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Safety Profile of Sulbactam-Durlobactam (SUL-DUR) versus Colistin Therapy in Patients with *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Infections from The Phase III, Global, Randomized, Active-Controlled Trial (ATTACK)

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Abstract

Background: SUL-DUR is a β-lactam/β-lactamase inhibitor combination in development for the treatment of ABC, a cause of severe infections associated with substantial mortality. ATTACK was conducted to evaluate the efficacy and safety of SUL-DUR versus colistin, both in combination with imipenem/cilastatin, for patients with serious ABC infections, including multidrug-resistant strains.

Methods: The ATTACK trial was a 2-part trial. Part A was a randomized, assessor blinded, non-inferiority study in ABC hospital-acquired pneumonia, ventilator-associated bacterial pneumonia, ventilated pneumonia, or bacteremia that randomized patients 1:1 to SUL-DUR (1g/1g over 3 h q6h) or colistin (2.5mg/kg over 30 minutes q12h) for 7 to 14 days. Part B enrolled patients with ABC infections who did not tolerate colistin/polymyxin B or whose pathogens were resistant to colistin/polymyxin B and received open label SUL-DUR. All subjects received imipenem/cilastatin (1g/1g over 1 h q6h) as background therapy. Safety endpoints included treatment-emergent adverse events (TEAEs) occurring or worsening after treatment was initiated and a primary safety objective of nephrotoxicity as assessed by the RIFLE classification.
β-lactamase inhibitor
Results: 207 patients were randomized/enrolled in both parts of the trial. Overall summary and common TEAEs are presented in Table 1. Nephrotoxicity (RIFLE classification) occurred significantly less often with SUL-DUR: 13.2% (12/91) and 37.6% (32/85), difference -24.4% [p=0.0002].

Table 1. Overall Summary of Treatment-Emergent Adverse Events (TEAEs)

Category	PART A SUL-DUR + IMI (N=91) n (%)	PART A Colistin + IMI (N=86) n (%)	PART B SUL-DUR + IMI (N=28) n (%)
Any TEAEs	80 (87.9)	81 (94.2)	24 (85.7)
Drug-related TEAEs	11 (12.1)	26 (30.2)	3 (10.7)
Serious AEs	36 (39.6)	42 (48.8)	9 (32.1)
Drug-related serious AEs	1 (1.1)	2 (2.3)	1 (3.6)
Serious AEs leading to death	24 (26.4)	30 (34.9)	4 (14.3)
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)

Conclusions: In patients with serious ABC infection, SUL-DUR demonstrated a favorable safety profile, significantly reduced incidence of nephrotoxicity compared to colistin, and was generally well-tolerated; no new safety signals were identified.

Introduction

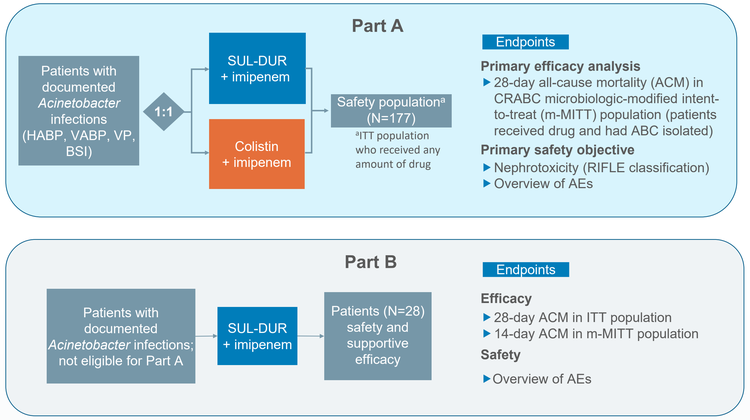
The Gram-negative *Acinetobacter baumannii-calcoaceticus* complex (ABC) have emerged as serious pathogens[1]. The ABC complex includes *A. baumannii*, *A. nosocomialis*, *A. pittii* and *A. calcoaceticus*. *A. baumannii* is considered the most clinically important species of the complex due to its association with nosocomial outbreaks. Globally, the susceptibility of ABC to all antimicrobial agents has declined over the last 20 years[2].

Sulbactam (SUL) is an approved β-lactamase inhibitor (BLI) with antibacterial activity against *Acinetobacter spp.* due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis[3]. However, degradation of sulbactam by the β-lactamases present in most contemporary ABC isolates limits its clinical use. Durlobactam (DUR, ETX2514) is a diazabicyclooctane BLI with potent activity against class A, C and D serine β-lactamases[4]. DUR protects SUL from degradation, restoring antibacterial activity against ABC organisms.

SUL-DUR was noninferior to colistin for treatment of carbapenem-resistant ABC (CRABC) hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, ventilated pneumonia and bacteremia in the global, pivotal, phase 3 ATTACK trial.

SUL-DUR demonstrated a favorable safety profile compared with colistin, with a significantly lower incidence of nephrotoxicity.

ATTACK Trial Design

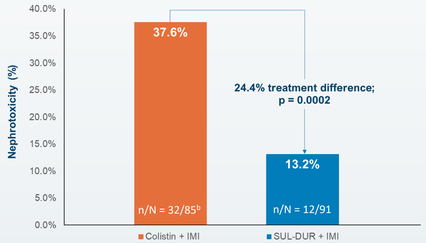


SUL-DUR Achieved the Primary Safety Objective of Lower Nephrotoxicity than Colistin

Primary Safety Objective Achieved

Statistically significant reduction in nephrotoxicity

SUL-DUR vs colistin, safety population, as assessed with the RIFLE classification[a]



[a] Part A, RIFLE: risk, injury, and failure; loss; and end-stage kidney disease (measured by creatinine level or glomerular filtration rate). Hartzell JD, Neff R, Ake J, et al. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. *Clin Infect Dis*. 2009;48(12):1724–1728.

[b] One patient in the colistin treatment group was on dialysis at study entry

Renal and Urinary Disorders SOC and Severity, TEAEs

System Organ Class Severity, n (%)	Part A SUL-DUR + IMI (N=91)	Part A Colistin + IMI (N=86)	Part B SUL-DUR + IMI (N=28)
Renal and urinary disorders	**9 (9.9)**	**27 (31.4)**	**3 (10.7)**
Mild	4 (4.4)	12 (14.0)	1 (3.6)
Moderate	4 (4.4)	8 (9.3)	1 (3.6)
Severe	1 (1.1)	7 (8.1)	1 (3.6)

Extent of Exposure

Category, n (%)	Part A SUL-DUR + IMI (N=91)	Part A Colistin + IMI (N=86)	Part B SUL-DUR + IMI (N=28)
Days, mean (SD)	**9.3 (3.67)**	**8.1 (4.02)**	**10.6 (4.25)**
Days 1–3	6 (6.6)	14 (16.3)	2 (7.1)
Days 4–7	15 (16.5)	24 (27.9)	4 (14.3)
Days 8–10	37 (40.7)	24 (27.9)	7 (25.0)
Days >10	33 (36.3)	24 (27.9)	15 (53.6)

SD, standard deviation

The Favorable Safety Profile of SUL-DUR

Category, n (%) System organ class Preferred term	Part A SUL-DUR + IMI (N = 91)	Part A Colistin + IMI (N = 86)	Part B SUL-DUR + IMI (N = 28)
Any adverse event (AE)	80 (87.9)	81 (94.2)	25 (89.3)
Drug-related TEAEs	11 (12.1)	26 (30.2)	3 (10.7)
Infections and infestations	**3 (3.3)**	**6 (7.0)**	**0 (0)**
Pneumonia	2 (2.2)	1 (1.2)	0 (0)
C. difficile colitis, infection/pseudomembranous colitis*	0 (0) 0 (0) 1 (1.1)	3 (3.5) 1 (1.2) 0 (0)	0 (0) 0 (0) 0 (0)
Fungal skin infection Oral fungal infection Peritonitis	0 (0)	1 (1.2)	0 (0)
Renal and urinary disorders	**0 (0)**	**8 (9.3)**	**1 (3.6)**
Acute kidney injury, renal impairment, renal failure, toxic nephropathy* Proteinuria	0 (0) 0 (0)	8 (9.3) 0 (0)	0 (0) 1 (3.6)
Gastrointestinal disorders	**2 (2.2)**	**4 (4.7)**	**1 (3.6)**
Diarrhea	2 (2.2)	3 (3.5)	0 (0)
Abdominal compartment syndrome Nausea	0 (0) 0 (0)	1 (1.2) 0 (0)	0 (0) 1 (3.6)
Serious AEs	36 (39.6)	42 (48.8)	9 (32.1)
Serious TEAEs leading to discontinuation of study drug	7 (7.7)	7 (8.1)	3 (10.7)

Category, n (%) System organ class Preferred term	Part A SUL-DUR + IMI (N = 91)	Part A Colistin + IMI (N = 86)	Part B SUL-DUR + IMI (N = 28)
Drug-related serious AEs	1 (1.1)	2 (2.3)	1 (3.6)
Infections and infestations	**1 (1.1)**	**2 (2.3)**	**0 (0)**
Pneumonia	1 (1.1)	1 (1.2)	0 (0)
Pseudomembranous colitis	0 (0)	1 (1.2)	0 (0)
Blood and lymphatic system disorders	**0 (0)**	**0 (0)**	**1 (3.6)**
Neutropenia	0 (0)	0 (0)	1 (3.6)
TEAEs leading to discontinuation of study drug	10 (11.0)	14 (16.3)	4 (14.3)
Nervous system disorders	**1 (1.1)**	**5 (5.8)**	**0 (0)**
Seizure	0 (0)	4 (4.7)	0 (0)
Brain oedema	1 (1.1)	0 (0)	0 (0)
Cerebral hemorrhage	0 (0)	1 (1.2)	0 (0)
Infections and infestations	**2 (2.2)**	**3 (3.5)**	**0 (0)**
Pneumonia bacterial	1 (1.1)	0 (0)	0 (0)
Pneumonia pseudomonal	1 (1.1)	0 (0)	0 (0)
Septic shock	0 (0)	1 (1.2)	0 (0)
Stenotrophomonas sepsis	0 (0)	1 (1.2)	0 (0)
Tuberculosis	0 (0)	1 (1.2)	0 (0)
Renal and urinary disorders	**0 (0)**	**3 (3.5)**	**0 (0)**
Acute kidney injury	0 (0)	3 (3.5)	0 (0)

>3% in any treatment group by SOC, Safety Population (patients randomized who received any amount of study drug)

* Preferred Terms grouped when clinical condition is similar; each Preferred Term is noted

Conclusions

In the ATTACK trial, sulbactam-durlobactam:

- **achieved the primary safety objective of significantly reduced incidence of nephrotoxicity compared with colistin,**
- **was generally well tolerated in severely ill patients, and**
- **demonstrated a favorable safety profile with no new safety signals identified.**

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

Disclosures

All authors are full-time employees of Entasis Therapeutics or were employees of Entasis at the time of this study

References

1. El Chakhtoura *et al.* (2018) *Expert Rev. Anti-infect. Ther.* 16: 89-110 **2.** Gales *et al.* (2019) *Open Forum Infect. Dis.* 6:S34-S46 3. Penwell *et al.* (2015) *Antimicrob. Agents Chemother.* 59: 1680-1689 **4.** Durand-Reville, T. *et al.* (2017) *Nature Microbiol.* 2:17104.

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