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Efficacy and Safety of Sulbactam-Durlobactam are Consistent Across Regions in the Global ATTACK Phase 3 Trial in the Treatment of Carbapenem-Resistant *Acinetobacter baumannii-calcoaceticus* Complex (CRABC) Infections

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Abstract

Background: ATTACK is a randomized, active-controlled, noninferiority trial that evaluated the efficacy and safety of sulbactam-durlobactam (SUL-DUR) compared to colistin for CRABC infections. The primary efficacy endpoint of all-cause mortality (ACM) at day 28 and the primary safety objective of incidence of nephrotoxicity based on RIFLE criteria were met. Due to the global variation of carbapenem and multi-drug resistance, geographic subgroups were evaluated to explore consistency of efficacy and safety across regions.

Methods: Patients were randomized to SUL-DUR or colistin treatment for 7-14 days and all patients received imipenem/cilastatin as background therapy. The primary efficacy analysis in the CRABC population consisted of 125 patients: SUL-DUR (N=63) and colistin (N=62). The primary safety population included 177 patients who received any amount of drug. Secondary efficacy endpoints included ACM at day 14, clinical cure and microbiological favorable assessment at end-of treatment (EOT), test-of-cure (TOC) and late follow-up (LFU). Results are described geographically by the following regions: the Americas, Asia-Pacific and Europe.

Results: Overall, ACM at day 28 in the SUL-DUR arm and colistin arm was 12/63 (19.0%) vs. 20/62 (32.3%), respectively; ACM at day 14 overall in the SUL-DUR arm and colistin arm was 4/63 (6.3%) vs. 12/62 (19.4%), respectively. Day 28 ACM, and secondary endpoints were similar across the geographic regions and consistent with overall findings. Criteria for RIFLE nephrotoxicity were met more often in the colistin arm than the SUL-DUR arm in all regions.

Conclusions: ACM, clinical outcomes, microbiological favorable assessment, and RIFLE-assessed nephrotoxicity were consistently favorable in patients treated with SUL-DUR versus colistin across regions. These findings suggest, that if approved, SUL-DUR could be an important global therapeutic option for *Acinetobacter* infections including carbapenem-resistant and multidrug-resistant strains.

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

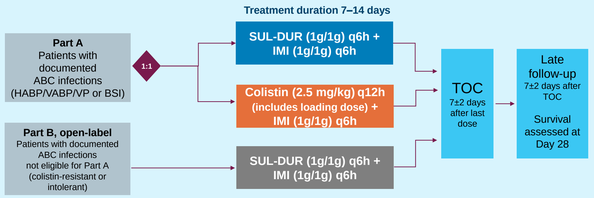
- Using a pathogen-focused approach, sulbactam-durlobactam (SUL-DUR) was developed to target ABC infections
- SUL is an approved β-lactamase inhibitor with antibacterial activity against *Acinetobacter* spp. due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis[3]. DUR is a diazabicyclooctane 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[5] was met with SUL-DUR treatment (13.2%) vs colistin (37.6%) (p=0.0002).

Due to the global variation of carbapenem and multi-drug resistance, geographic subgroups were evaluated to explore consistency of efficacy and safety across regions.

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

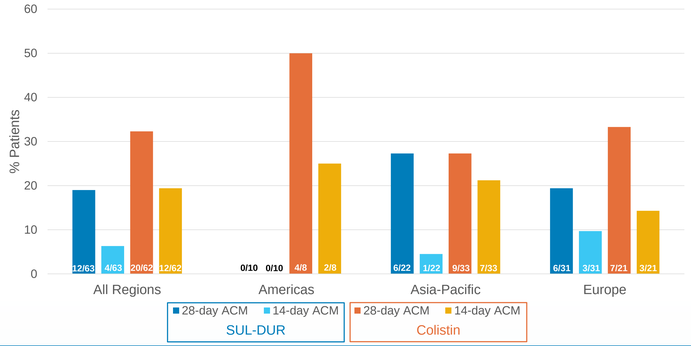
Results

Key baseline demographics were comparable across treatment groups

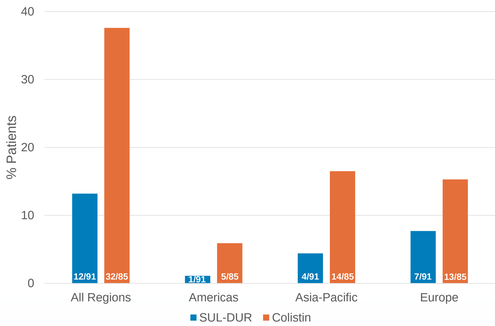
CRABC population	SUL-DUR N = 64	Colistin N= 64
Age (Years) – Mean ± SD	61.6 ± 16.1	65.1 ± 17.0
Age Group, n (%)		
<65 years	36 (56.3)	31 (48.4)
65 – 75 years	16 (25.0)	12 (18.8)
>75 years	12 (18.8)	21 (32.8)
Gender, Male, n (%)	46 (71.9)	49 (76.6)
APACHE II Score – Mean ± SD	16.4 ± 5.1	17.2 ± 5.2
Severity 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)
Region, n (%)		
Americas	10 (15.6)	9 (14.1)
Asia-Pacific	23 (35.9)	34 (53.1)
Europe	31 (48.4)	21 (32.8)
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)

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

28-Day and 14-Day All-Cause Mortality (ACM) was Consistent Across Geographic Regions (CRABC Population)



Nephrotoxicity Based on RIFLE Criteria Occurred More Often with Colistin Treatment Across Regions



RIFLE = Risk-Injury-Failure-Loss-End stage renal disease
1 patient was excluded from the colistin arm due to chronic hemodialysis

Clinical Cure and Microbiological Favorable Outcome were Consistent Across Geographic Regions

Clinical Cure (CRABC Population[1])

		All Regions	Americas	Asia-Pacific	Europe
SUL-DUR	N	64	10	23	31
	EOT (N', %)	47 (73)	9 (90)	13 (57)	25 (81)
	TOC (N', %)	39 (61)	8 (80)	9 (39)	22 (71)
	LFU (N', %)	27 (42)	6 (60)	5 (22)	16 (52)
Colistin	N	64	9	34	21
	EOT (N', %)	30 (47)	6 (67)	12 (35)	12 (57)
	TOC (N', %)	26 (41)	6 (67)	11 (32)	9 (43)
	LFU (N', %)	19 (30)	3 (33)	8 (24)	8 (38)

EOT = End of Treatment; TOC = Test of Cure; LFU = Late Follow-up; N = number of patients; N' = number of patients with outcome; [1]includes patients who withdrew consent prior to survival status;

Microbiological Favorable Outcome* (CRABC Population[1])

		All Regions	Americas	Asia-Pacific	Europe
SUL-DUR	N	64	10	23	31
	EOT (N', %)	54 (84)	8 (80)	20 (87)	26 (84)
	TOC (N', %)	43 (67)	7 (70)	14 (61)	22 (71)
	LFU (N', %)	30 (47)	6 (60)	5 (22)	19 (61)
Colistin	N	64	9	34	21
	EOT (N', %)	40 (62)	6 (67)	20 (59)	14 (67)
	TOC (N', %)	27 (42)	4 (44)	11 (32)	12 (57)
	LFU (N', %)	25 (39)	2 (22)	9 (26)	14 (67)

*includes eradication and presumed eradication (clinical cure and no sample could be obtained for microbiological testing); EOT = End of Treatment; TOC = Test of Cure; LFU = Late Follow-up; N = number of patients; N' = number of patients with outcome; [1]includes patients who withdrew consent prior to survival status

Conclusions

- **Results were consistently favorable for SUL-DUR vs colistin across regions for**
  - **28-day and 14-day ACM**
  - **Clinical cure**
  - **Microbiological favorable outcome**
  - **Nephrotoxicity based on RIFLE criteria**
- **If approved, SUL-DUR could be an important therapeutic option for CRABC infections including multi-drug resistant strains**

Disclosures

All authors are full-time employees of Entasis Therapeutics

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