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Sulbactam-Durlobactam Treatment is Associated with Lower Mortality from Index *Acinetobacter* Infections in The ATTACK Phase 3 Registrational Trial

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Abstract

Rationale Sulbactam-durlobactam (SUL-DUR) is an investigational antibiotic in development for treating *Acinetobacter baumannii-calcoaceticus* (ABC) complex, a cause of severe infections with substantial mortality. SUL-DUR was evaluated for efficacy and safety compared to colistin, both in combination with imipenem/cilastatin, in a global, randomized, active-controlled, Phase 3 registrational study. SUL-DUR met the primary endpoint of 28-day all-cause mortality, demonstrating statistical non-inferiority to colistin. The mortality rate at 28 days was 19.0% in the SUL-DUR arm and 32.3% in the colistin arm. Deaths that occurred through 28 days in patients infected with carbapenem-resistant ABC (CRABC) are presented.

Methods Patients with ABC hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia were randomized to either SUL-DUR or colistin treatment for 7 - 14 days. All patients received imipenem/cilastatin as background therapy. Survival status was evaluated at 28 days post-randomization.

Results The Kaplan-Meier curves for time to death by day 28 are shown. By day 28, there were 12 deaths in the SUL-DUR arm and 20 deaths in the colistin arm. Twice as many deaths due to index CRABC infection occurred by day 28 in the colistin arm. Mortality rates during the first 5 days of treatment were similar in both arms. Most of these deaths (5/7) were considered not related to the index CRABC infection and were most likely due to comorbidities. During days 6-14, 1 death in the SUL-DUR arm and 5 deaths in the colistin arm were considered related to the index CRABC infection. Most deaths (8/9) during these days occurred in the colistin arm. During days 15-28, after treatment was completed, the mortality rates were again similar between the two arms, and most of the deaths (12/16) were also considered not related to the index CRABC infections.

Conclusions Mortality rates diverged between days 6 and 14 after treatment was started with more deaths due to the index CRABC infection occurring in the colistin arm. Mortality rates were comparable in both arms during the early days of treatment and post-treatment, and most deaths that occurred during these days were not related to the index CRABC infection. The survival advantage seen at days 6-14 in index CRABC infections indicate that SUL-DUR, if approved, could be an important therapeutic option for CRABC infections.

Introduction

The Gram-negative organisms collectively named the *Acinetobacter baumannii-calcoaceticus* complex (ABC) have emerged as serious pathogens[1]. The ABC complex, includes *A. baumannii*, *A. nosocomialis*, *A. pittii, A. dijkshoorniae, A. seifertii* 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].

Rationale

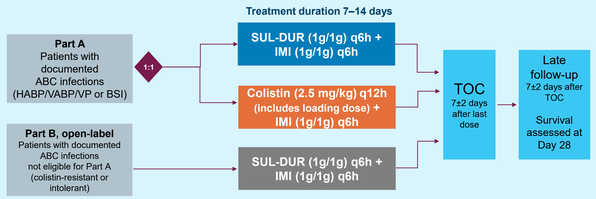
- Using a pathogen-focused approach, sulbactam-durlobactam (SUL-DUR) was developed to target ABC infections
- SUL is an approved β-lactamase inhibitor (BLI) with antibacterial activity against *Acinetobacter* spp. due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis[3]. DUR is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

The ATTACK study, a Phase 3 registrational trial for the treatment of infections caused by carbapenem-resistant ABC (CRABC) organisms has been completed. The study demonstrated the non-inferiority of SUL-DUR treatment compared to colistin (noninferiority margin = +20%). The all-cause mortality rate at 28 days was 19.0% in the SUL-DUR arm and 32.3% in the colistin arm (95% CI, -30.0, 3.5). The primary safety objective of incidence of nephrotoxicity based on RIFLE criteria was met with SUL-DUR treatment (13.2%) vs colistin (37.6%) (p=0.0002).

Deaths that occurred through day 28 are described.

Methodology

Part A of ATTACK was the pivotal, randomized, comparative, non-inferior part of the study in patients with documented ABC hospital-acquired bacterial pneumonia (HABP), ventilator associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia (BSI).



All patients received imipenem/cilastatin (IMI) as background therapy to treat non-ABC co-infecting pathogens; TOC=Test of Cure.

Study Populations

Primary Efficacy Population
CRABC patients (N=125),
SUL-DUR (N=63)
Colistin (N=62)
3 patients withdrew consent prior to assessing survival status

Safety Population (N=177)
SUL-DUR (N=91)
Colistin (N=86)
Received any amount of drug

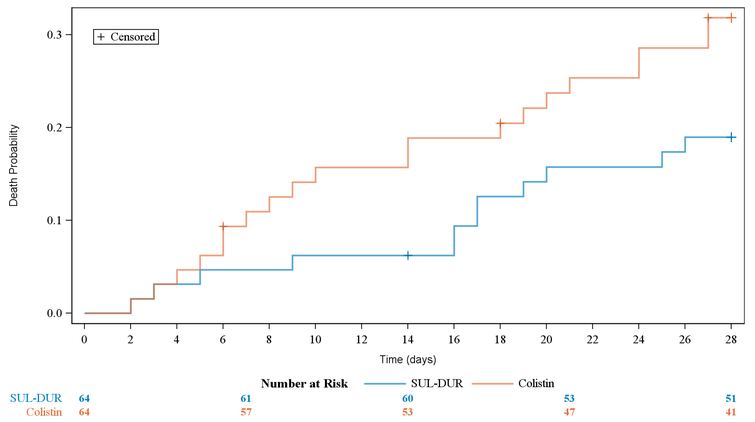
Results

Key baseline demographics were comparable across treatment groups

CRABC population	SUL-DUR N = 64	Colistin N= 64
Age (Years) – Mean ± SD	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)
Gender, Male, n (%)	46 (71.9)	49 (76.6)
APACHE II Score – Mean ± SD	16.4 ± 5.1	17.2 ± 5.2
Severity of Illness, n (%)		
APACHE II Score 10-19/SOFA Score 7-9/qSOFA Score 2	47 (73.4)	44 (68.8)
APACHE II Score 20-30/SOFA Score ≥10/qSOFA Score 3	16 (25.0)	20 (31.3)
Infection Type, n (%)		
Bacteremia	2 (3.1)	1 (1.6)
HABP	24 (37.5)	31 (48.4)
VABP	38 (59.4)	30 (46.9)
VP	0 (0.0)	2 (3.1)
Duration of ICU Stay at Baseline, n (%)		
No ICU Stay	21 (32.8)	19 (29.7)
<5	2 (3.1)	3 (4.7)
5-14	23 (35.9)	24 (37.5)
>14	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)

ICU: Intensive Care Unit; SD: Standard Deviation
Note: APACHE II score was evaluated first, when not available SOFA or qSOFA were used

Reduced Mortality Over Time with SUL-DUR Treatment



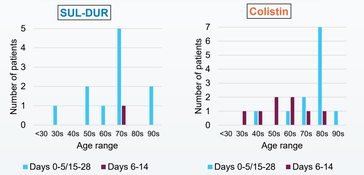
Number of Deaths Due to the Index CRABC Infection

	Deaths related to index infection/total deaths	
Days after start of treatment	SUL-DUR	Colistin
0-5	1/3	1/4
6-14	1/1	5/8
15-28	2/8	2/8
Total	4/12	8/20

Treatment Difference in All-Cause Mortality at Days 14 and 28

	Treatment difference (% all-cause mortality)	95% confidence interval
Day 14	-12.8	(-25.7, 0.1)
Day 28	-13.2	(-30.0, 3.5)

In the colistin arm, patients who died during days 6-14 tended to be younger than those who died during days 0-5 and days 15-28



- The all-cause mortality rates were similar in the SUL-DUR and colistin treatment arms during days 0-5 and 15-28 after the start of therapy. There was a notable divergence in all-cause mortality between days 6-14
- Twice as many deaths occurred in the colistin arm than in the SUL-DUR arm through Day 28
- Investigator-assessed deaths related to the index CRABC infection occurred more frequently during days 6-14 in the colistin arm
- Patients in the colistin arm who died during days 6-14 (60 ± 16 years) were younger than patients who died during days 0-5/15-28 (78 ± 12 years)
- These observations suggest that deaths early in treatment were more attributed to failure of treatment of *Acinetobacter* while deaths later in treatment were due to underlying co-morbidities

Overall Safety Profile Favors SUL-DUR

n (%)	SUL-DUR N = 91	Colistin N = 86
Incidence of Nephrotoxicity based on RIFLE criteria (Primary Safety Objective)	12 (13.2)*	32 (37.6)*
Renal and Urinary AEs – Moderate and Severe	5 (5.5)	15 (17.4)
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)
Drug-related Serious AEs	1 (1.1)	2 (2.3)
Infections and infestations	1 (1.1)	2 (2.3)

RIFLE = Risk, Injury, Failure, Loss, or End-stage renal disease
SOC = System organ class
*p=0.0002
#1 patient was excluded for chronic hemodialysis

Fatal adverse events

Treatment arm	Days of death	Age	Sex	Fatal adverse event(s)	Death considered related to Index CRABC infection (Y/N)
SUL-DUR	0-5	71	F	Hemorrhagic shock	N
		58	F	Shock	Y
	6-14	38	M	Gastrointestinal hemorrhage	N
		75	M	Septic shock	Y
	15-28	77	M	Coronary artery arteriosclerosis	N
		75	M	Intra-abdominal hemorrhage	N
		71	M	Acute respiratory distress syndrome (ARDS)	N
		56	M	Malignant neoplasm progression	N
		91	F	Sepsis	N
		75	F	Septic shock	Y
		69	M	Mesenteric vessel thrombosis Peripheral artery thrombosis	N
		91	M	Sepsis	Y
Colistin	0-5	83	M	Septic shock	Y
		66	M	Septic shock	N
		86	M	ARDS	N
		91	M	Cardiac arrest	N
	6-14	45	M	Multiple organ dysfunction syndrome Sepsis	N
		37	M	Septic shock	Y
		61	M	Cerebral hemorrhage	N
		79	M	Pneumonia	Y
		63	M	None reported	N
		54	F	Pneumonia	Y
		85	M	Pneumonia	Y
		57	M	ARDS	Y
	15-28	85	M	Weaning failure	N
		79	M	Pneumonia	N
		80	M	Ischemic stroke	N
		83	M	Progression of ALS	N
		89	M	Sepsis	Y
		81	F	Cardiac arrest	Y
		47	M	Pseudomonal pneumonia	N
		73	M	Multiple organ dysfunction syndrome	N

Conclusions

- **SUL-DUR met the primary efficacy endpoint of 28-day all cause mortality for non-inferiority compared to colistin in the CRABC m-MITT Population of Part A**
- **A lower rate of all-cause mortality for SUL-DUR was observed between days 6-14**
  - **This observation may indicate that the survival benefit seen between days 6-14 is reflective of the efficacy of SUL-DUR in treating the index CRABC infection at this critical time point**
- **Twice as many deaths due to the index CRABC infection occurred through day 28 in the colistin arm**
- **If SUL-DUR is approved, it could be an important therapeutic option for CRABC infections**

Disclosures

All authors are full-time employees of Entasis Therapeutics

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