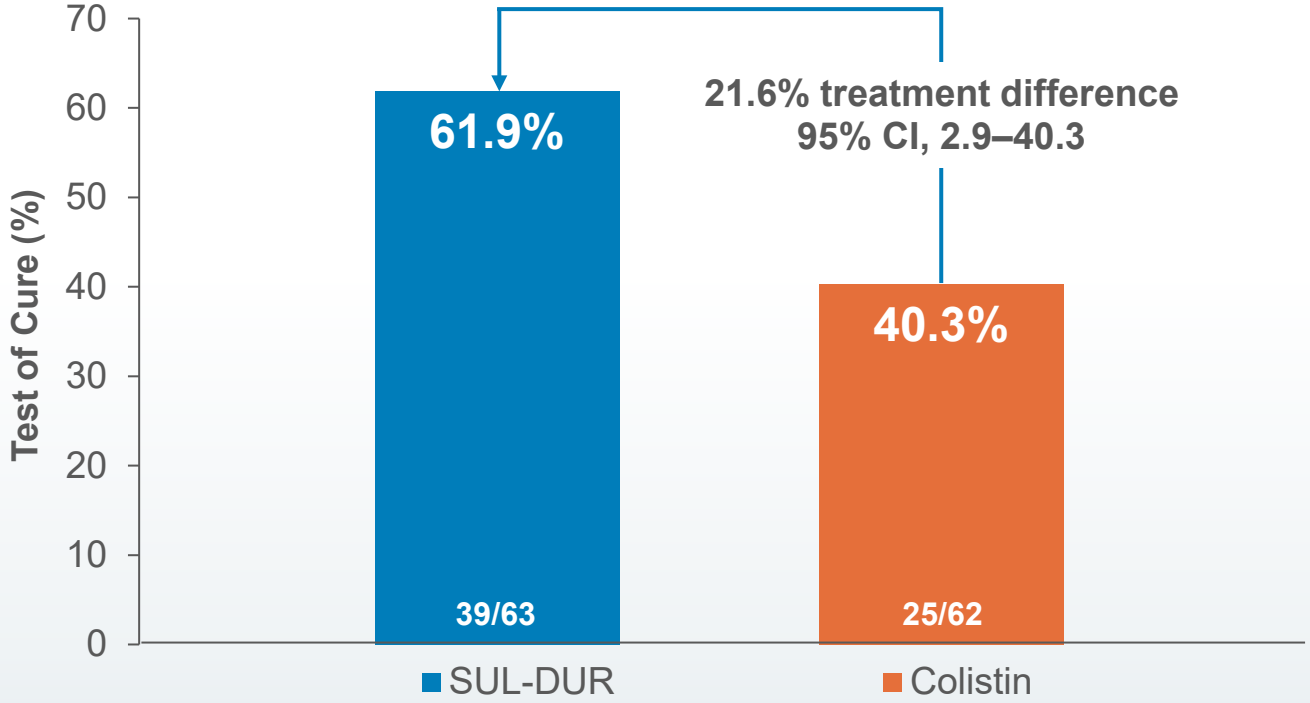
Mortality difference for SUL-DUR vs colistin was consistent across study populations and endpoints



ACM, all-cause mortality.

Statistically Significant Difference in Clinical Cure

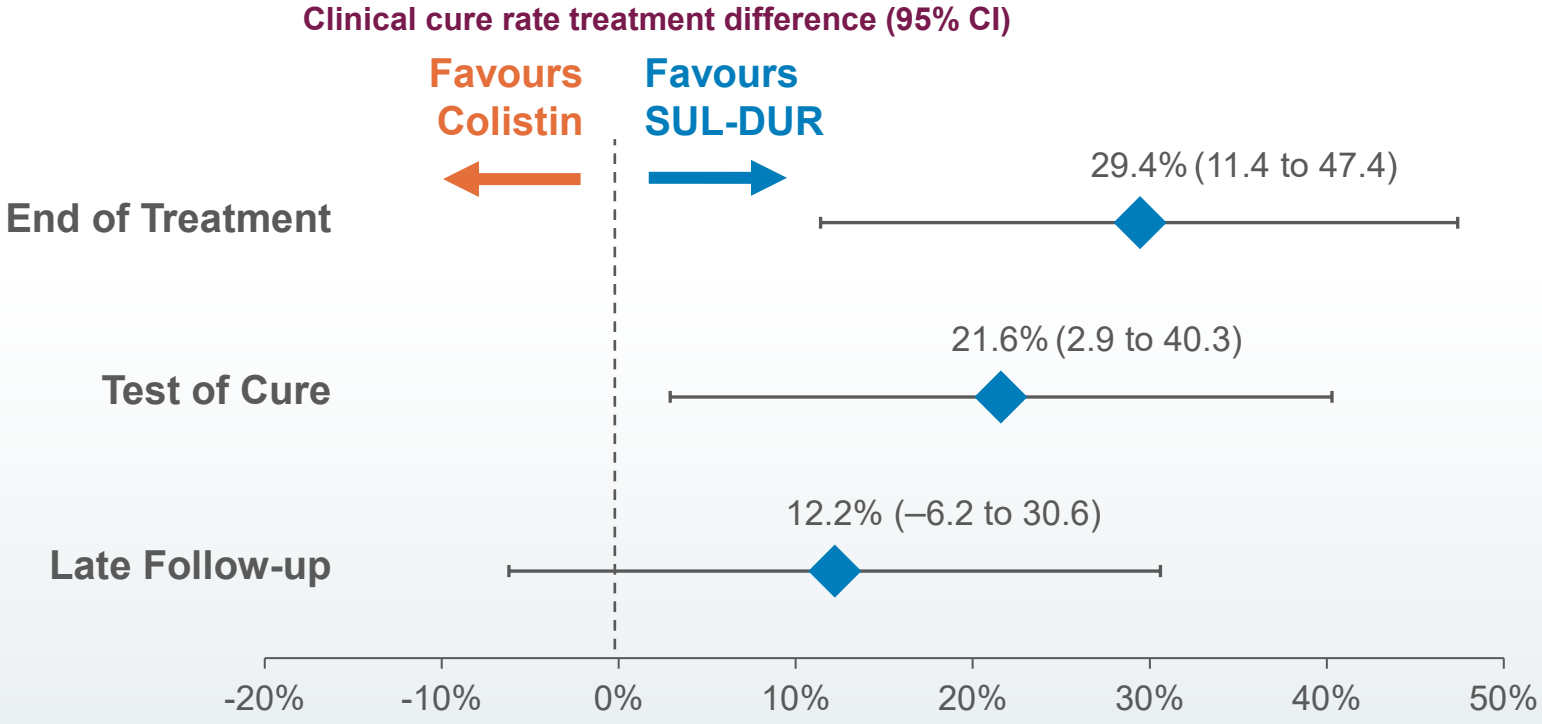
SUL-DUR vs colistin at test of cure in the CRABC m-MITT population



Test of cure was 7 ± 2 days after end of treatment.

Clinical Cure Rates Higher With SUL-DUR at All Measured Timepoints

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



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.

Safety Profile SUL-DUR vs Colistin

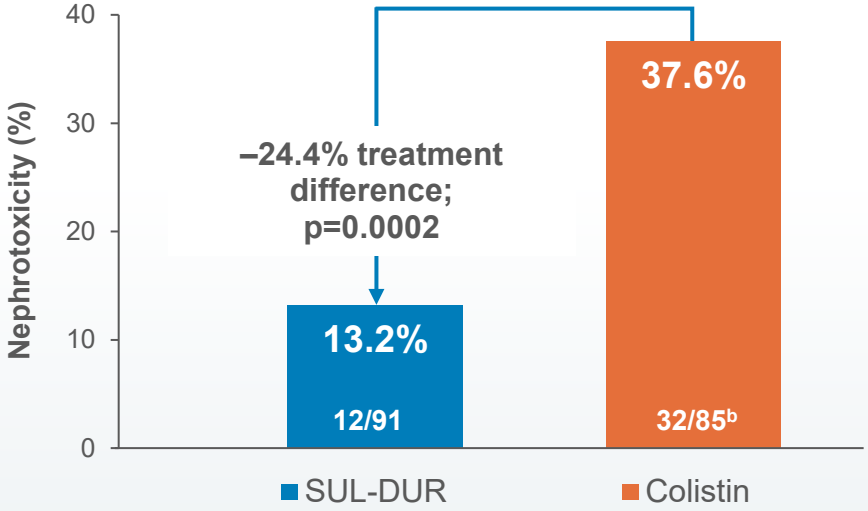
Fewer drug-related AEs, serious AEs, and AEs leading to discontinuation with SUL-DUR

n (%)	SUL-DUR N = 91	Colistin N = 86
Any AE	80 (87.9)	81 (94.2)
Drug-related AEs	11 (12.1)	26 (30.2)
>3% in any treatment group by SOC		
Infection and infestations	3 (3.3)	6 (7.0)
Renal and urinary disorders	0 (0)	8 (9.3)
Gastrointestinal disorders	2 (2.2)	4 (4.7)
Serious AEs	36 (39.6)	42 (48.8)
Drug-related serious AEs	1 (1.1)	2 (2.3)
Infections and infestations	1 (1.1)	2 (2.3)
AEs leading to study drug discontinuation	10 (11.0)[a]	14 (16.3)[b]
Serious AEs leading to study drug discontinuation	7 (7.7)	7 (8.1)

Safety population included patients who received at least 1 dose of study drug. Please see ECCMID abstract 02145 for additional safety data.
[a]Considered related to SUL-DUR: hypersensitivity, n = 1.
[b]Considered related to colistin: acute kidney injury, n = 2; rash, n = 1; seizure, n = 1.
SOC, system organ class.

Statistically Significant Reduction in Nephrotoxicity, Consistent With Lower Incidence of Renal/Urinary AEs

SUL-DUR vs colistin as measured by the RIFLE criteria[a] at any post-baseline visit



AEs n (%)	SUL-DUR N = 91	Colistin N = 86
Renal and urinary disorders	9 (9.9)	27 (31.4)
Mild	4 (4.4)	12 (14.0)
Moderate	4 (4.4)	8 (9.3)
Severe	1 (1.1)	7 (8.1)

Please see ECCMID abstract 02145 for additional safety data.

[a]RIFLE (risk, injury, failure, loss, or end-stage renal disease) measured by creatinine level or glomerular filtration rate, but not urinary output, per Hartzell JD, et al. *Clin Infect Dis*. 2009;48:1724–1728. Nephrotoxicity defined as meeting any of the RIFLE criteria at any post-baseline visit; if patients had multiple RIFLE events, the patient was counted only once at the highest severity. No patients in this study experienced end-stage renal disease.

[b]Nephrotoxicity analysis excluded 1 patient in the colistin group with chronic haemodialysis at baseline.

Conclusions

- 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

- Relative to the colistin-treated group, patients who received SUL-DUR had
  - Lower all-cause mortality at Day 28 (difference –13.2%) and Day 14 (difference –12.8%)
  - Significantly higher clinical cure rates at TOC (difference 21.6%)
  - Significantly reduced incidence of nephrotoxicity (difference –24.4%)

- If approved, SUL-DUR could be an important treatment option for infections caused by ABC including carbapenem-resistant and multidrug-resistant strains

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

SUL-DUR Presentations at ECCMID 2022

- **Abstract 02093:** Rana K, 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 02051:** Miller A, et al. Characterisation of *Acinetobacter baumannii-calcoaceticus* complex (ABC) pathogens isolated at baseline from patients enrolled in the ATTACK phase 3 trial.
- **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.
- **Abstract 02037:** O'Donnell J, et al. Sulbactam-durlobactam (SUL-DUR) in vitro dose response studies with and without imipenem or meropenem against carbapenemase-producing *Acinetobacter baumannii* utilizing the hollow-fiber infection model.
- **Abstract 01106:** Hackel M, et al. In vitro activity of sulbactam-durlobactam against *Acinetobacter baumannii-calcoaceticus* complex isolates from a five year surveillance program (2016-2020).