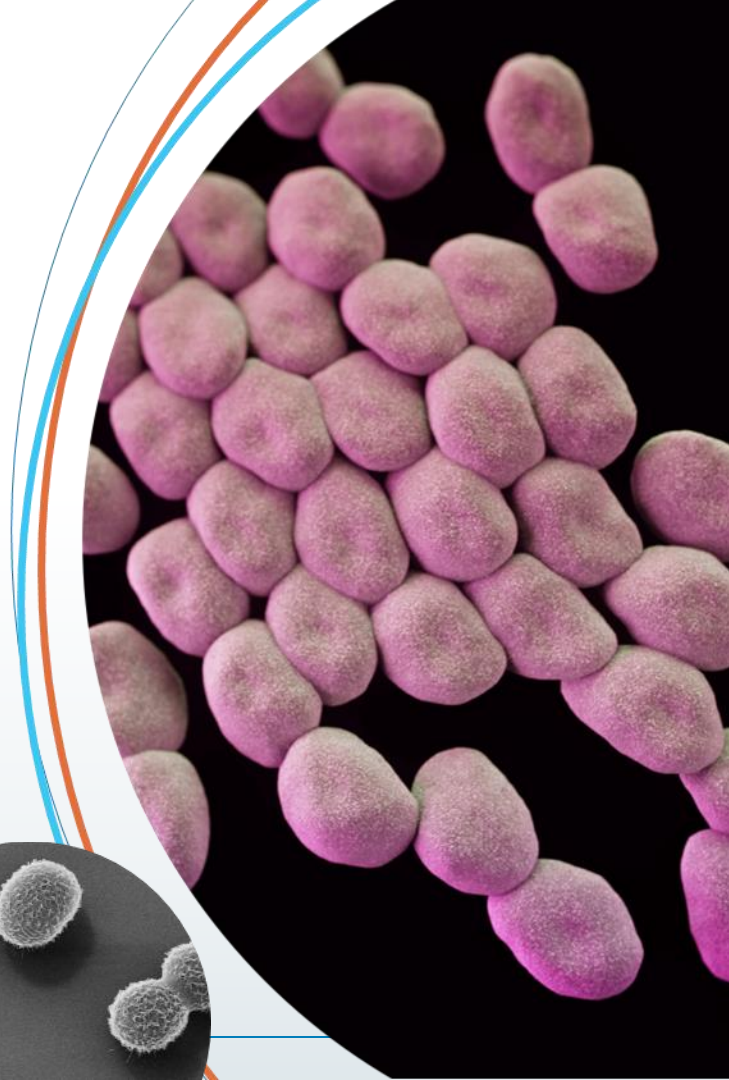# Administration of Sulbactam-Durlobactam

ICD-10-PCS Coordination & Maintenance Committee Meeting

# Sulbactam-Durlobactam (SUL-DUR) Indication and How It Works

Sulbactam-durlobactam is a pathogen-targeted β-lactam/β-lactamase inhibitor combination being developed for the treatment of infections caused by *Acinetobacter baumannii-calcoaceticus* complex (ABC), including carbapenem-resistant and multidrug-resistant isolates.

**Naming Convention:**

| Non-proprietary name: Sulbactam-Durlobactam | Proprietary name: SUL-DUR |
|---|---|

**How it works:**

- Sulbactam is a penicillin derivative and is used widely as an inhibitor of a subset of Ambler Class A β-lactamases. In addition to its β-lactamase inhibitor activity, sulbactam also has antibacterial activity against a limited number of bacterial species, including *Acinetobacter* spp.

- Sulbactam itself is a substrate for many β-lactamases encoded by *Acinetobacter* spp., including Class D (OXA) carbapenemases, and therefore its clinical utility has been eroded in recent decades.

- Durlobactam (ETX2514) is a diazabicyclooctane (DBO) β-lactamase inhibitor with broad-spectrum activity against Ambler Classes A, C, and D serine β-lactamases, but it has no activity against Class B metallo-β-lactamases.

- Durlobactam effectively restores sulbactam activity against ABC organisms due to its potent inhibition of serine β-lactamases.

Source: Entasis Therapeutics SUL-DUR Draft Prescribing Information, 2022.

# SUL-DUR Preparation and Administration

**Upon Food and Drug Administration (FDA) approval, SUL-DUR will be administered via IV Infusion with the recommended dose of:**

- 1 g sulbactam and 1 g durlobactam every 6 hours by intravenous (IV) infusion over 3 hours in adults with a creatinine clearance (CLcr) of 45 to 129 mL/min.

- Adjustments to the dosing regimen for SUL-DUR are recommended for patients with CLcr <45 mL/min.

- A higher dose of SUL-DUR (1.5 g sulbactam/1.5 g durlobactam every 6 hours) is recommended for patients with CLcr ≥130 mL/min.

## SUL-DUR Preparation and Procedural Steps to Administration

- The prepared solution should be brought to ambient room temperature (over 15-30 min) prior to infusion to the patient. All doses of SUL-DUR should be administered by IV infusion over 3 hours.
- SUL-DUR is supplied in 3-vials that contain sterile powders that must be reconstituted and further diluted using aseptic technique prior to intravenous infusion. SUL-DUR does not contain a bacteriostatic preservative and the prepared solution must be used within 24 hours. Discard unused portion.

1. Reconstitute the sulbactam vial with 5 mL of sterile water for injection and gently shake to dissolve. Each reconstituted vial contains 1 g of sulbactam per 5.0 mL of clear, colorless to slightly yellow solution. Use reconstituted solution immediately.
2. Reconstitute each durlobactam vial with 2.5 mL of sterile water for injection and gently shake to dissolve. Each reconstituted vial contains 0.5 g of durlobactam per 2.5 mL of clear, light yellow to orange solution. Use reconstituted solution immediately.
3. To prepare the required SUL-DUR dose, withdraw the appropriate reconstituted volume of sulbactam and durlobactam determined from the dosing table. Add the withdrawn volume of both sulbactam and durlobactam to a 100 mL infusion bag of 0.9% Sodium Chloride for Injection, USP. Discard unused portion.

> It is estimated that at least 99% of SUL-DUR utilization will be in the Inpatient setting and documentation of administration would be found in the Progress Notes and medication administration record (MAR).

Source: Entasis Therapeutics SUL-DUR Draft Prescribing Information, 2022; SUL-DUR: sulbactam-durlobactam

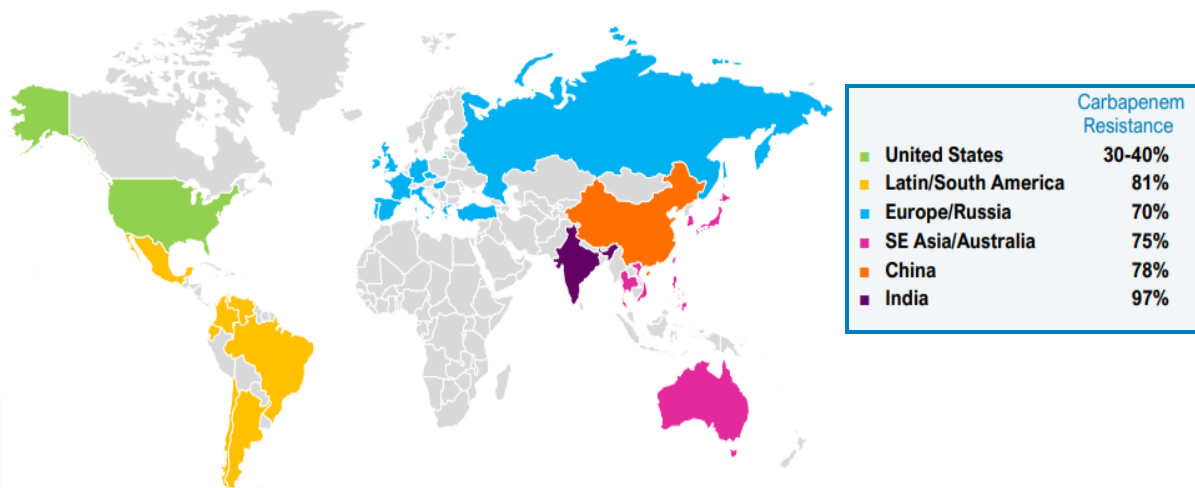# SUL-DUR Treats Many Infectious Conditions Caused by *Acinetobacter Baumannii-Calcoaceticus* Complex (ABC)

## Conditions Commonly Associated With carbapenem- resistant *Acinetobacter baumannii* (CRAB)

| ICD-10-CM | Description |
|-----------|-------------|
| T80.211A | Bloodstream infection due to central venous catheter, initial encounter |
| T83.511A | Infection and inflammatory reaction due to indwelling urethral catheter, initial encounter |
| T83.518A | Infection and inflammatory reaction due to other urinary catheter, initial encounter |
| R78.81 | Bacteremia |
| N39.0 | Urinary tract infection, site not specified |
| N10 | Acute pyelonephritis |
| J95.851 | Ventilator associated pneumonia |
| J15.8 | Pneumonia due to other specified bacteria |
| J15.6 | Pneumonia due to other Gram-negative bacteria |
| J18.8 | Other pneumonia, unspecified organism |
| J18.0 | Bronchopneumonia, unspecified organism |
| Z16.19 | Resistance to other specified beta lactam antibiotics |

SUL-DUR: sulbactam-durlobactam

# Unmet, Urgent and Significant Medical Need

Sulbactam-durlobactam: An opportunity for Patients and HCP

| | Carbapenem Resistance |
|---|---|
| United States | 30-40% |
| Latin/South America | 81% |
| Europe/Russia | 70% |
| SE Asia/Australia | 75% |
| China | 78% |
| India | 97% |

*Clinical Infectious Diseases*

**IDSA GUIDELINE**

IDSA — Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

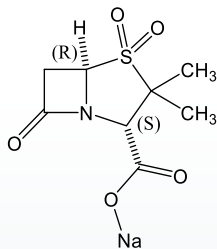**"…there is no clear 'standard of care' antibiotic regimen for CRAB infections…"**

*Sources: Chung DR, et al; Asian Network for Surveillance of Resistant Pathogens Study Group. *Am J Respir Crit Care Med.* 2011;184:1409-1417. CARSS (China Antimicrobial Resistance Surveillance system), 2017 Annual Report. Data on file. Entasis Therapeutics

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# SUL-DUR: A β-Lactam/β-Lactamase Inhibitor Combination in Development for Treatment of Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex
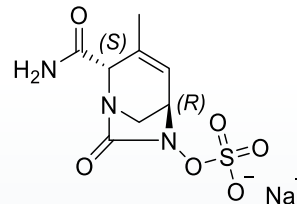
► The *Acinetobacter baumannii-calcoaceticus* (ABC) complex is a group of closely related *Acinetobacter* species that cause serious infections associated with substantial mortality

**Sulbactam**



**Durlobactam (ETX2514)**



► Penicillin derivative with intrinsic activity against ABC

► Clinically used as a β-lactamase inhibitor, often in combination with cefoperazone or ampicillin

► β-lactamase–mediated resistance is common[2] ($MIC_{90}$ = 64 µg/mL; N = 5,032 global clinical isolates[3])
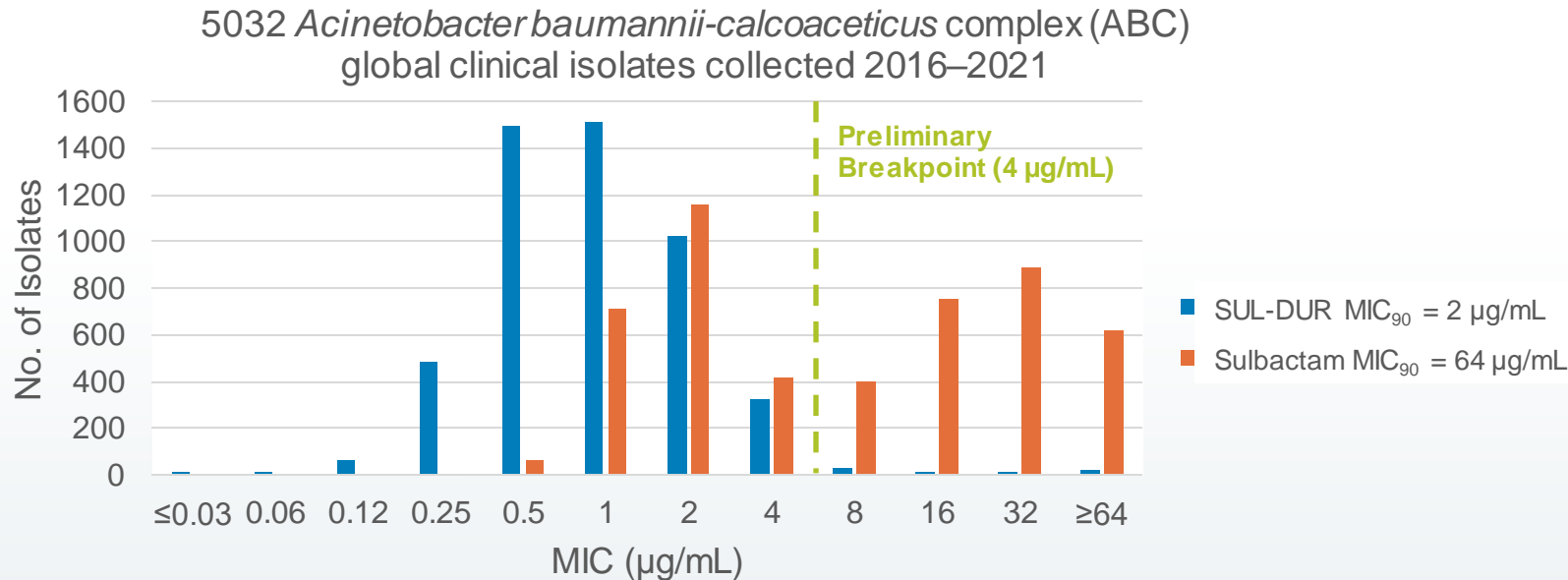
► Diazabicyclooctane β-lactamase inhibitor[1]

► 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. Noguchi JK and Gil MA. *Clin Pharm.* 1988; 7(1):37-51  2. Karlow sky JA et al. *AAC* 2022;e007812  3. Durand-Reville TF et al. *Nat Microbiol* 2017; 2:17104.

# Durlobactam Restores Sulbactam Activity in Vitro

Global surveillance conducted from 2016 to 2021



5032 *Acinetobacter baumannii-calcoaceticus* complex (ABC) global clinical isolates collected 2016–2021

Preliminary Breakpoint (4 µg/mL)

- SUL-DUR $MIC_{90}$ = 2 µg/mL
- Sulbactam $MIC_{90}$ = 64 µg/mL

98.3% of isolates had a SUL-DUR MIC ≤4 µg/mL

Karlowsky JA, et al. Antimicrob Agents Chemother. 2022;e007812; SUL-DUR: sulbactam-durlobactam; $MIC_{90}$, minimum inhibitory concentration

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# Sulbactam-Durlobactam Clinical Development

Eight clinical studies were conducted for this pathogen-focused clinical program

## Phase 1

1. CS2514-2016-0001
   - FIH: SAD, MAD, DDI
2. CS2514-2017-0001
   - Lung penetration
3. CS2514-2017-0002
   - Renal Impairment
4. CS2514-2018-0002
   - Human ADME
5. ZL-2402-001
   - China PK
6. CS2514-2018-0003
   - TQT

## Phase 2

- Primary Objective was safety
  - Favorable safety profile in cUTI patients
- PK was consistent with Phase 1 data
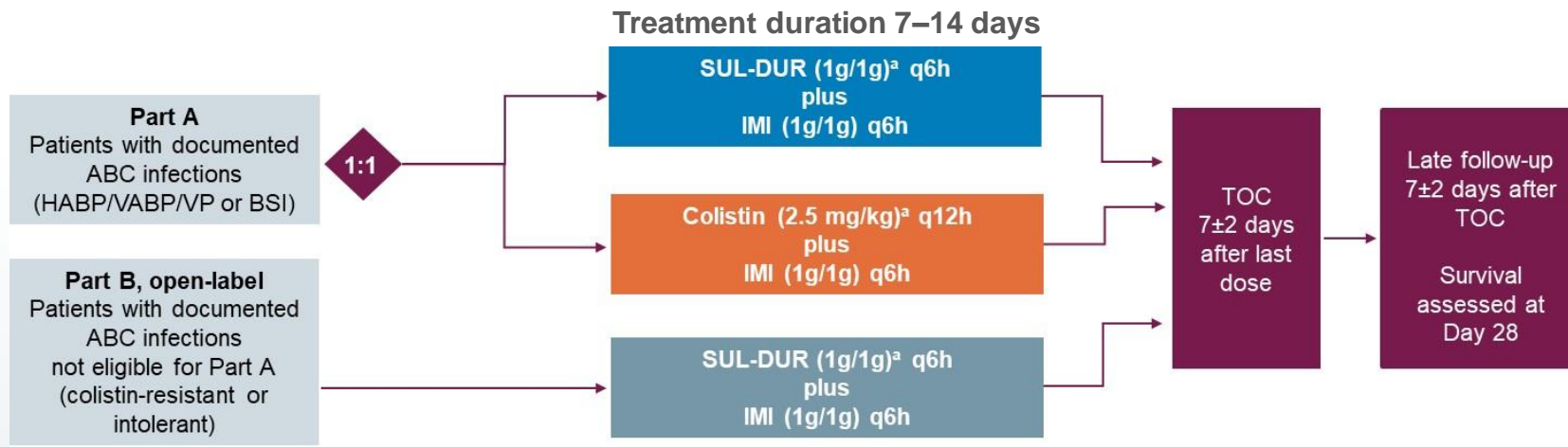- Secondary Objective was efficacy

## Phase 3

- Primary efficacy endpoint achieved
  - Secondary ACM endpoints similar to primary ACM
- Primary safety objective achieved
  - Additional safety analyses reinforces overall safety profile

**This pathogen-focused clinical program followed the FDA guidance document *Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases* and FDA discussions.**

Abbreviations: cUTI: complicated Urinary Tract Infection; FDA: Food and Drug Administration; PK: pharmacokinetics; QIDP: qualified infectious disease product; SUL-DUR: sulbactam-durlobactam; FIH: First in human; SAD: Single ascending dose; MAD: Multiple ascending dose; DDI: Drug-drug interactions; ADME: Absorption, distribution, metabolism, excretion; TQT: Thorough QT study; ACM: All-cause mortality

# Phase 3 Pivotal Trial: 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 carbapenem-resistant strains (CRABC)



**Treatment duration 7–14 days**

**Part A**
Patients with documented ABC infections (HABP/VABP/VP or BSI)

**1:1**

**Part B, open-label**
Patients with documented ABC infections not eligible for Part A (colistin-resistant or intolerant)

SUL-DUR (1g/1g)[a] q6h plus IMI (1g/1g) q6h

Colistin (2.5 mg/kg)[a] q12h plus IMI (1g/1g) q6h

SUL-DUR (1g/1g)[a] q6h plus IMI (1g/1g) q6h

TOC 7±2 days after last dose

Late follow-up 7±2 days after TOC

Survival assessed at Day 28

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; ATTACK: *Acinetobacter* Treatment Trial Against
Colistin; ABC: *Acinetobacter baumannii-calcoaceticus* complex; SUL-DUR: sulbactam-durlobactam

# ATTACK Was Conducted From September 5, 2019, to July 26, 2021
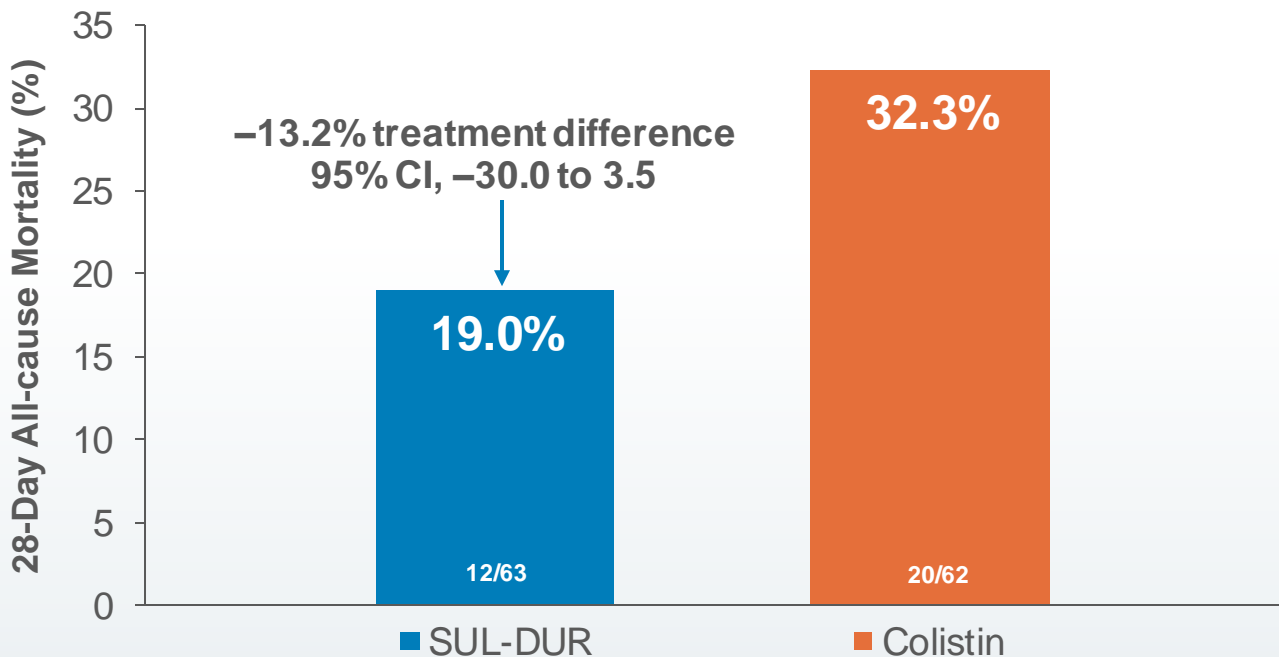
71 clinical sites screened patients
59 clinical sites randomized/enrolled patients in 16 countries



This trial is registered at ClinicalTrials.gov: NCT03894046

# The Primary Endpoint Was Achieved: The Results of ATTACK Clinical Trial Showed SUL-DUR Noninferiority Vs Colistin
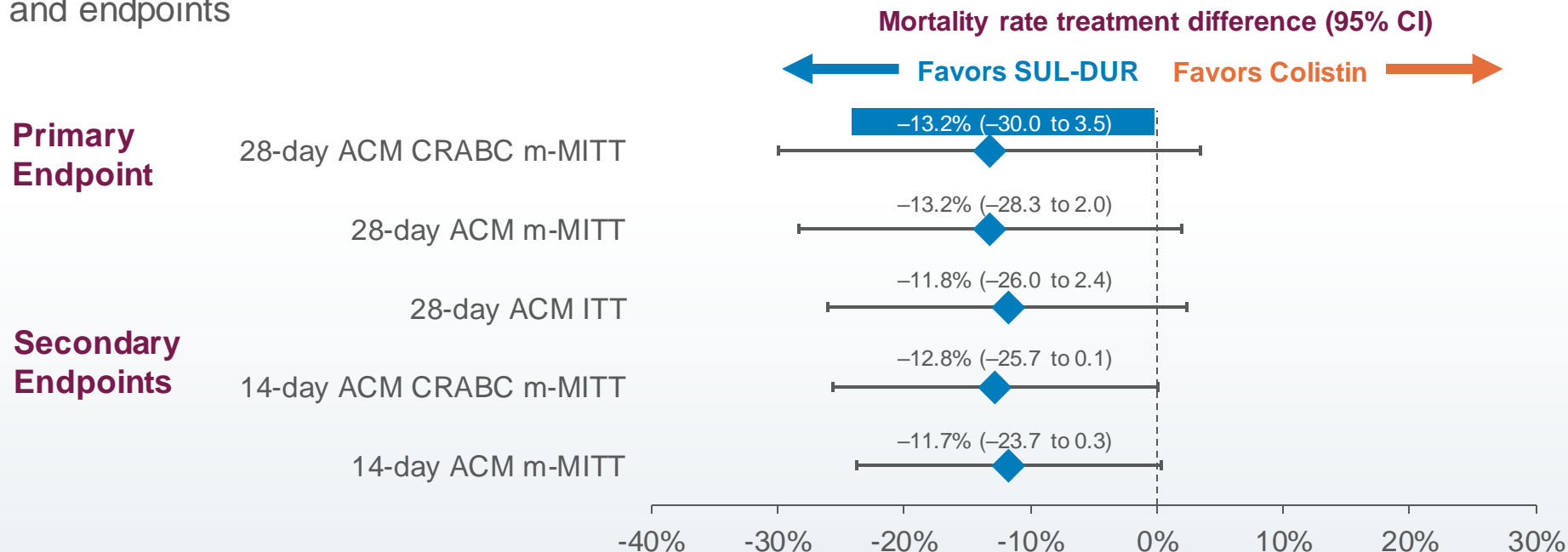
SUL-DUR noninferior on 28-day all-cause mortality vs colistin in the CRABC m-MITT population



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%.
*CRABC m-MITT: Carbapenem-resistant Acinetobacter baumannii-calcoaceticus Complex Microbiologically Modified Intent-to-Treat Population*
David Altarac et al; Microbiologic and clinical outcome concordance in the global phase 3 ATTACK trial: sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections, Oral presentation at IDWeek2022, Washington D.C.

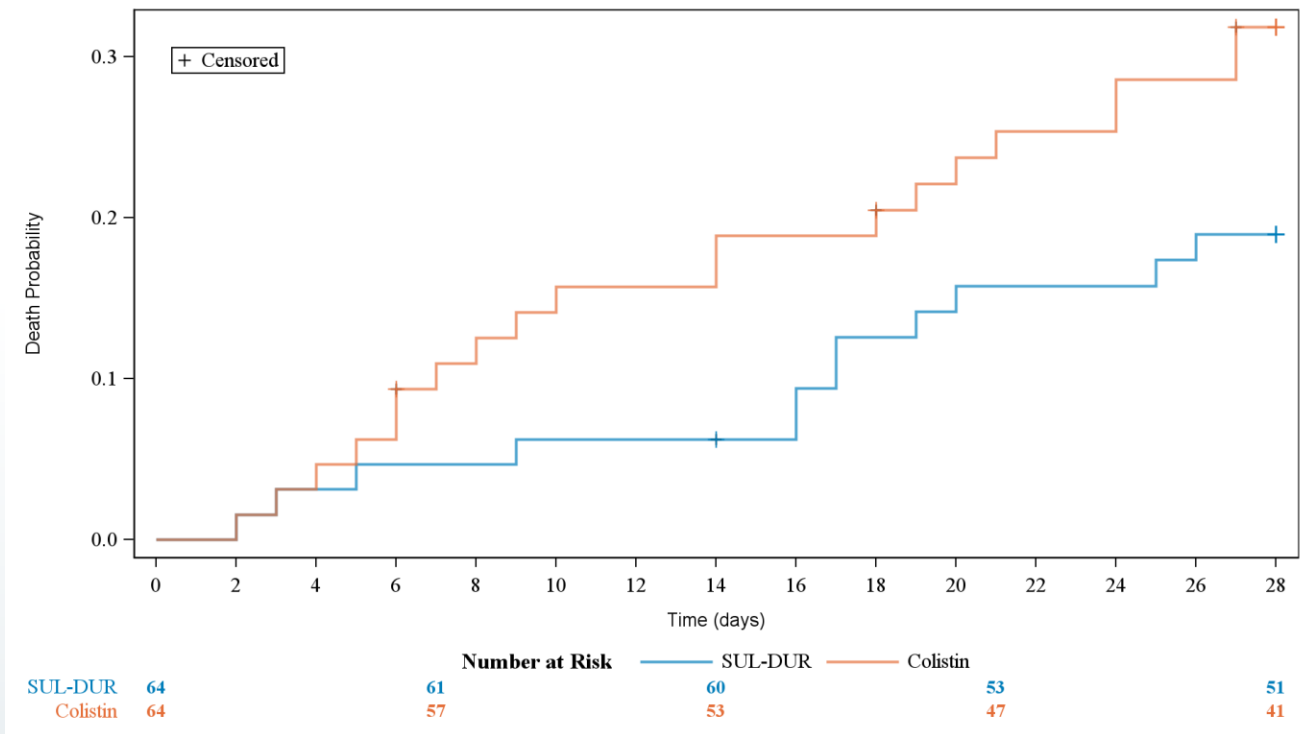# ATTACK Clinical Trial Results Showed Lower All-Cause Mortality Rates for Each Treatment Group

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

**Mortality rate treatment difference (95% CI)**

← **Favors SUL-DUR**   **Favors Colistin** →

**Primary Endpoint**

28-day ACM CRABC m-MITT — −13.2% (−30.0 to 3.5)

28-day ACM m-MITT — −13.2% (−28.3 to 2.0)

28-day ACM ITT — −11.8% (−26.0 to 2.4)

**Secondary Endpoints**

14-day ACM CRABC m-MITT — −12.8% (−25.7 to 0.1)

14-day ACM m-MITT — −11.7% (−23.7 to 0.3)

-40%   -30%   -20%   -10%   0%   10%   20%   30%

David Altarac, Alita Miller, Sarah McLeod, Adam Shapiro, Khurram Rana, Drew Lewis, Gabrielle Poirier, and Daria Chabas; Microbiologic and clinical outcome concordance in the global phase 3 ATTACK trial: sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections, Oral presentation at IDWeek2022, Washington D.C.; ACM: All-cause mortality; *CRABC m-MITT: Carbapenem-resistant Acinetobacter baumannii-calcoaceticus Complex Microbiologically Modified Intent-to-Treat Population*

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# All-Cause Mortality Consistently Lower with SUL-DUR

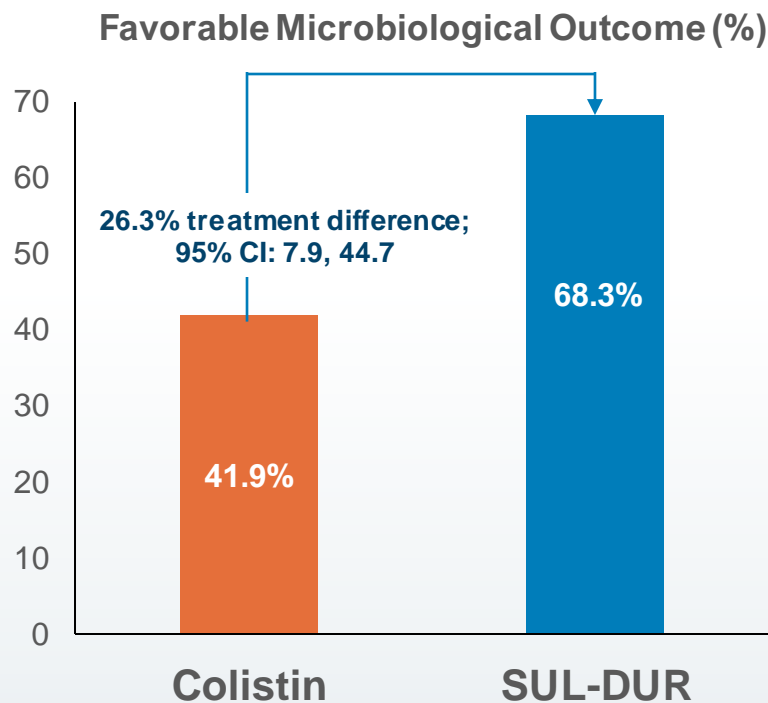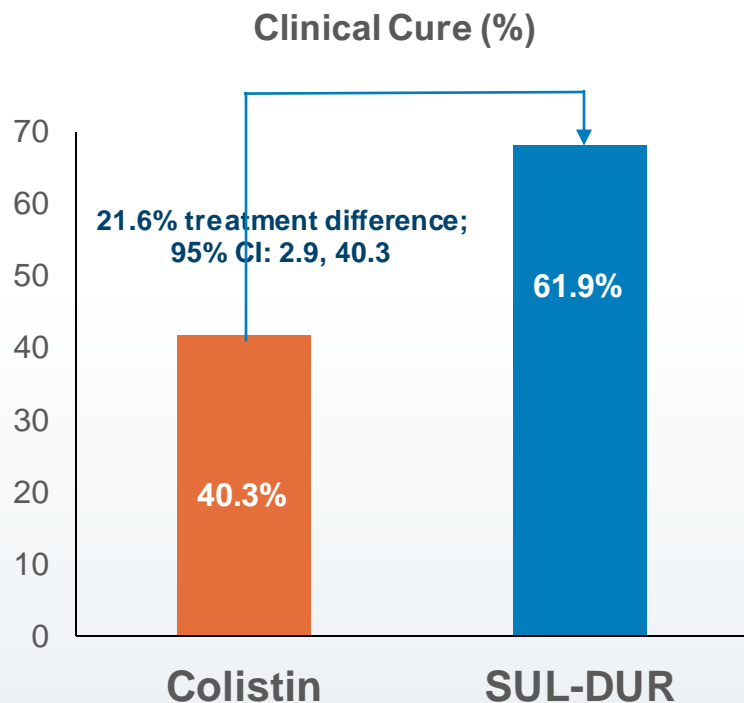Reduced mortality over time with SUL-DUR treatment in the CRABC m-MITT population

David Altarac et al: Microbiologic and clinical outcome concordance in the global phase 3 ATTACK trial: sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections, Oral presentation at IDWeek2022, Washington D.C.; SUL-DUR: sulbactam-durlobactam; *CRABC m-MITT: Carbapenem-resistant Acinetobacter baumannii-calcoaceticus Complex Microbiologically Modified Intent-to-Treat Population*

# Concordance of Clinical Cure and Microbiological Outcome

SUL-DUR compared to colistin at Test of Cure



**Clinical Cure (%)**

21.6% treatment difference;
95% CI: 2.9, 40.3

Colistin: 40.3%
SUL-DUR: 61.9%

**Favorable Microbiological Outcome (%)**

26.3% treatment difference;
95% CI: 7.9, 44.7

Colistin: 41.9%
SUL-DUR: 68.3%

David Altarac; Microbiologic and clinical outcome concordance in the global phase 3 ATTACK trial: sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections, Oral presentation at IDWeek2022, Washington D.C.

# Favorable Safety Profile With SUL-DUR

Part B profile supportive of favorable safety observed in Part A

| Category | PART A SUL-DUR + IMI (N=91) n (%) | PART A Colistin + IMI (N=86) n (%) | PART B SUL-DUR + IMI (N=28) n (%) |
|---|---|---|---|
| Drug-Related TEAEs | 11 (12.1) | 26 (30.2) | 3 (10.7) |
| Drug-Related Serious AEs | 1 (1.1) | 2 (2.3) | 1 (3.6) |
| TEAEs Leading to Discontinuation of Study Drug | 10 (11.0) | 14 (16.3) | 4 (14.3) |
| Serious TEAEs Leading to Discontinuation of Study Drug | 7 (7.7) | 7 (8.1) | 3 (10.7) |

**The most common adverse reaction reported in more than one patient (>2% of patients) treated with SUL-DUR was diarrhea, which was reported in 4/91 (4.4%) of patients treated with SUL-DUR.**

Part A: Patients with documented ABC infections (HABP/VABP/VP or BSI)
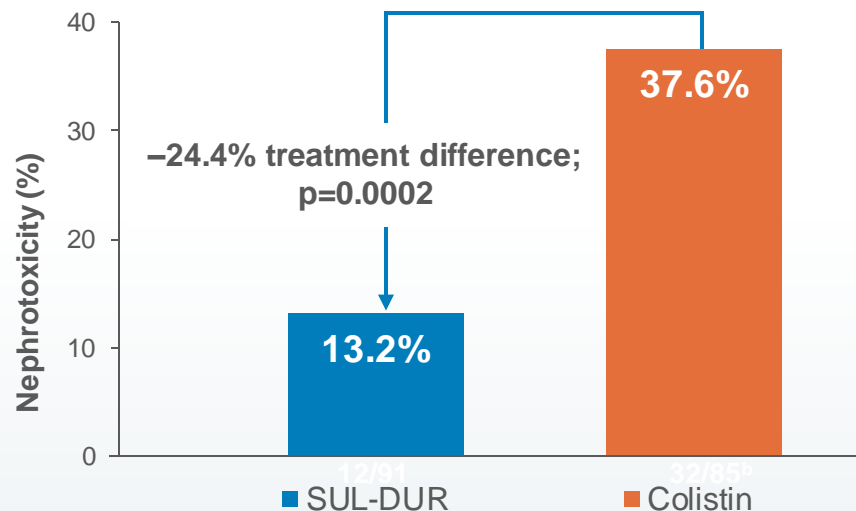Part B: Patients with documented ABC infections not eligible for Part A (colistin-resistant or intolerant)
45% of participants in the ATTACK trial were age 65 and older
SUL-DUR: sulbactam-durlobactam; IMI: imipenem/cilastatin; TEAE: Treatment Emergent Adverse Events; AE: Adverse Event; HABP: hospital-acquired bacterial pneumonia; ABC: *Acinetobacter baumannii-calcoaceticus* complex; VABP: ventilator-associated bacterial pneumonia; VP: ventilator pneumonia; BSI: bloodstream infection

# 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) |

[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 hemodialysis at baseline. David Altarac, Alita Miller, Sarah McLeod, Adam Shapiro, Khurram Rana, Drew Lewis, Gabrielle Poirier, and Daria Chabas; Microbiologic and clinical outcome concordance in the global phase 3 ATTACK trial: sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections, Oral presentation at IDWeek2022, Washington D.C.; AE: Adverse Event

# Conclusions From Pivotal Phase 3 ATTACK Trial

► 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 higher microbiological response at TOC (difference of 26.3%)

  • Significantly reduced incidence of nephrotoxicity (difference –24.4%)

  • Fewer drug-related AEs, serious AEs, and AEs leading to discontinuation

► Results from observational cohort supportive of the efficacy and safety of SUL-DUR in patients with colistin- or polymyxin B-resistant ABC infections

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

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