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Safety and Efficacy of Salvecin™ (AR-301), a Human Monoclonal Antibody, in Patients with Severe Pneumonia Caused by S. aureus, a Phase 2 Study

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Abstract

INTRODUCTION
The frequency of Hospital-acquired bacterial pneumonia (HABP) is increasing steadily over time, most significantly in older patients. HABP due to *Staphylococcus aureus* (Sa) affects over 500,000 patients in the U.S., Europe, and Japan alone, and is often associated with mechanical ventilation. Ventilator associated bacterial pneumonia (VABP) is the most common infection in the intensive care unit (82% of HABP cases) and one of the most frequent causative pathogens is Sa. The emergence of multi-drug resistant strains makes treatment more complex escalating the need for new therapeutic approaches. Human monoclonal antibodies (mAb) are a promising new anti-infective immunotherapy used as adjunctive treatment. Salvecin™ (AR-301) is a human mAb that neutralizes the alpha-toxin of Sa thus protecting host cells, including immune cells, to enable a more effective immune response.
Study objectives were to assess safety and tolerability of single ascending doses of Salvecin™, and to explore its clinical and microbiological efficacy.

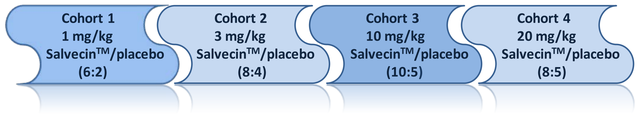
METHODS
Randomized, double-blind, placebo-controlled, phase 1/2, first in human trial in 5 countries and 13 ICUs. Key inclusion criteria were a microbiologically-confirmed severe pneumonia caused by Sa and an APACHE II score < 30. The treatment was to start < 36 hrs after onset of severe pneumonia. Salvecin™ was administered in ascending doses to 4 sequential cohorts (1, 3, 10 and 20 mg/kg) of 8, 12, 15 and 13 patients respectively, including 16 placebo subjects overall. Antibiotic treatment and duration were left to investigators' judgment. Data were collected until EOS (Day 107(±7)) or study discontinuation. Clinical outcomes were adjudicated by a blinded committee. Time of extubation, discharge from ICU and from hospital, and antibiotic use were recorded. Microbiological assessment was performed at test of cure (TOC). *Sa* was considered eradicated or not if the culture obtained in follow-up was negative or positive, and presumed eradicated or not if no culture was obtained in the presence of clinical success or failure, respectively.

RESULTS
From 16 May 2012 to 28 May 2016, 48 patients were enrolled (79.2% men, age: 56±15 years, BMI: 29±6). Pneumonia was severe (PaO2/FiO2 = 147±41.32 and/or catecholamine required), 6 related to MRSA, 42 to MSSA. APACHE II was 18.7±4.48, CPIS, 9.6±1.58, SOFA, 6.9±2.62. In total, 343 AEs were reported, 8 (2.3%) being related to treatment; 36 were serious, none related. The study population was unbalanced in regard to several factors that favored the placebo cohort. For example, there were five out of 16 (31.3%) VABP subjects in the placebo group, compared to 21 out of 32 (65.6%) among those treated with active product. Despite the imbalance, there was a trend toward a better and faster microbiological eradication on day 28, and toward a decrease in ventilation days in patients with VABP in treated patients compared to placebo.

CONCLUSIONS
Adjunctive treatment of severe Sa HABP with Salvecin™ appears feasible and safe. Exploratory analyses show a decrease in ventilation days, and improved microbiological outcome in treated patients. This treatment approach could represent an important new therapeutic option for bacterial infections in critically ill patients.

Methods

- **Inclusion criteria: >** 18 years old, microbiologically-confirmed severe HABP or VABP caused by Sa, APACHE II < 30
- **Exclusion criteria:** Pregnancy, hypersensitivity to one of the excipients or to antibody, cancer, long-term tracheostomy, HIV, immunosuppressive treatment, liver function deficiency and moribund patients



Results

Study Population

Out of the 48 patients initially included, 12 did not complete the study: 6 died, 5 were lost to follow-up and 1 was transferred in another ICU. The study population was unbalanced in regard to several factors that favored the placebo cohort in age, percent of VABP, and APACHE II as shown in Table 1 (below). For example, VAPB accounted for 55.3% of pneumonia in all patients, 31.3% in placebo group, 83.3% in cohort 1, 50.0% in cohort 2, 77.8% in cohort 3 and 62.5% in cohort 4.

Table 1. Patients characteristics

	Placebo	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Age [years (SD)]	52 (25-80)	65 (50-78)	49 (21-69)	62 (47-74)	61 (39-76)
VABP (%)	31	83	50	78	63
Apache II	17.5 (8-25)	18.3 (16-24)	21.5 (15-28)	17.9 (9-23)	19.3 (12-24)
Antibiotics (n) Adequate / not adequate	15 / 1	6 / 0	8 / 0	9 / 1	7 / 1

A trend for better and faster bacterial eradication was observed in treated patients.

Table 2 : Time to eradication

Eradicated	Placebo (16)	Cohort 1 (6)	Cohort 2 (8)	Cohort 3 (10)	Cohort 4 (8)
Yes	7	1	5	5	4
Day to eradicate	10.86	8.00	9.60	9.40	8.75
No	5	0	0	2	0
ND (Not determined)	3	5	3	3	4

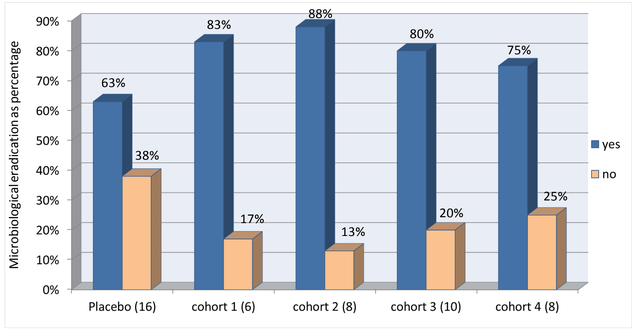


Figure 1. Microbiological eradication & presumed eradication at Day 28 (percentage)

No major safety issue was reported. Anti-drug antibody signal at certain time points was increased compared to baseline in one patient, but without consequence.

Table 3. Safety data

	Placebo	Cohort 1	Cohort 2	Cohort 3	Cohort 4
AEs related to treatment	2 (2.4%)	1 (3.3%)	0 (0%)	1 (1.3%)	4 (6.8%)
SAE	8 (9.8%)	4 (13.3%)	10 (10.9%)	13 (16.3%)	1 0.7%)
SAE related to treatment	N.A.	0	0	0	0
Death	1	1	2	2	0

A decrease in ventilation days was observed in patients receiving Salvecin™ compared to placebo.

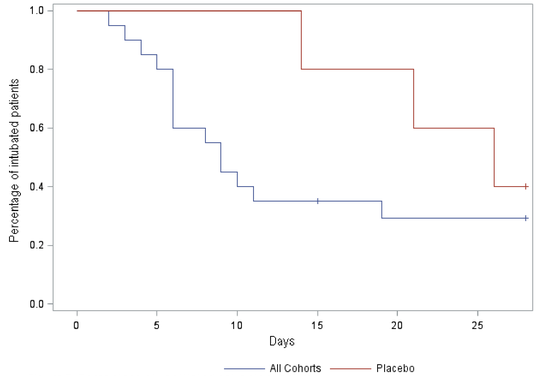


Figure 2. Percentage of ventilated patients over time

There was no difference in mortality, probably because of the small study sample size.

Conclusions

Adjunctive treatment of severe Sa HABP in the ICU using Salvecin™, an anti-Staphylococcal mAb, appears feasible and safe. It also appears to decrease ventilation time and improve microbiological outcome.