02145

Safety Profile of Sulbactam-Durlobactam (SUL-DUR) Versus Colistin Therapy in Patients With *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Infections from the Global, Randomized, Active-Controlled Phase 3 Trial (ATTACK)

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Background Sulbactam-durlobactam (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. The trial achieved the primary efficacy endpoint.

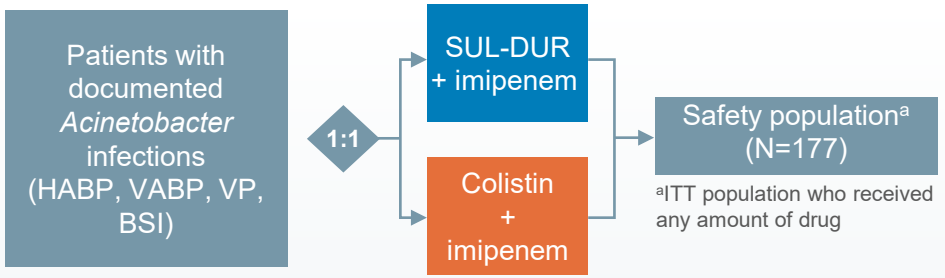
Methods ATTACK was a 2-part trial.

Part A was a randomized, assessor blinded, noninferiority study in ABC hospital-acquired pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia (BSI) that randomized patients 1:1 to SUL-DUR (1 g/1 g over 3 h q6h) or colistin (2.5 mg/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 patients in Part A and Part B received imipenem/cilastatin (1g/1g over 1 h q6h) as background therapy.

Part A (ECCMID 2022 abstract #02060)

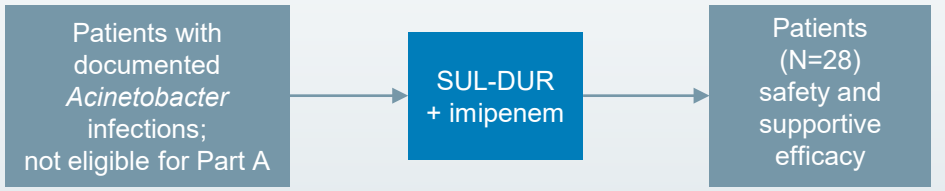


Endpoints

Primary efficacy analysis
- 28-day all-cause mortality in carbapenem-resistant ABC m-MITT population (patients received drug and had ABC isolated)

Primary safety objective
- Nephrotoxicity (RIFLE classification)
- Overview of AEs

Part B (ECCMID 2022 abstract #02093)



Endpoints

Efficacy
- 28-day ACM in ITT population
- 14-day ACM in m-MITT population

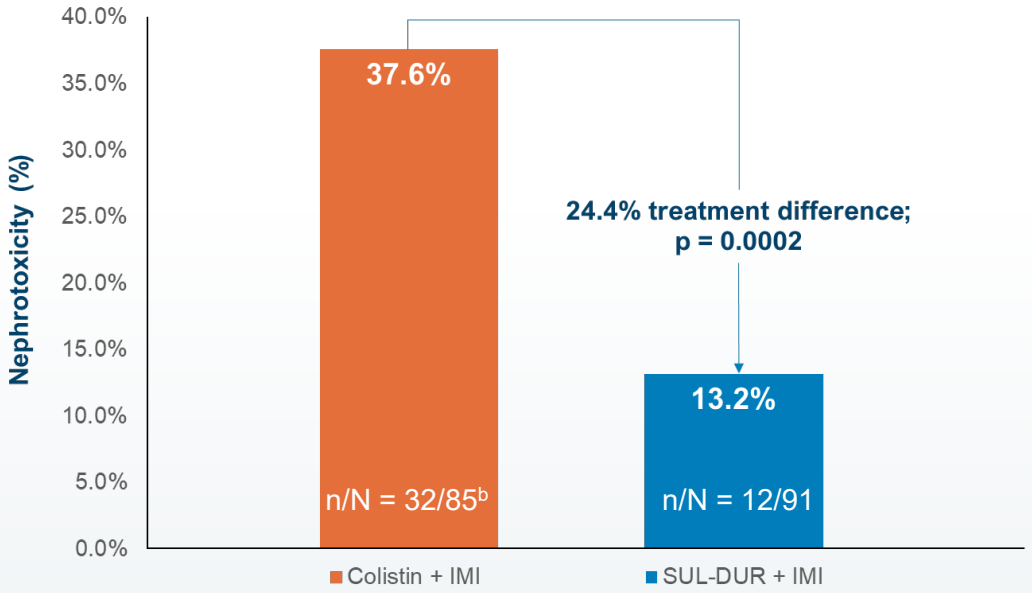
Safety
- Overview of AEs

Results

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; TEAE, treatment-emergent adverse event; IMI, imipenem/cilastatin.

Results: Favorable Safety Profile with 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)	3 (3.5)	0 (0)
Fungal skin infection	0 (0)	1 (1.2)	0 (0)
Oral fungal infection	1 (1.1)	0 (0)	0 (0)
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*	0 (0)	8 (9.3)	0 (0)
Proteinuria	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	0 (0)	1 (1.2)	0 (0)
Nausea	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
- demonstrated a favorable safety profile with no new safety signals identified

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

Other sulbactam-durlobactam presentations at ECCMID 2022

02060: Efficacy data are presented in “Efficacy and safety of SUL-DUR vs. colistin in patients with ABC infections: a global, randomized, active-controlled phase 3 trial (ATTACK)” Oral Presentation 26/04/2022 Hall G 09:30 - 11:30 (CET)
02051: Characterization of ABC pathogens isolated at baseline from patients enrolled in the ATTACK phase 3 trial, Oral Presentation: 24/04/2022 Hall H, 17:15 - 19:15 (CET)
02093: Efficacy and safety of SUL-DUR therapy in patients with ABC infections in the open label part B of the ATTACK phase 3 trial
02037: SUL-DUR in vitro dose response studies with and without imipenem or meropenem against carbapenemase-producing *A. baumannii* utilizing the hollow-fiber infection model
01106: In vitro activity of SUL-DUR against ABC isolates from a five-year surveillance program (2016-2020)
02091: Characterization of co-infecting Gram-negative pathogens isolated in addition to ABC at baseline from patients enrolled in the ATTACK Phase 3 trial