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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Presented at 32nd ECCMID, 23–26 April 2022, Lisbon, Portugal
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.
- Zai Labs, China, provided financial and operational support for the ATTACK trial in China.
- Editorial assistance for this presentation was provided by Stacey Human and Jean Turner of Parexel, and was funded by Entasis Therapeutics.
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 therapies¹
  - Carbapenem-resistant *A. baumannii* (CRABC) is the fourth leading cause of death attributable to antimicrobial resistance globally¹

![Chemical structures of Sulbactam and Durlobactam](image)

- Penicillin derivative with intrinsic activity against ABC
- β-lactamase–mediated resistance is common² (MIC₉₀ 64 mg/L; N = 4252 global clinical isolates)³
  - Diazabicyclooctane β-lactamase inhibitor
  - Potent inhibitor of class A, C, and D β-lactamas
  - Restores sulbactam activity in vitro and in vivo

MIC₉₀, minimum inhibitory concentration that inhibits 90% of the microbial strains; SUL-DUR, sulbactam-durlobactam, WHO, World Health Organization.
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.

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

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

Treatment duration 7–14 days

- **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

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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.

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

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.

**Baseline Characteristics Generally Comparable Between Groups**

Most patients had HABP/VABP at baseline and severe illness

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

*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%.

-13.2% treatment difference
95% CI, –30.0 to 3.5

28-Day All-cause Mortality (%)

- SUL-DUR: 12/63 (19.0%)
- Colistin: 20/62 (32.3%)

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.

Primary Endpoint
28-day ACM CRABC m-MITT

Secondary Endpoints
28-day ACM m-MITT
28-day ACM ITT
14-day ACM CRABC m-MITT
14-day ACM m-MITT

Mortality rate treatment difference (95% CI)

-13.2% (-30.0 to 3.5) Favours SUL-DUR
-13.2% (-28.3 to 2.0)
-11.8% (-26.0 to 2.4)
-12.8% (-25.7 to 0.1)
-11.7% (-23.7 to 0.3)

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

<table>
<thead>
<tr>
<th></th>
<th>SUL-DUR N = 91</th>
<th>Colistin N = 86</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE</strong></td>
<td>80 (87.9)</td>
<td>81 (94.2)</td>
</tr>
<tr>
<td><strong>Drug-related AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3% in any treatment group by SOC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection and infestations</td>
<td>11 (12.1)</td>
<td>26 (30.2)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (3.3)</td>
<td>6 (7.0)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2 (2.2)</td>
<td>8 (9.3)</td>
</tr>
<tr>
<td><strong>Serious AEs</strong></td>
<td>36 (39.6)</td>
<td>42 (48.8)</td>
</tr>
<tr>
<td><strong>Drug-related serious AEs</strong></td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td><strong>AEs leading to study drug discontinuation</strong></td>
<td>10 (11.0)(^a)</td>
<td>14 (16.3)(^b)</td>
</tr>
<tr>
<td><strong>Serious AEs leading to study drug discontinuation</strong></td>
<td>7 (7.7)</td>
<td>7 (8.1)</td>
</tr>
</tbody>
</table>

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

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 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.