Efficacy and safety of suvratoxumab for prevention of Staphylococcus aureus ventilator-associated pneumonia (SAATELLITE) : a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2 pilot trial

Efficacy and safety of suvratoxumab for prevention of *Staphylococcus aureus* Ventilator-Associated Pneumonia (SAATELLITE): a randomized clinical trial.

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Abstract

Background: *Staphylococcus aureus* remains a common cause of ventilator-associated pneumonia, with little change in infection rates over the past 15 years. This phase 2 study evaluated suvratoxumab, an anti-alpha-toxin monoclonal antibody, in reducing incidence of *S. aureus* pneumonia in intensive care unit (ICU) subjects on mechanical ventilation (MV).

Methods: We did a multicenter, single-dose, randomized, placebo-controlled, double-blind, phase 2 pilot trial in 9 countries. Eligible subjects were patients in an ICU ≥18 years of age, currently intubated and on MV, positive for *S. aureus* lower respiratory tract (LRT) colonization as assessed by polymerase chain reaction (PCR) of endotracheal aspirate, and with no diagnosis of new-onset pneumonia. Subjects were excluded if they had confirmed or suspected acute ongoing staphylococcal disease; had received anti–*S. aureus* antibiotics for >48 hours; had a CPIS ≥6, APACHE-II score ≥25, a SOFA score ≥9; or had active pulmonary disease that would impair the ability to diagnose pneumonia. Subjects were screened for *S. aureus* lower respiratory tract (LRT) colonization using real-time polymerase chain reaction (PCR).Colonized subjects were randomly assigned 1:1:1 to a single intravenous infusion of suvratoxumab 2000 mg, 5000 mg or placebo. Randomization was stratified by country and by whether subjects received anti–*S. aureus* systemic antibiotic therapy. Based on pre-defined PK criteria, the 2000 mg arm was discontinued upon the recommendation of the data monitoring committee at an interim analysis. Primary efficacy endpoint was incidence of *S. aureus* pneumonia, adjudicated by a blinded independent panel, through 30 days post dose in the modified intent-to-treat study population. Primary safety endpoints were

treatment-emergent AEs assessed through 30 and 90 days, treatment-emergent SAEs, adverse events of special interest, and new onset chronic disease, all assessed through 190 days.

Findings: PCR screening of 737 ICU subjects identified 213 with *S. aureus* colonization; of these, 96 were randomized to receive suvratoxumab 5000 mg and 100 to placebo. At 30 days, 17/96 (17·7%) suvratoxumab and 26/100 (26·0%) placebo subjects had developed *S. aureus* pneumonia (relative risk reduction, 31.9%; 90% confidence interval [CI], −7·5 to 56·8; P = 0·166). At 30 days, incidences of treatment-emergent adverse events (AEs) and serious AEs were similar in suvratoxumab and placebo groups (90·6% [87/96] vs. 90·0% [90/100] and 37·5% [36/96] vs 32·0% [32/100], respectively). At 90 and 190 days, incidence of treatment-emergent AEs was still similar in suvratoxumab and placebo groups (92.7% [89/96] vs. 92.0% [92/100] and 93.8% [93/96] vs. 93.0% [93/100], respectively).

Interpretation: Among ICU subjects on MV with PCR-documented LRT *S. aureus* colonization, incidence of *S. aureus* pneumonia at 30 days was not significantly lower with suvratoxumab than with placebo. Despite these negative results, mAbs still represent one promising therapeutic option to reduce antibiotic consumption that requires further exploration and studies.

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INTRODUCTION

Ventilator-associated pneumonia (VAP) affects 8 to 28% of all intubated patients with important variations among intensive care units (ICUs).[1,2] *Staphylococcus aureus* accounts for approximately 25% of these cases[3] corresponding to an overall rate of 2 to 7% for *S. aureus* VAP in the ICU population. VAP results in significant morbidity and is responsible for more than 50% of antibiotics prescribed in ICUs[4] and an additional five to ten days of mechanical ventilation (MV) time and ICU stay. [1,2,5] Despite current clinical guidelines and practices aimed at VAP prevention, [6,7] diagnostic, and treatment challenges persist, and the incidence of VAP has remained largely unchanged over the past 15 years. [8]

Routine VAP prevention by prophylactic antibiotic treatment is not encouraged by guidelines due to concerns over the development of resistance.[1,2] Therefore, prevention of VAP with monoclonal antibodies (mAbs) by targeting specific pathogenic agents has been proposed as a prophylactic alternative to treatment with antibiotics, even if one VAP prevention trial targeting *S. aureus* have failed to demonstrate efficacy. [9] These types of molecules have multiple advantages when compared to antibiotics, such as a better specificity with no impact on the beneficial microbiome, a good safety profile with no host interaction, a very long half-life and no antibiotic cross-resistance.
Suvratoxumab is a human mAb with extended serum half-life targeting the pore-forming alpha-toxin of *S. aureus*.[10] Alpha-toxin is a broadly conserved virulence factor that mediates tissue disruption, programmed cell death of leukocytes and endothelial cells, bacterial dissemination, and immune dysregulation. [11-15] Preclinical studies

demonstrated that suvratoxumab had protective activity against experimental lethal infection in murine models of *S. aureus*-induced pneumonia and sepsis. [12,16]

The use of rapid diagnostic techniques, such as real-time polymerase chain reaction (PCR), in ICU settings enables prompt detection of patients with lower respiratory tract (LRT) bacterial colonization prior to the onset of nosocomial infection. Patients colonized with *S. aureus* at the time of ICU admission have an up to 15-fold greater risk for developing VAP compared with noncolonized patients. [17] Accordingly, rapid identification of patients with respiratory *S. aureus* colonization could assist in the timely initiation of preemptive or curative therapies.

The aim of the SAATELLITE phase 2 pilot trial was to determine whether prophylactic administration of suvratoxumab, in conjunction with standard of care treatment, would reduce the incidence of pneumonia in mechanically ventilated ICU patients with LRT *S. aureus* colonization.

METHODS

TRIAL OVERSIGHT

SAATELLITE was a multicenter, single-dose, parallel-group, placebo-controlled, double-blind, phase 2 pilot trial. The study was designed within the public–private consortium Combatting Bacterial Resistance in Europe (COMBACTE), which includes clinical and academic VAP experts and investigators, [9] as well as the study sponsor, AstraZeneca. To ensure uniformity of inclusion criteria across sites, all subjects were approved by a Clinical Coordinating Center with an expert ICU physician on call. An independent data monitoring committee from COMBACTE with access to unblinded

data provided safety oversight, reviewed serious adverse events (SAEs) and deaths on an ongoing basis, and was responsible for making dose-selection decisions. Based on data monitoring committee review after the prespecified interim pharmacokinetic (PK) analysis, the 2000 mg MEDI4893 cohort was discontinued one year after trial start. To ensure diagnostic uniformity across participating sites, incidences of *S. aureus* pneumonia, all-cause pneumonia, and all-cause pneumonia or death were reviewed by an independent blinded endpoint adjudication committee (EAC).

ETHICAL COMPLIANCE

The study was performed in accordance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from independent ethics committees were obtained, and all subjects or their legal representative(s) provided written informed consent in accordance with local requirements prior to enrollment and the performance of any protocol-related procedures, including polymerase chain reaction (PCR) screening.

PATIENTS

Eligible subjects were patients in an ICU ≥18 years of age, currently intubated and on MV (and expected to remain intubated and mechanically ventilated for ≥3 days), positive for *S. aureus* LRT colonization as assessed by PCR analysis of endotracheal aspirate, and with no diagnosis of new-onset pneumonia (subjects with evidence of resolved pneumonia were eligible for inclusion). Subjects were excluded from the study

if they had confirmed or suspected acute ongoing staphylococcal disease; had received anti–*S. aureus* antibiotics for >48 hours within 72 hours prior to randomization; had a Clinical Pulmonary Infection Score (CPIS)[18] ≥6; had an Acute Physiology and Chronic Health Evaluation (APACHE-II)[19] score ≥25 with a Glasgow Coma Scale (GCS) score >5 or ≥30 with a GCS score ≤5; had a Sequential Organ Failure Assessment (SOFA)[20] score ≥9; or had active pulmonary disease that would impair the ability to diagnose pneumonia. To complete screening, all subjects had to be approved by the Clinical Coordinating Center ICU physician on call. Complete inclusion and exclusion criteria and screening procedures are provided in the study protocol (Supplementary Appendix).

RANDOMIZATION AND MASKING

Subjects were randomly assigned 1:1:1 to receive a single intravenous (IV) infusion of suvratoxumab 2000 mg, suvratoxumab 5000 mg, or placebo within 36 hours of confirmation of *S. aureus* LRT colonization. Randomization was stratified by country and by whether subjects received anti–*S. aureus* systemic antibiotic therapy for ≤48 hours within 72 hours prior to randomization. A blocked randomization schedule was generated with records pre-allocated to each of the strata, with a block size of 4.

An interactive voice/web response system (IVRS/IWRS) was used for randomization to a treatment group and assignment of blinded investigational product kit number. Suvratoxumab and placebo were identical in appearance. Neither the subject/legal representative nor any of the investigator or sponsor staff who were involved in the treatment or clinical evaluation of the subjects was aware of the treatment received. The

investigational products were handled by an unblinded investigational product manager at the site. Routine use of VAP prevention bundles (elevation of the head of the bed, daily sedation vacations and extubation readiness assessment, peptic ulcer disease prophylaxis, deep vein thrombosis prophylaxis, and daily oral care with chlorhexidine) was highly recommended and specific attention was given at time of site initiation to standardize patient care. To check if correctly done, sites were asked to report VAP bundle application in the e-case report form for every single enrolled patient. Investigational product was administered on study day 1 and subjects were followed through 190 days post dose. Data monitoring committee review of the prespecified interim PK analysis indicated that serum exposure of suvratoxumab 2000 or 5000 mg in ICU subjects on MV (AstraZeneca, data on file) was approximately two-fold lower than the exposure observed in healthy adults.[10] Based on data monitoring committee recommendation, enrollment in the suvratoxumab 2000 mg group was discontinued, and the study proceeded with enrollment in suvratoxumab 5000 mg and placebo groups only. The final study diagram is shown in Figure S1.

PRIMARY AND SECONDARY ENDPOINTS

The primary efficacy endpoint was the incidence of *S. aureus* pneumonia through 30 days in the modified intent-to-treat (mITT) study population as determined by the EAC, using radiographic, clinical, and microbiologic (culture) criteria for diagnosis of *S. aureus* pneumonia in the context of a preventive pilot study developed in accordance with regulatory guidance.[9] In contrast to the positive PCR needed for randomization, the microbiological documentation for *S. aureus* pneumonia endpoint mandated a positive

culture for *S. aureus* from a pulmonary (bronchoalveolar lavage or endotracheal aspirate, according to local practice), blood or pleural fluid sample. Complete predefined VAP diagnostic criteria are provided in the study protocol (Supplementary Appendix).

Prespecified subgroup analyses were performed according to predose anti–*S. aureus* antibiotics stratum (yes vs. no), age (≤65 years vs. >65 years), body mass index (≤30 kg/m^2 vs. >30 kg/m^2), and 5-element VAP preventative bundle usage (5 bundles vs. fewer than 5 bundles). A post hoc subgroup analysis consisting of *S. aureus* colonization load at baseline (PCR cycle threshold [CT] ≥29 vs. <29) was also performed. The high/low colonization load cutoff of CT = 29 was determined by a receiver-operating characteristic curve analysis[21] using culture as the reference. Approximately 85% of cultures negative for *S. aureus* had CT values ≥29 whereas 80% of cultures positive for *S. aureus* had CT values <29 (AstraZeneca, data on file).

The primary safety endpoints were treatment-emergent AEs assessed through 30 and 90 days, treatment-emergent SAEs, adverse events of special interest, and new onset chronic disease, all assessed through 190 days in the complete as-treated population. Initially protocol was through 360 days, but it was changed to 190 days after the interim PK analysis demonstrated a shorter half-life in mechanically ventilated patients.

Secondary endpoints were suvratoxumab concentrations and PK parameters in serum and antidrug antibody (ADA) responses, both through 90 days. Key exploratory endpoints included incidences of all-cause pneumonia and all-cause pneumonia or death. Additional exploratory endpoints included incidence of overall mortality assessed

through 30 days and duration of healthcare resource utilization assessed through 90 days. Exploratory endpoints are listed in the Supplementary Appendix.

STATISTICAL ANALYSIS

At study start, approximately 462 subjects were to be randomized to one of three treatment arms: suvratoxumab 2000 mg, suvratoxumab 5000 mg, or placebo. A study with a sample size of 154 per arm would allow an 80% power at a two-sided significance level of α = 0·1 to detect a relative risk reduction (RRR) of 50% comparing each suvratoxumab treatment group versus placebo calculated using a Poisson regression model with robust variance,[22] assuming a *S. aureus* pneumonia incidence rate of 25% in the placebo group. The design of the study used the significance level of α = 0·1 given the exploratory nature of this study. After the determination that the current study would not serve as a possible single pivotal study, the steering committee made a decision to reduce the power to 70% in the final study design, where approximately 206 subjects were to be randomized 1:1 to suvratoxumab 5000 mg or placebo treatment, in order for this exploratory proof of concept study to provide data for a future confirmatory efficacy trial. The intent-to-treat (ITT) population consisted of all randomized subjects. The mITT population consisted of subjects who received suvratoxumab or placebo and were analyzed according to their randomized treatment group. The as-treated population consisted of subjects who received suvratoxumab or placebo and were analyzed according to the treatment received.

For subjects with multiple *S. aureus* pneumonia events, only the first occurrence was used in the primary analysis. Subjects with mixed culture results that included

S. aureus were counted towards the primary endpoint. It was anticipated that the main reason for data missing in the primary analysis would be subjects who died before completing the study due to their underlying disease. If no *S. aureus* pneumonia was diagnosed prior to death in these subjects, they were classified as not infected in the primary efficacy analysis. No other imputation was applied to the primary efficacy analysis. Time to EAC-determined *S. aureus* pneumonia was estimated using Kaplan–Meier methods.

Subgroup analyses were performed for EAC-determined *S. aureus* pneumonia (primary efficacy endpoint), as well as for EAC-determined all-cause pneumonia, and EAC-determined all-cause pneumonia or death (exploratory efficacy endpoints). Healthcare resource utilization in the mITT population through 90 days was summarized for durations of hospitalization, ICU stay, MV use, and systemic antibiotic use and for durations following adjustment for individual patient follow-up time.

Additional statistical methods and the study statistical analysis plan are provided in the Supplementary Appendix.

ROLE OF THE FUNDING SOURCE

The study received financial support from the Innovative Medicines Initiative Joint Undertaking under grant agreement number 115523, resources of which are composed of financial contribution from the European Union Seventh Framework Program (FP7/2007-2013) and European Federation of Pharmaceutical Industries and Associations (EFPIA) companies in kind contribution.

The study sponsor was responsible for overseeing the collection, statistical analysis, and interpretation of data with input from the authors. All the authors had full

access to all the study data and wrote the manuscript with medical writing assistance funded by the sponsor. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol.

RESULTS

A total of 767 ICU patients were screened by PCR for *S. aureus* LRT colonization; of those, 213 met the study eligibility requirements and were randomized at 31 sites across nine European countries between October 2014 and March 2018. The mITT population comprised 211 subjects: 100 randomized to placebo, 15 to suvratoxumab 2000 mg, and 96 to suvratoxumab 5000 mg. Patient disposition is shown in Figure 1.

In the early-discontinued suvratoxumab 2000 mg group, patients' outcomes were not different from the other groups: at 30 days, the incidence of EAC-determined *S. aureus* pneumonia was 20·0% [3/15] and 3/15 patients (20·0%) were deceased on day 190. Mean MV and ICU hospitalization durations were 16·17 days and 20·96 days, respectively.

Baseline characteristics of subjects randomized to suvratoxumab 5000 mg or placebo were similar, including primary reason for ICU admission, duration of healthcare resource utilization prior to randomization, use of predose anti–*S. aureus* antibiotics, baseline clinical severity scores, and methicillin-resistant *S. aureus* (MRSA) colonization incidence (Table 1). Most subjects did not receive prior *S. aureus*–specific antibiotics (placebo 87·0% [87/100]; suvratoxumab 87·5% [84/96]).

At 30 days, the incidence of EAC-determined *S. aureus* pneumonia was 17·7% [17/96] in the suvratoxumab arm and 26·0% [26/100] in the placebo arm (RRR = 31·9%, 90% CI, −7·5 to 56·8, P = 0·166) (Table 2). The probability of developing *S. aureus* pneumonia at any time appeared to be slightly reduced for suvratoxumab compared with placebo based on Kaplan-Meier time to event analysis, although the difference was not significant (log-rank P value = 0·1938) (Fig. S2). No marked difference between the placebo and suvratoxumab groups was observed for any of the other serious *S. aureus* infections (bacteremia or deep skin and soft tissue infection).

Short-course systemic antibiotics administered within 2 days of dosing were used in similar proportions of suvratoxumab (30·2% [29/96]) and placebo (29·0% [29/100]) subjects. The RRR for EAC-determined *S. aureus* pneumonia was 25·4% for subjects who received systemic antibiotics within 2 days of dosing and 32·6% for those who did not receive short-course antibiotics (Table S1).

Treatment-emergent AEs through 190 days were reported by the blinded investigator in roughly equal proportions of suvratoxumab and placebo subjects (Table 3, Table S2). The incidence of treatment-emergent AEs related to study drug treatment through 30 days was 2·0% (2/100) in the placebo group and 6·3% (6/96) in the suvratoxumab group. The incidence of treatment-emergent AEs was greater for suvratoxumab than placebo subjects at 30 days (37·5% [36/96] vs. 32·0% [32/100]), 90 days (46·9% [45/96] vs. 37·0% [37/100]), and 190 days (52·1% [50/96] vs. 40% [40/100]). Through 30 days, no subjects randomized to placebo experienced treatment-emergent SAEs related to treatment, AEs of special interest, or new onset chronic diseases; these events were reported in 1·0%, 2·1%, and 2·1% of suvratoxumab

subjects, respectively. In an analysis of cases of mortality, none was considered related to study drug treatments by the blinded investigators or the unblinded independent data monitoring committee. Safety results in the as-treated patient population through day 190 are summarized in Table S2.

Results of the prespecified subgroup analyses of the primary endpoint are shown in Figure 2. Compared with placebo, suvratoxumab treatment was associated with a non-significant reduction of *S. aureus* pneumonia in subjects ≤65 years of age (RRR = 47·4%, 90%CI, 3·5% to 71·4%, P=0·210) and in subjects who received all 5 VAP bundles during the course of MV (RRR = 46·3%, 90%CI, 2·2% to 70·5%, P=0·249) (Fig. 2). Post hoc analysis also demonstrated a reduction of *S. aureus* pneumonia in suvratoxumab-treated subjects with a low *S. aureus* LRT colonization load (RRR = 66·7%, 90%CI, 21·3% to 86·2%, P=0·069) (Fig. 2).

Mean (SD) serum concentration of suvratoxumab was 296 (131) μg/mL at 30 days and 192 (84) at 90 days post dose. Based on population PK modeling and simulation, suvratoxumab's half-life was estimated to be 48·3 days (AstraZeneca, data on file). At 30 days, mean serum levels of suvratoxumab were above the 211 μg/mL target concentration in 77·2% of subjects (Fig. S3). A single occurrence of *S. aureus* pneumonia was reported in subjects with antibody levels below the target concentration. Serum concentration of suvratoxumab correlated linearly with the concentration of anti-AT neutralizing antibodies (Fig. S4). In the placebo group, ADAs were detected in 3 (3%) of 100 subjects at baseline, in 4 (5·4%) of 74 subjects at 30 days, in 2 (2·9%) of 68 subjects at 60 days, and in 1 (1·6%) of 62 subjects at 90 days. In the suvratoxumab

group, 2 (2·1%) of 96 subjects tested positive for ADAs at baseline; no suvratoxumab subjects tested positive for ADAs post dose.

The incidences of EAC-determined all-cause pneumonia and all-cause pneumonia or death were 20·8% (20/96) and 32·3% (31/96), respectively, in the suvratoxumab arm and 30·0% (30/100) (RRR = 30·6%, 90%CI, –4·9% to 54·0%; P = 0·146) and 42·0% (42/100) (RRR = 23·1%, 90%CI, –4·9% to 43·6%;P = 0·164) respectively in the placebo arm (Table 2). In a subgroup analysis, the RRRs for all-cause pneumonia and all-cause pneumonia or death were 46·8% (90%CI, 6·3% to 69·9%, p=0·197) and 31·4% (90%CI, –5·4% to 55·2%, p= 0·479), respectively, for subjects ≤65 years, and −4·7% (90%CI, –110% to 46·4%) and 9·8% (90%CI, –49·8% to 45·6%), respectively, for subjects >65 years (Table S3).

Through 90 days, healthcare resource utilization duration was unchanged or slightly reduced for subjects receiving suvratoxumab compared with placebo (0 to 3·0 adjusted days saved). Subgroup analysis of healthcare resource utilization by age demonstrated reduced healthcare resource utilization durations for subjects ≤65 years of age receiving suvratoxumab vs. placebo (2·1 to 10·1 adjusted days saved). The greatest reduction was seen in duration of hospitalization stay followed in order by duration of overall systemic antibiotics, anti−*S. aureus* systemic antibiotics, ICU stay, and MV. No between-group differences were noted in subjects >65 years of age (Table S4).

DISCUSSION

In this phase 2 pilot study, the incidence of EAC-determined 30-day *S. aureus* pneumonia was not significantly different in subjects receiving suvratoxumab vs. placebo. The proportion of subjects with at least one treatment-emergent AE was similar between the treatment groups through 30 and 90 days. While treatment-emergent SAEs were higher in the suvratoxumab group vs. the placebo group, no individual SAEs appeared to contribute to this difference. ADAs were not detected post baseline in subjects randomized to suvratoxumab through 90 days. Secondary PK analyses demonstrated an extended half-life for suvratoxumab in *S. aureus* colonized ICU subjects on MV (AstraZeneca, data on file), similar to what was observed in a phase 1 dose-ranging study in healthy volunteers.[10] Incidence of *S. aureus* pneumonia was not associated with serum antibody concentration since most subjects had serum concentrations above the target level through 30 days.

The observed incidence rate of *S. aureus* pneumonia in placebo-treated subjects (26·0%) suggests that the PCR screening strategy employed here identified an ICU patient population at increased risk for pneumonia and enabled a preemptive, superiority trial design based on pulmonary *S. aureus* colonization. PCR has two major advantages for identifying patients colonized with *S. aureus*: PCR screening results can be obtained rapidly, permitting much faster identification and prompt treatment of *S. aureus*-colonized patients (≤ 75 min for PCR in comparison to ≥ 24 h for the conventional culture methods). In addition, the specificity of PCR is useful for selecting those patients who could benefit the most from specific interventions.[9] Interestingly, patients with the highest CT values (meaning the lower bacterial load) are the ones

more likely to benefit from a molecule targeting alpha-toxin while the ones with heavy bacterial load (low CT value) are possibly already "moving" to VAP (Figure 2). Studies describing the sensitivity, specificity, and cost-effectiveness of PCR for identifying patients colonized with *S. aureus* have been published. [23,24]

The benefit of mAbs targeting *S. aureus* cytotoxins, including alpha-toxin, has been studied in previous clinical trials. Recent post hoc subgroup analyses of a small Phase 2a study in patients receiving adjunctively administered anti−*S. aureus* alpha-toxin mAb, AR-301, demonstrated a reduction in MV duration following onset of severe VAP for AR-301 compared with placebo, thereby providing the rationale for the ongoing phase 3 trial (ClinicalTrials.gov NCT03816956) to confirm the Phase 2a findings.[25] A phase 2 study of ASN100, a mAb combination targeting six *S. aureus* cytotoxins,[26] in ICU patients on MV who were heavily colonized by *S. aureus* was recently halted for futility. In addition to a low (<10%) observed incidence of *S. aureus* pneumonia in the placebo group, ASN100, unlike suvratoxumab, does not have an extended half-life, which might have contributed to the lack of efficacy. Despite strong efficacy in animal models for the ASN100, these negative results together with our findings support close consideration of trial design and outcomes for these types of drugs when used preventively. In addition, a mAb targeting alginate has recently failed to demonstrate efficacy in *Pseudomonas aeruginosa* VAP. Finally, both target and outcome should be carefully considered when testing mAbs in pneumonia. While mAbs have been suggested as a promising alternative or adjunctive therapy to antibiotics, short-course antibiotic treatment has been shown to be effective in preventing early-onset VAP in some specific clinical settings,[27-29] in addition to this study.

Limitations

First, our results are limited by a relatively small sample size in a complex, mechanically ventilated ICU patient population. It should be noted that the PCR screening strategy combined with diagnostic adjudication resulted in an enriched pneumonia incidence in placebo subjects. Also, as only a few subjects in our study were colonized with MRSA, no inferences regarding potential benefits of suvratoxumab in such patients can be made. The “neuro-trauma” patients (including stroke, cerebral hemorrhage, sub-arachnoid bleeding, traumatic brain injury, etc.) account for nearly 80% of the entire study population, which may not be representative of all ICUs. Therefore, the generalization of our results to all ICUs must be cautiously considered. Last, adequacy of prevention of *S. aureus* pneumonia as primary endpoint may be relatively unprecedented but remains a potentially viable outcome for superiority trials. In contrast, mortality reduction would be almost impossible to demonstrate due to low rates of VAP attributable mortality, while ventilator-free days may be more driven by the underlying disease than by VAP itself, e.g. in case of neurological disease vs trauma.

Even though the study failed to meet its primary endpoint (50% reduction in *S. aureus* pneumonia), a preventative VAP strategy based on rapid detection of *S. aureus* colonization in ICU patients and preemptive treatment with an anti-staphylococcal mAb appears feasible and safe. Additional, larger studies are warranted to further assess the benefit of suvratoxumab in critically ill ICU patients, particularly in those younger than 65 years and those with low staphylococcal colonization load.

Research in context

Evidence before this study

Search strategy included terms such as “HAP”/”VAP”/”sepsis” and the different targeted designs: “randomized”, “double-blind” or “open label”, “observational” or “interventional” trials. We also included the following terms “*Staphylococcus aureus*”, “prevention”, “pre-emptive design” to focus on pathogen-specific infections due to *Staphylococcus aureus*, in colonized or non-colonized patients. Search was mainly conducted on PubMed Central and included published studies involving antibiotics or antibody trials. *Staphylococcus aureus* remaining one of the major threats especially when considering HAP/VAP, 3 drug candidates have been recently developed for this indication. In order not to miss them in our search, we included the terms “monoclonal antibody” and “antibiotic drug”. One mAb targeting alpha-toxin has shown promising effect when used adjunctively to treat staphylococcal HAP/VAP. Another mAb targeting cytotoxins and leucocidins has failed to demonstrate efficacy when used pre-emptively in heavy colonized patients documented with microbiological cultures (no publication available). Suvratoxumab which also targets alpha-toxin has demonstrated efficacy in prevention of pneumonia in murine models. We performed a first literature search before the beginning of the study in 2014 and checked the literature again while writing the article. The last search was performed before finalization of the article, in May 2020.

Added value of this study

This is the first clinical study investigating efficacy of an anti-staphylococcal mAb targeting alpha-toxin to prevent staphylococcal VAP to be submitted for publication. This phase II placebo-controlled, randomized, trial incorporated several completely new

innovations. A pre-emptive design based on enrichment strategy utilizing pulmonary *Staphylococcus aureus* colonization has been used. Colonization was documented homogenously across sites using a real-time PCR. Stringent endpoints definitions have been developed by a board of HAP/VAP experts to fit with the prevention/pre-emptive approach and agreed upon by both FDA and EMA. A superiority design as opposed to the traditional non-inferiority design of antibiotics trials was chosen. Planned interim pharmacokinetics analysis was utilized to determine the PK profile of a large molecule in critically ill patients.

Implications of all the available evidence

Despite improvement of infection prevention in the ICU, *Staphylococcus aureus* remains with *Pseudomonas aeruginosa,* among the two main drivers of HAP/VAP and by consequences of antibiotic consumption in critically ill patients. Therefore, new strategies to overcome increasing resistance to antibiotics are urgently needed and despite few negative trials, mAbs still represent one of the most promising therapeutic options that require further studies, and their exploration as a prophylactic option is warranted.

Contributors

- BF : conception or design of the work, data collection, accessed and verified the data, data analysis and interpretation, drafting the article, critical revision of the article
- HSJ : conception or design of the work, accessed and verified the data, data analysis and interpretation, drafting the article, critical revision of the article
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Declaration of interests

Dr. François reports personal fees outside the submitted work from AM-Pharma, Aridis, Ashai-Kasai, Biomérieux, Enlivex, Ferring, Inotrem, Polyphor, Transgene; Dr. Chastre reports personal fees during the conduct of the study from Combacte Magnet, personal fees from outside the submitted work from Bayer, Inotrem, Shionogi, Tigenix/Takeda, and grants from AstraZeneca/Medimmune; Dr. Eggiman reports other support from COMBACTE-MAGNET Consortium during the conduct of the study; Dr. Dequin reports other support during the conduct of this study from the Association pour la Promotion de la Réanimation Médicale à Tours, France, University Hospital, Tours, France; Dr. Bonten reports grants from Jansen Vaccines, Merck, Sanofi, consultancy fees from Jansen Vaccines, and Data and Safety Monitoring Board fees from Merck (all paid to University Medical Center Utrecht); Drs. Jafri, Ali, Shoemaker, Ren, Ruzin, Pierre, Esser, and Dubovsky and Wu, Colbert, and Bellamy are or were employees of and may hold stock and/or stock options in AstraZeneca; Dr. Ali is an employee of and may hold stock and/or stock options in Viela Bio; Drs. Sánchez-García, Huberlant, Viña Soria, Boulain, Bretonnière, Pugin, Trenado, Hernandez Padilla, Coenjaerts, Barraud, Timbermont, Goossens, Laterre, and Ms. Lammens and Vignaud have nothing to disclose.

Data Sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Figure Legends

Figure 1. Patient Flow Diagram (All Screened Subjects).

*Subjects signed informed consent.

†Primary reason for exclusion was negative *S. aureus* PCR test result.

‡ITT population.

§mITT population.

excl denotes exclusion, incl inclusion, ITT intent-to-treat, mITT modified intent-to-treat, PCR polymerase chain reaction, *S. aureus Staphylococcus aureus*.

Figure 2. Overall and Subgroup Analysis of Suvratoxumab 5000 mg Efficacy.

Overall RRR and 90% CI based on Poisson regression with robust variance. Subgroup analyses were prespecified. Subgroup RRRs and 90% CIs based on unconditional confidence interval on ratio of proportions.

*Subgroup analysis of staphylococcal colonization load was conducted post hoc; all other analyses were prespecified. †Preventative VAP measures (bundles) were elevation of the head of the bed, daily sedation vacations and extubation readiness assessment, peptic ulcer disease prophylaxis, deep vein thrombosis prophylaxis, and daily oral care with chlorhexidine.

BMI denotes body mass index, CI confidence interval, mITT modified intent-to-treat, PCR CT polymerase chain reaction cycle threshold, RRR relative risk reduction, *S. aureus Staphylococcus aureus,* VAP ventilator-associated pneumonia.

Figure 1

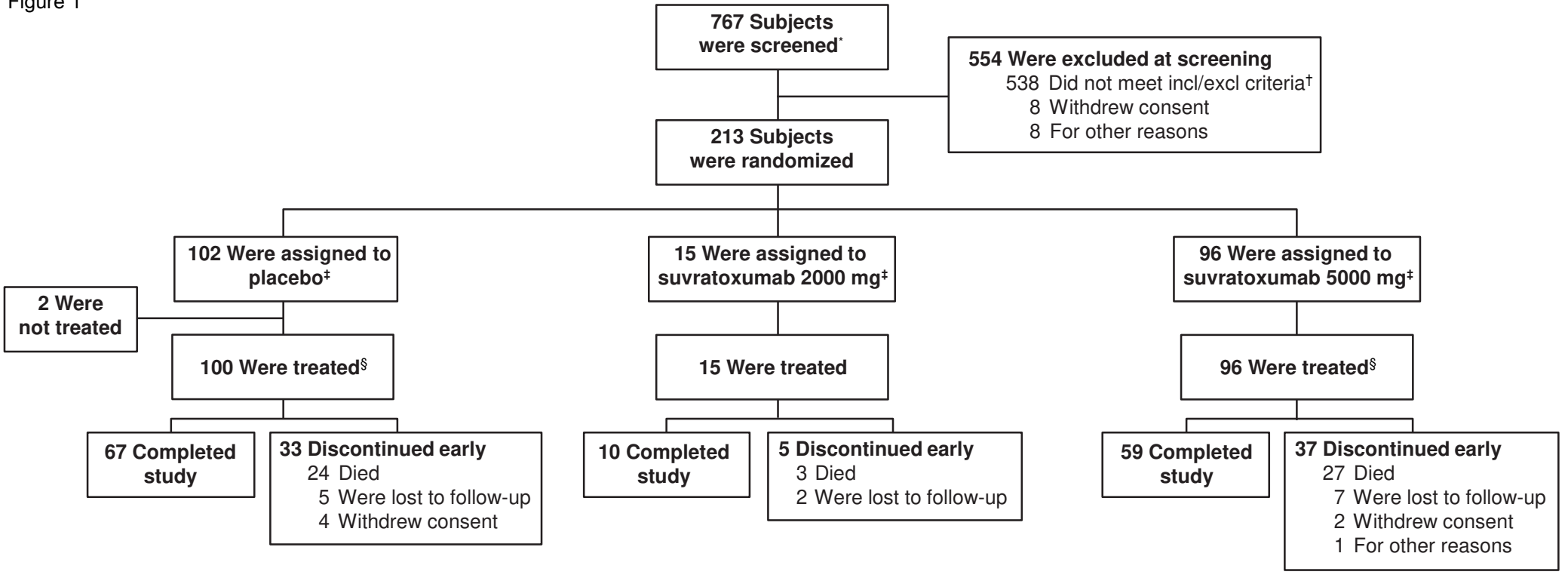
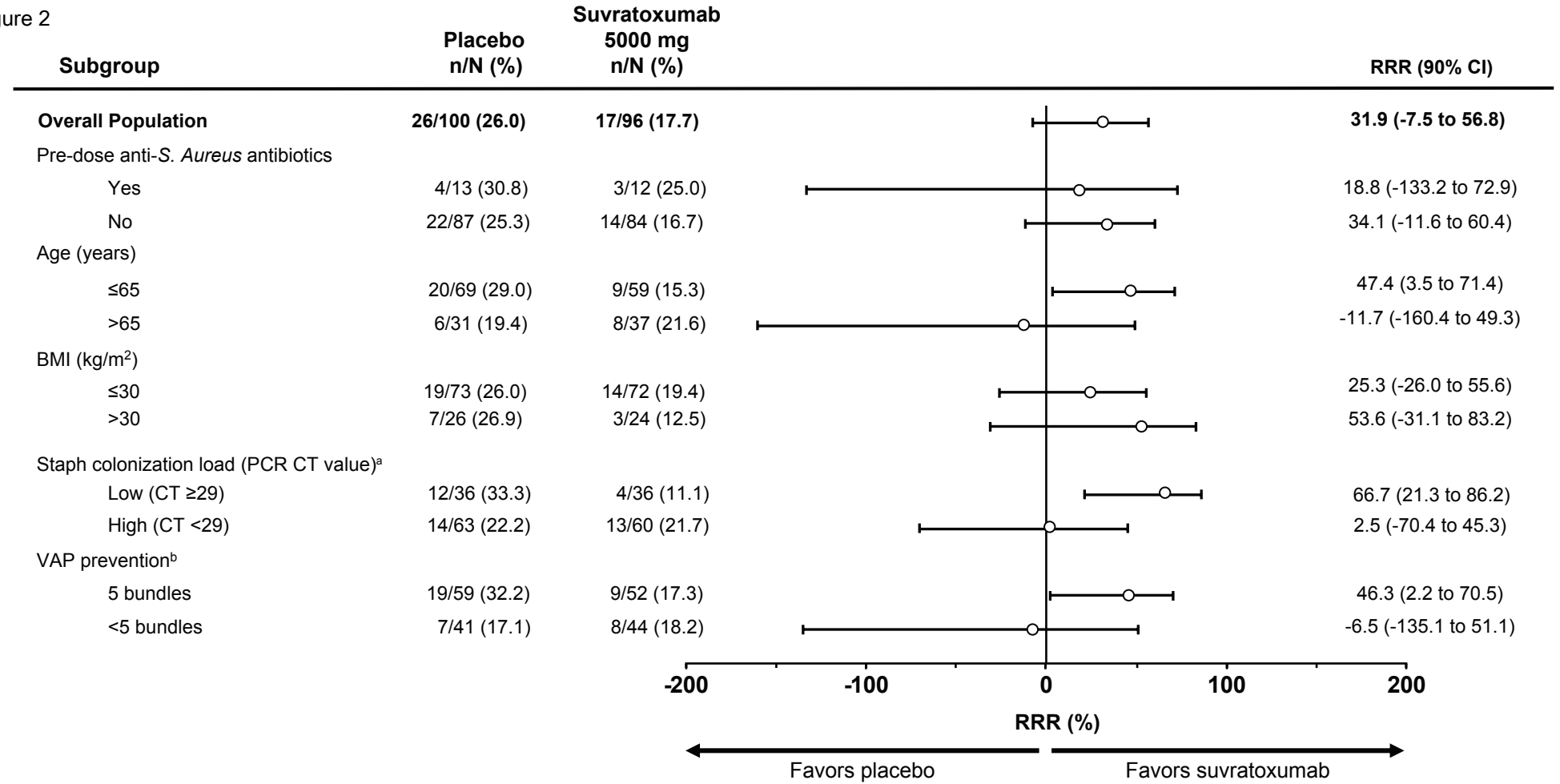

767 Subjects were screened*
554 Were excluded at screening
538 Did not meet incl/excl criteria†
8 Withdrew consent
8 For other reasons
213 Subjects were randomized
102 Were assigned to placebo‡
15 Were assigned to suvratoxumab 2000 mg‡
96 Were assigned to suvratoxumab 5000 mg‡
2 Were not treated
100 Were treated§
15 Were treated
96 Were treated§
67 Completed study
33 Discontinued early
24 Died
5 Were lost to follow-up
4 Withdrew consent
10 Completed study
5 Discontinued early
3 Died
2 Were lost to follow-up
59 Completed study
37 Discontinued early
27 Died
7 Were lost to follow-up
2 Withdrew consent
1 For other reasons

Figure 2


Subgroup
Placebo n/N (%)
Suvratoxumab 5000 mg n/N (%)
RRR (90% CI)
Overall Population
26/100 (26.0)
17/96 (17.7)
31.9 (-7.5 to 56.8)
Pre-dose anti-S. Aureus antibiotics
Yes
4/13 (30.8)
3/12 (25.0)
18.8 (-133.2 to 72.9)
No
22/87 (25.3)
14/84 (16.7)
34.1 (-11.6 to 60.4)
Age (years)
≤65
20/69 (29.0)
9/59 (15.3)
47.4 (3.5 to 71.4)
>65
6/31 (19.4)
8/37 (21.6)
-11.7 (-160.4 to 49.3)
BMI (kg/m2)
≤30
19/73 (26.0)
14/72 (19.4)
25.3 (-26.0 to 55.6)
>30
7/26 (26.9)
3/24 (12.5)
53.6 (-31.1 to 83.2)
Staph colonization load (PCR CT value)a
Low (CT ≥29)
12/36 (33.3)
4/36 (11.1)
66.7 (21.3 to 86.2)
High (CT <29)
14/63 (22.2)
13/60 (21.7)
2.5 (-70.4 to 45.3)
VAP preventionb
5 bundles
19/59 (32.2)
9/52 (17.3)
46.3 (2.2 to 70.5)
<5 bundles
7/41 (17.1)
8/44 (18.2)
-6.5 (-135.1 to 51.1)
-200
-100
0
100
200
RRR (%)
Favors placebo
Favors suvratoxumab

Tables

Table 1. Baseline Characteristics of the mITT Primary Efficacy Population.

Characteristic	Placebo (n = 100)	Suvratoxumab 5000 mg (n = 96)
Age group — no. of subjects (%)		
≤65 years	69 (69·0)	59 (61·5)
>65 years	31 (31·0)	37 (38·5)
Sex — no. of subjects (%)		
Female	45 (45·0)	37 (38·5)
Male	55 (55·0)	59 (61·5)
BMI — no. of subjects (%)[a]		
BMI ≤30 kg/m^3	73 (73·7)	72 (75·0)
BMI >30 kg/m^3	26 (26·3)	24 (25·0)
Primary reason for ICU admission — no. of subjects (%)		
Brain trauma	10 (10·0)	8 (8·3)
Cardiovascular disorders	5 (5·0)	10 (10·4)
Infection	3 (3·0)	2 (2·1)
Neurologic disorders	53 (53·0)	53 (55·2)
Respiratory disease	12 (12·0)	9 (9·4)
Trauma	14 (14·0)	12 (12·5)
Other	3 (3·0)	2 (2·1)
Mean duration of HRU prior to		

randomization (SD) — days		
Hospitalization	6·3 (8·3)	6·9 (8·7)
ICU stay	5·3 (7·4)	5·4 (6·6)
MV	5·4 (7·2)	5·3 (6·7)
Predose anti–*S. aureus* antibiotic stratum — no. of subjects (%)		
Yes	13 (13·0)	12 (12·5)
No	87 (87·0)	84 (87·5)
Mean clinical severity score (SD)		
APACHE-II*	15·2 (5·2)	15·1 (5·2)
SOFA†	4·5 (2·0)	4·8 (2·0)
CPIS†	3·0 (1·5)	3·0 (1·3)
Median PCR CT value (*S. aureus* colonization load) (min, max)	26·10 (12·7, 35·3)	26·65 (15·0, 35·6)
Positive tracheal staphylococcal culture — no. of subjects (%)	45 (45·0)	47 (49·0)
MRSA colonization — no. of subjects (%)	6 (6·0)	6 (6·3)

*Data available for n=99 placebo subjects. †Data available for n = 96 placebo subjects.

APACHE-II denotes Acute Physiology and Chronic Health Evaluation II, BMI body mass index, CPIS Clinical Pulmonary Infection Score, CT cycle threshold, HRU healthcare resource utilization, ICU intensive care unit, mITT modified intent-to-treat; MRSA methicillin-resistant *Staphylococcus aureus*, MV mechanical ventilation, PCR

polymerase chain reaction, SD standard deviation, *S. aureus Staphylococcus aureus,* SOFA Sepsis-related Organ Failure Assessment.

Table 2. Primary and Key Exploratory Efficacy Results Through Day 30 (mITT population).

Endpoint — no. of subjects (%)	Placebo (n = 100)	Suvratoxumab 5000 mg (n = 96)	RRR (90% CI)*	ARR	P value*
EAC-determined *S. aureus* pneumonia	26 (26·0)	17 (17·7)	31·9 (−7·5 to 56·8)	8·3	0·166
EAC-determined all-cause pneumonia	30 (30·0)	20 (20·8)	30·6 (−4·9 to 54·0)	9·2	0·146
EAC-determined all-cause pneumonia or death	42 (42·0)	31 (32·3)	23·1 (−4·9 to 43·6)	9·7	0·164

*RRR (suvratoxumab vs. placebo), 90% CI, and *P* value based on modified Poisson regression with robust variance.

ARR denotes absolute risk reduction, CI confidence interval, EAC endpoint adjudication committee; mITT modified intent-to-treat, RRR relative risk reduction, *S. aureus Staphylococcus aureus*.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects Through Day 30 (As-Treated Population).

Events* — no. of subjects (%)†	Placebo (n = 100)	Suvratoxumab 5000 mg (n = 96)
At least 1 event	76 (76·0)	76 (79·2)
Blood and lymphatic system disorders	13 (13·0)	15 (15·6)
Anemia	10 (10·0)	11 (11·5)
Thrombocytosis	3 (3·0)	6 (6·3)
Gastrointestinal disorders	22 (22·0)	13 (13·5)
Constipation	12 (12·0)	6 (6·3)
Diarrhea	7 (7·0)	5 (5·2)
General disorders and administration site conditions	13 (13·0)	9 (9·4)
Pyrexia	12 (12·0)	8 (8·3)
Hepatobiliary disorders	8 (8·0)	9 (9·4)
Cholestasis	4 (4·0)	6 (6·3)
Hepatocellular injury	5 (5·0)	7 (7·3)
Infections and infestations	46 (46·0)	47 (49·0)
Urinary tract infection *Escherichia*	9 (9·0)	14 (14·6)
Pneumonia bacterial	16 (16·0)	7 (7·3)
Pneumonia staphylococcal	15 (15·0)	14 (14·6)
Bacteremia staphylococcal	7 (7·0)	3 (3·1)
Urinary tract infection pseudomonal	1 (1·0)	5 (5·2)
Injury, poisoning, and procedural complications	5 (5·0)	6 (6·3)
Weaning failure	5 (5·0)	4 (4·2)
Metabolism and nutrition disorders	15 (15·0)	12 (12·5)
Hypokalemia	7 (7·0)	10 (10·4)

Psychiatric disorders	9 (9·0)	13 (13·5)
Agitation	3 (3·0)	5 (5·2)
Anxiety	4 (4·0)	7 (7·3)
Respiratory, thoracic, and mediastinal disorders	16 (16·0)	15 (15·6)
Atelectasis	3 (3·0)	6 (6·3)
Hypoxia	5 (5·0)	0
Pleural effusion	3 (3·0)	6 (6·3)
Vascular disorders	9 (9·0)	13 (13·5)
Hypertension	6 (6·0)	7 (7·3)
Hypotension	2 (2·0)	8 (8·3)
Deaths	16 (16·0)	15 (15·6)

*System organ class and preferred term (MedDRA version 21).

†Subjects are counted once for each category regardless of the number of events.

MedDRA denotes Medical Dictionary for Regulatory Activities.

SUPPLEMENTARY APPENDIX

François B, Jafri HS, Chastre J, et al. Suvratoxumab for Prevention of *Staphylococcus aureus* Ventilator-Associated Pneumonia

SUPPLEMENTARY APPENDIX

Suvratoxumab for Prevention of *Staphylococcus aureus* Ventilator-Associated Pneumonia

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Ethical Compliance

The study was performed in accordance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from independent ethics committees were obtained, and all subjects or their legal representative(s) provided written informed consent in accordance with local requirements prior to enrollment and the performance of any protocol-related procedures, including polymerase chain reaction (PCR) screening.

Study Design

This study was designed to determine if prophylactic administration of suvratoxumab reduces the incidence of *S. aureus* pneumonia when added to standard-of-care therapy. The study was randomized, double blinded, and placebo controlled. Because there is no established medicinal product with proven prophylactic value in this indication with which to compare suvratoxumab, placebo was used in the control arm to maintain the blinded assessment of therapeutic effect and adverse events (AEs). All subjects received standard of care. The use of placebo did not replace or result in the withholding of a currently proven intervention during the study period.

Two single doses of suvratoxumab, 2000 mg and 5000 mg, were selected to be evaluated in this study based on the pharmacokinetic/pharmacodynamic (PK/PD) data from preclinical pharmacology studies and PK data from the clinical phase 1 study.[1] A peak serum concentration of 211 µg/mL was the 90% effective concentration in an *S. aureus*-induced preclinical mouse pneumonia model (data not shown). Hence, the serum concentration of 211 µg/mL was considered as the target level in the clinic. A single dose of 2250 mg suvratoxumab in healthy adult subjects in the phase 1 study maintained serum concentration above the target level of 211 µg/mL for at least 30 days in all subjects. Based on these data and PK simulation, a dose of 2000 mg suvratoxumab was selected as the likely efficacious dose because it was the lowest dose expected to maintain a serum exposure above 211 µg/mL for 30 days. A higher dose of 5000 mg suvratoxumab, which was the highest dose evaluated in the phase 1 study and was not associated with any major safety findings, was selected to explore

maximal efficacy in subjects. The higher dose also ensured appropriate drug exposure in case there was significantly greater drug clearance in the ICU subjects on mechanical ventilation (MV) compared to healthy subjects enrolled in the phase 1 study.

The study population included ICU subjects on MV at the time of enrollment who were colonized with *S. aureus* in the lower respiratory tract but without a diagnosis of acute pneumonia or *S. aureus* infection. Despite the limited data on variables that contribute to the risk of *S. aureus* pneumonia, respiratory colonization with *S. aureus* and the prolonged need for MV with endotracheal intubation (>48 hours) are widely recognized as 2 major contributing factors. The rate of *S. aureus* pneumonia among intubated patients on MV colonized with *S. aureus* has been reported to be up to 35%.[2,3]

Since the objective of the study was to investigate how to prevent nosocomial pneumonia in high-risk patients on MV, subjects were excluded if they had preexisting confirmed or suspected *S. aureus* infections, had an underlying condition that would impede a diagnosis of pneumonia, were not expected to have a reasonable probability to survive through the study evaluation period, or had received potentially effective systemic antibiotic therapy active against *S. aureus* for >48 hours within 72 hours prior to dosing.

These enrollment criteria were expected to result in a population representative of patients encountered in clinical practice with a high risk of developing *S. aureus* pneumonia and to minimize confounding factors for characterization of the efficacy of suvratoxumab in preventing pneumonia in patients on MV.

The study was conducted between October 10, 2014 and October 2, 2018.

Study Protocol

Complete inclusion/exclusion criteria, patient screening procedures, endpoint assessments, and criteria for diagnosis of *S. aureus* pneumonia are provided in the approved study protocol (available at https://s3.amazonaws.com/ctr-med-7111/CD-ID-MEDI4893-1139/516e4676-ac10-48ef-8f1b-f2c3bacfc92f/dd5f4d36-44fe-420c-97fc-ba475e4c2a3a/CD-ID-MEDI4893-1139_Protocol_amendment_5_redacted_FINAL_APPROVED-v1.pdf)..

Exploratory Study Endpoints

- Incidence of serious *S. aureus* infections, defined as events of pneumonia, bacteremia, bone and joint infections, deep skin or tissue infection, meningitis, endocarditis, or death attributable to *S. aureus*, through 30 days post dose
- Severity of serious *S. aureus* infections through 30 days post dose as measured by:
  - Days of hospital stay
  - Days of ICU stay
  - Days of antibiotic usage
  - Mortality
- Severity of *S. aureus* pneumonia through 30 days post dose as measured by:
  - Days of MV
- Magnitude of healthcare utilization through 30 days post dose in all subjects

- Suvratoxumab concentration and PK parameters in tracheal aspirate through 90 days post dose
- Serum and tracheal aspirate anti-AT neutralizing antibody levels at baseline and through 90 days post dose
- Serum and tracheal aspirate anti-AT specific IgG levels at baseline and through 90 days post dose

Primary and Exploratory Efficacy Endpoints Statistical Analyses

Primary analysis of the primary endpoint was carried out using a Poisson regression model with robust variance[4] to estimate the relative risk of *S. aureus* pneumonia through 30 days post dose between suvratoxumab 5000 mg and placebo, using the term of treatment group as a covariate. The relative risk reduction (RRR), its corresponding 2-sided 90% confidence interval (CI), and the 2-sided P value testing the null hypothesis that the incidence of having *S. aureus* pneumonia between suvratoxumab 5000 mg and placebo groups are the same were also obtained from the model. Statistically significant treatment effect was claimed if the 2-sided P value ≤0.1.

Treatment-by-subgroup interactions were tested for the primary efficacy endpoint (EAC-determined *S. aureus* pneumonia) and the secondary efficacy endpoints (EAC-determined all-cause pneumonia, and EAC-determined all-cause pneumonia or death) using a Poisson regression with robust variance model with terms of treatment, subgroup, and treatment-by-subgroup interaction. Within each level of a subgroup, the RRR and its corresponding 90% CI for the ratio of proportions were estimated using unconditional confidence interval on ratio of proportions.[5] A post hoc subgroup analysis

examined the effect of staphylococcal colonization load (PCR cycle threshold value <29 vs. PCR cycle threshold value ≥29) on the primary efficacy endpoint.

Statistical Analysis Plan

Complete statistical procedures are provided in the approved statistical analysis plan (available at https://s3.amazonaws.com/ctr-med-7111/CD-ID-MEDI4893-1139/3b2d9a7a-eaa9-4651-be9d-7271be664bb1/44a1deb6-dfb3-4d84-86bc-e8b7a314be4e/CD-ID-MEDI4893-1139_Statistical_Analysis_Plan_Final_v4.0_Redacted_FINAL_APPROVED-v1.pdf).

Protocol and Statistical Analysis Plan Amendments

Key details of global protocol and statistical analysis plan amendments, as well as other important changes to study conduct, are provided in the following tables.

Protocol Amendments

Amendment Number Version Number (Date of Approval)	Key Details of Amendment	Reason for Amendment
Amendments Made Prior to the Start of Patient Recruitment		
Amendment 1 Version 2.0 (07Aug2014)	Text was added to indicate that enrollment would continue in only the 5000 mg suvratoxumab and placebo arms during interim analyses. A second interim analysis for futility assessment was added to be conducted when approximately 33% to 40% of the enrolled subjects were followed through 30 days post dose	Clarity
	Under microbiologic confirmation, it was clarified that at least 1 of the confirmations (i.e., not just the first confirmation) should be obtained within 24 hours of onset of the event for mechanically ventilated subjects and within 72 hours of onset of the event for non-mechanically ventilated subjects	Clarity
	Added a section for unblinding for futility analysis purposes	To indicate that the sponsor site personnel would remain blinded to the treatment assignment of individual subjects until the last patient completed the study and the database was locked and the sponsor personnel would remain blinded to the treatment assignment of individual subjects until the Stage 1 analysis (i.e., primary analysis)
	The point at which the sample size may be modified was changed from after 40% to 50% of subjects enrolled to after 33% to 40% of subjects enrolled, and the sample size reassessment was to be performed prior to the futility assessment	The percentage of subjects enrolled that would trigger the sample size reassessment was lowered. This allowed the analysis to be performed in an expeditious manner in order to facilitate planning and decision making for the suvratoxumab clinical development program. Also clarified that sample size reassessment was to be performed prior to

		the futility assessment
	Added the interim analysis for futility	A second interim analysis for futility assessment was added to facilitate planning and decision making for the suvratoxumab clinical development program
Amendments Made After the Start of Patient Recruitment		
Amendment 2 Version 3.0 (04Jun2015)	Modified text to indicate that the DMC would review PK data and recommend dose adjustment or study termination during the interim analysis	Clarity
	Modified exclusion criterion for SOFA score based on the GCS score	The scores were modified to facilitate enrollment into the study
	Modified text to clarify that the criterion of dullness to percussion was not elicited by auscultation and it was a separate criterion. It was clarified that the acute changes in PaO2/FiO2 have to be maintained for at least 4 hours	Clarity
	Added details regarding the PK analysis and presentation to the DMC to further describe how the DMC would recommend dose adjustments or potential study termination	To further describe how the DMC would recommend dose adjustments or potential study termination
	Modified text to note that assessment of time to first *S. aureus* pneumonia might have been analysed by survival methods, which could have been potentially broader than the specific Kaplan-Meier approach originally indicated. In addition, language for subgroup analysis was modified to match the Statistical Analysis Plan	To further describe analysis of time to first *S. aureus* pneumonia
	It was added that the DMC would be responsible for recommending dose adjustment or potential study termination	Clarity
Amendment 3 Version 4.0 (14Aug2015)	Tracheal/bronchial aspirates for both Gram stain and culture were added to the screening procedures and removed from the post-dose procedures	Correction
	Clarified that the adjudication committee could have requested to review all data relevant to a potential case, including radiographic and imaging studies, as well as other clinical and/or microbiologic data	Clarity
Amendment 4 Version 5.0 (20Oct2016)	Modified text to reflect that an independent DMC reviewed the PK interim analysis data and, per protocol, recommended that the 2000 mg suvratoxumab group be discontinued and that a dose adjustment to 3000 mg suvratoxumab should not be made, since the lower dose PK profile in mechanically ventilated subjects was well below the target drug exposure, thus unlikely to offer	To include DMC recommendation

	efficacy. In addition, modified text to reflect the new number of subjects that will be enrolled and randomized to 1 of 2 treatment groups: 5000 mg suvratoxumab or placebo	
	Modified text to reflect change in terms of stratification by receipt of anti-*S. aureus* systemic antibiotic (treatment for ≤48 hours [rather than ≤24 hours]) within the 72 hours (rather than within the 48 hours) prior to randomization to align with the updated exclusion criterion 6 language. In addition, the restriction to ensure that no more than approximately 75% of the study population would consist of subjects in either stratification level of prior anti-*S. aureus* systemic antibiotic treatment was removed	To facilitate study enrollment and randomization
	Modified text to reflect that as the 2000 mg suvratoxumab would no longer be enrolled and randomized, the overall sample size of the study had been reduced. Consequently, due to the smaller overall sample size, futility analysis would be performed at a later time point based on the operating characteristics; thus, modified text to clarify that futility assessment would be conducted when 100 to 120 enrolled subjects (40% to 50%) were followed through 30 days instead of 33% to 40% of enrolled subjects	To reflect DMC recommendation
	Modified inclusion criterion 9 to reflect new follow-up duration of 190 days post dose instead of 360 days	Given the results of the PK interim analysis (and specifically, data on the shortened half-life of suvratoxumab in mechanically ventilated subjects), a 190-day post-dose safety follow-up was considered to be adequate, as it covered a duration of 5 half-lives of the IP. Also, a 190-day post-dose follow-up was deemed to be more operationally feasible than a 360-day post-dose follow-up
	Modified exclusion criterion 6 to exclude enrollment of subjects who received anti-*S. aureus* antibiotics for >48 hours (instead of >24 hours) within 72 hours (instead of 48 hours) prior to randomization. Modified exclusion criterion 8 to exclude enrollment of subjects with SOFA score of ≥9 at time of randomization and to clarify that vasopressors only used to improve cerebral perfusion pressure will not be entered in the calculation of the cardiovascular component of the SOFA score. Modified exclusion criterion 11 to allow enrollment of	To facilitate study enrollment and randomization

	subjects with asymptomatic HIV infection. Modified exclusion criterion 14 to change the time frame for exclusion of subjects receiving chemotherapy from 6 months to 2 months	
	Under "*S. aureus* Pneumonia Criteria for Subjects Who Are Mechanically Ventilated at the Time of Diagnosis", clarified that in subjects who were not intubated but met the protocol definition of mechanical ventilation, a specimen of expectorated sputum would be acceptable for microbiologic confirmation	Clarity
	Under "*S. aureus* Pneumonia Criteria for Subjects Who Are Not Mechanically Ventilated at the Time of Diagnosis", clarified that a patient was not considered to be mechanically ventilated when an endotracheal or nasotracheal tube was not in place and that the patient did not require positive ventilation support for at least 8 hours	Clarity
	Modified text to clarify that no adjustments were made when the 2000 mg dose was discontinued. In addition, the 3000 mg dose was removed from the key efficacy analyses	Clarity
	The sample size methodology was modified to use Poisson regression with robust variance	To be consistent with planned primary efficacy analysis
Amendment 5 Version 6.0 (15Mar2018)	Removed the following secondary objective from the study: "To evaluate the effect of suvratoxumab in reducing the incidence of *S. aureus* pneumonia by mechanical ventilation status." The corresponding endpoint was also removed	Per feedback from regulators
	Revised the timelines for analysis of exploratory endpoints 1 to 8, 12, and 15 to 30 days post dose only; mentions to 90 days post dose removed	To align with the primary efficacy analysis
	Reduced the total number of subjects planned to be enrolled from 285 to approximately 221	Due to enrollment challenges and need to maintain development timeline for suvratoxumab
	Modified the power calculation number from 80% to 70% and removed text describing sample size reassessment	Due to smaller planned sample size
	Removed mention of futility analysis as analysis would not be performed	It would not be informative due to the smaller planned sample size
	Revised text to indicate that Stage 1 analysis would be conducted after the last patient had completed follow-up through 30 days post dose (instead of 90 days), and that this analysis would be the primary analysis for efficacy only. Clarified that the safety, serum PK, and ADA would be summarized through 30	To keep with the development timelines for suvratoxumab

	days post dose	
	Modified text to indicate that for Stage 2 analysis, safety data would be summarized through 90 days post dose and through the end of the study	To keep with the development timelines for suvratoxumab
	The primary analysis population was changed from the ITT population to the mITT population	To account for those subjects who were randomized and not dosed
	Revised text to indicate that the stratification factors for country and prior systemic antibiotics would not be included in the analysis model. Further clarification regarding the analysis was also added	Per feedback from regulators
	Removed the secondary efficacy analysis section	Respective secondary efficacy endpoints were no longer conducted in the study

Statistical Analysis Plan Amendments

Planned in SAP	Key Details of Change	
	Changes Made After Unblinding of Study Data	
Not planned in the SAP	• Summary of Association Between Incidence of EAC-Determined *S. aureus* Pneumonia Through Study Day 31 and All Systemic Antibiotics Use - mITT Population • Exposure Adjusted Analysis for Incidence of EAC Determined All-Cause Pneumonia or Death Through Study Day 31 - mITT Population • Exposure Adjusted Analysis for Incidence of EAC Determined All-Cause Pneumonia Through Study Day 31 - mITT Population • Subgroup Analysis for Incidence of EAC-Determined *S. aureus* Only Pneumonia Through Study Day 31 by Age Group at Baseline - mITT Population • MV-Duration Adjusted Analysis for Incidence of EAC-Determined *S. aureus* Pneumonia Through Study Day 31 - mITT Population • Subgroup Analysis for Incidence of EAC-Determined All-Cause Pneumonia or Death Through Study Day 31 by Age Group at Baseline - mITT Population • Duration of All-Cause Healthcare Resource Utilization Through Study Day 31 mITT Population - Subjects with an EAC Determined *S. aureus* Pneumonia • Duration of All-Cause Healthcare Resource Utilization Through Study Day 91 - mITT Population • Duration of All-Cause Healthcare Resource Utilization Through Study Day 91 mITT Population - Subjects with an EAC-Determined *S. aureus* Pneumonia • Duration of All-Cause Healthcare Resource Utilization Through Study Day 91 by Primary Reason for ICU - mITT Population • Subgroup Summary of Duration of All Cause Healthcare Resource Utilization Through Study Day 91 by Age Group - mITT Population	To support clinical interpretation

	• Subgroup Summary of Duration of All-Cause Healthcare Resource Utilization Through Study Day 91 by Primary Reason for ICU and by Age Group - mITT Population • Exposure Adjusted Summary for Duration of Healthcare Resource Utilization Through Study Day 31 - mITT Population • Exposure Adjusted Summary for Duration of Healthcare Resource Utilization Through Study Day 31 by Age Group (≤ 65 vs > 65) - mITT Population • Exposure Adjusted Summary for Duration of Healthcare Resource Utilization Through Study Day 91 - mITT Population • Exposure Adjusted Summary for Duration of Healthcare Resource Utilization Through Study Day 91 by Age Group (≤ 65 vs > 65) - mITT Population • Exposure Adjusted Summary for Duration of Healthcare Resource Utilization Through Study Day 91 by Primary Reason for ICU - mITT Population • Exposure Adjusted Summary for Duration of Healthcare Resource Utilization Through Study Day 91 by Primary Reason for ICU and Age Group (≤ 65 vs > 65) - mITT Population	

References

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Supplementary Tables and Figures

Table S1. Incidence of S. aureus Pneumonia by Systemic Antibiotic Usage Within 2 Days Post Dose Through 30 Days (mITT Population).

EAC-determined *S. aureus* pneumonia — no. of subjects (%)	**No Antibiotic Use**				**Antibiotic Use**			
	Placebo (n = 71)	**Suvratoxumab 5000 (n = 67)**	**Suvratoxumab 2000 (n = 10)**	**RRR***	**Placebo (n = 29)**	**Suvratoxumab 5000 (n = 29)**	**Suvratoxumab 2000 (n = 5)**	**RRR***
With *S. aureus* pneumonia	22 (31·0)	14 (20·9)	1 (10·0)	32·6%	4 (13·8)	3 (10·3)	2 (40·0)	25·4%
Without *S. aureus* pneumonia	49 (69·0)	53 (79·1)	9 (90·0)	NA	25 (86·2)	26 (89·7)	3 (60·0)	NA

EAC endpoint adjudication committee, mITT denotes modified intent-to-treat; NA, not applicable; RRR, relative risk reduction

* RRR includes Suvratoxumab 5000 mg vs placebo. 2000 mg group was only planned as descriptive.

Table S2. Safety Summary in the As-Treated Population through 190 days Post-Dose

	30 Days Post Dose			90 Days Post Dose			190 Days Post Dose		
	Placebo	Suvratoxumab		Placebo	Suvratoxumab		Placebo	Suvratoxumab	
Subjects with, n (%)*	(n = 100)	5000 mg (n = 96)	2000 mg (n = 15)	(n = 100)	5000 mg (n = 96)	2000 mg (n = 15)	(n = 100)	5000 mg (n = 96)	2000 mg (n = 15)
At least 1 TEAE	90 (90·0)	87 (90·6)	15 (100)	92 (92·0)	89 (92·7)	15 (100)	93 (93·0)	90 (93·8)	15 (100)
At least 1 investigational product-related TEAE	2 (2·0)	6 (6·3)	4 (26·7)	2 (2·0)	6 (6·3)	4 (26·7)	2 (2·0)	6 (6·3)	4 (26·7)
At least 1 event of grade ≥3 severity†	51 (51·0)	50 (52·1)	9 (60·0)	54 (54·0)	55 (57·3)	10 (66·7)	55 (55·0)	59 (61·5)	10 (66·7)
Death (grade 5)†	16 (16·0)	15 (15·6)	1 (6·7)	20 (20·0)	21 (21·9)	2 (13·3)	22 (22·0)	27 (28·1)	3 (20·0)
At least 1 TESAE	32 (32·0)	36 (37·5)	4 (26·7)	37 (37·0)	45 (46·9)	6 (40·0)	40 (40·0)	50 (52·1)	7 (46·7)
At least 1 investigational product-related TESAE‡	0	1 (1·0)	1 (6·7)	0	1 (1·0)	1 (6·7)	0	1 (1·0)	1 (6·7)
At least 1 investigational product-related AESI§	0	2 (2·1)	2 (13·3)	0	2 (2·1)	2 (13·3)	0	2 (2·1)	2 (13·3)
At least 1 NOCD¶	0	2 (2·1)	0	2 (2·0)	0	3 (3·1)	2 (2·0)	0	3 (3·1)

*Subjects are counted once for each category regardless of the number of events. †Grade 3 = severe; grade 4 = life-threatening; grade 5 = fatal. ‡SAE criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject). §AESIs included targeted AEs of hypersensitivity (including anaphylaxis), infusion-related reactions, thrombocytopaenia, hepatic function abnormalities, and immune complex disease (e.g., vasculitis, endocarditis, neuritis, glomerulonephritis). ¶NCODs included diabetes, asthma, autoimmune disease (e.g., lupus, rheumatoid arthritis, and neurological disease (e.g., epilepsy).

AE denotes adverse event, AESI adverse event of special interest, NOCD new onset chronic disease, SAE serious adverse event, TEAE treatment-emergent adverse event, TESAE treatment-emergent serious adverse event.

Table S3. Prespecifed Analysis of Suvratoxumab Efficacy by Age Through Study Day 31 (mITT Population).

EAC-Determined Endpoint — no. of subjects (%)	Subjects ≤65 Years of Age				Subjects >65 Years of Age				Interaction P Value[†]
	Placebo (n = 69)	Suvratoxumab 5000 mg (n = 59)	Suvratoxumab 2000 mg (n = 14)	RRR (90% CI)[*]	Placebo (n = 31)	Suvratoxumab 5000 mg (n = 37)	Suvratoxumab 2000 mg (n = 1)	RRR (90% CI)*	
S. aureus pneumonia[‡]	20 (29·0)	9 (15·3)	3 (21·4)	47·4% (3·5 to 71·4)	6 (19·4)	8 (21·6)	0 (0·0)	-11·7% (-160·4 to 49·3)	0·210
All-cause pneumonia	22 (31·9)	10 (16·9)	4 (28·6)	46·8% (6·3 to 69·9)	8 (25·8)	10 (27·0)	0 (0·0)	-4·7% (-110 to 46·4)	0·197
All-cause pneumonia or death	29 (42·0)	17 (28·8)	5 (35·7)	31·4% (–5·4 to 55·2)	13 (41·9)	14 (37·8)	0 (0·0)	9·8% (-49·8 to 45·6)	0·479

*RRR (suvratoxumab 5000 mg vs. placebo) and 90% CI based on unconditional CI on ratio of proportions. [†]Interaction P value based on Poisson regression with robust variance, including the terms of treatment group, subgroup (age ≤65 years vs. age >65 years), and treatment by subgroup interaction. [‡]Primary efficacy analysis endpoint.

CI denotes confidence interval, EAC endpoint adjudication committee, mITT modified intent-to-treat, RRR relative risk reduction, *S. aureus Staphylococcus aureus*.

Table S4. Healthcare Resource Utilization by Age Through Study Day 91 (mITT Population).

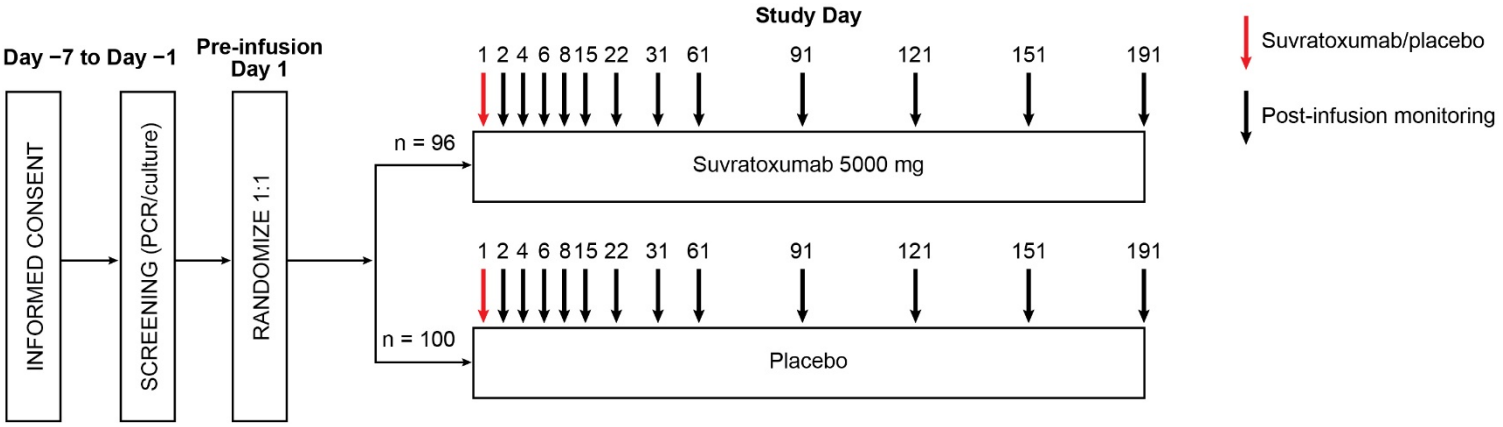
	Overall Study Population			Subjects ≤65 Years of Age			Subjects >65 Years of Age		
Health Resource	**Placebo (n = 100)**	**Suvratoxumab 5000 mg (n = 96)**	**Days Saved per Patient**	**Placebo (n = 69)**	**Suvratoxumab 5000 mg (n = 59)**	**Days Saved per Patient**	**Placebo (n = 31)**	**Suvratoxumab 5000 mg (n = 37)**	**Days Saved per Patient**
Hospitalization									
Mean hospital duration (SD) — days	37·9 (26·0)	35·2 (24·1)	2·7	39·1 (26·8)	30·3 (23·6)	8·8	35·1 (24·2)	43·1 (23·2)	-8·0
Hospital duration adjusted for 90 days study follow-up — days*	45·2	42·2	3·0	45·7	35·6	10·1	43·9	53·2	-9·3
ICU									
Mean ICU duration (SD) — days	20·5 (18·2)	18·5 (15·0)	2·0	20·0 (18·2)	16·7 (14·4)	3·3	21·6 (18·4)	21·3 (15·7)	0·3
ICU duration adjusted for 90 days study follow-up — days*	24·5	22·1	2·4	23·4	19·7	3·7	27·1	26·3	0·8
MV									
Mean MV duration mean (SD) — days	15·3 (15·9)	14·2 (14·4)	1·1	14·6 (15·1)	12·7 (15·7)	1·9	16·6 (17·7)	16·5 (11·8)	0·1
MV duration adjusted for 90 days study follow-up — days*	18·2	17·0	1·2	17·1	14·9	2·1	20·8	20·4	0·4
Systemic antibiotics									
Mean systemic antibiotic duration — days	21·4 (16·3)[†]	20·9 (20·7)[‡]	0·5	16·3 (14·8)	11·3 (11·1)	5·0	10·4 (8·6)	18·9 (22·2)	-8·5
Systemic antibiotic duration adjusted for 90 days study follow-	21·4	21·4	0	22·4	17·9	4·5	19·1	27·3	-8·2

up — days*									
Anti-*S. aureus* systemic antibiotics									
Mean anti-*S. aureus* systemic antibiotic duration — days	14·7 (13·6)[§]	14·3 (16·7)[¶]	0·4	23·6 (18·7)	18·0 (19·0)	5·6	16·9 (8·3)	25·5 (22·6)	-5·7
Anti-*S. aureus* systemic antibiotic duration adjusted for 90 days study follow-up — days*	11·1	9·8	1·3	12·7	7·5	5·2	7·1	13·8	-6·7

*Duration per 90 patient-days of exposure = (total duration of healthcare resource utilization measure/sum of follow-up time) x 90 days. [†]n = 84. [‡]n = 82. [§]n = 63. [¶]n = 55.

ICU denotes intensive care unit, mITT modified intent-to-treat, MV mechanical ventilation, NA not applicable, *S. aureus Staphylococcus aureus,* SD standard deviation.

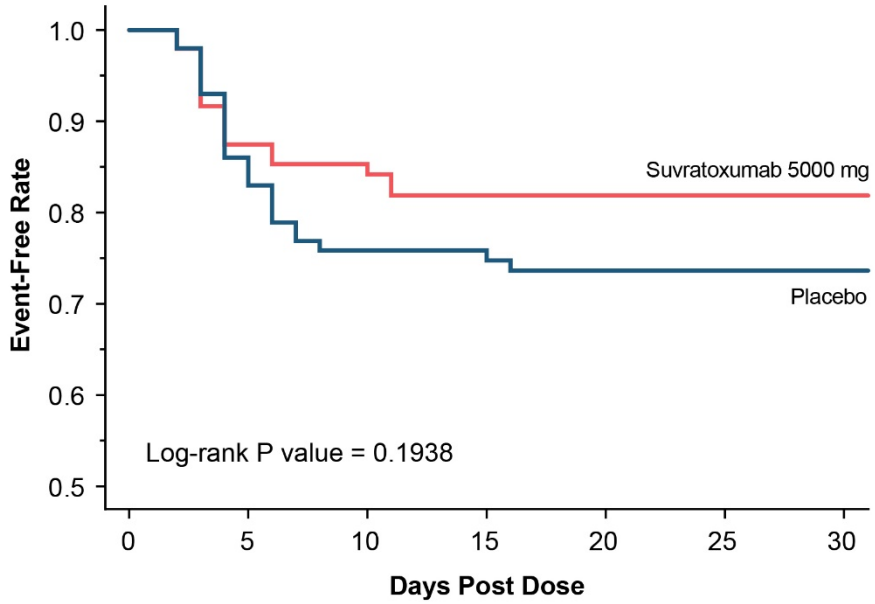
Figure S1. Study design.



Critically ill patients without pneumonia and requiring prolonged ventilation were enrolled and tested by polymerase chain reaction (PCR) to identify *Staphylococcus aureus* colonization in the lower respiratory tract. PCR-positive subjects were randomized to receive a single intravenous (IV) infusion of either placebo or suvratoxumab 5000 mg. Subjects were monitored closely for development of *S. aureus* pneumonia (primary endpoint), adjudicated by an independent panel of blinded HAP/VAP experts and radiologists.

HAP hospital-acquired pneumonia, VAP ventilator-associated pneumonia.

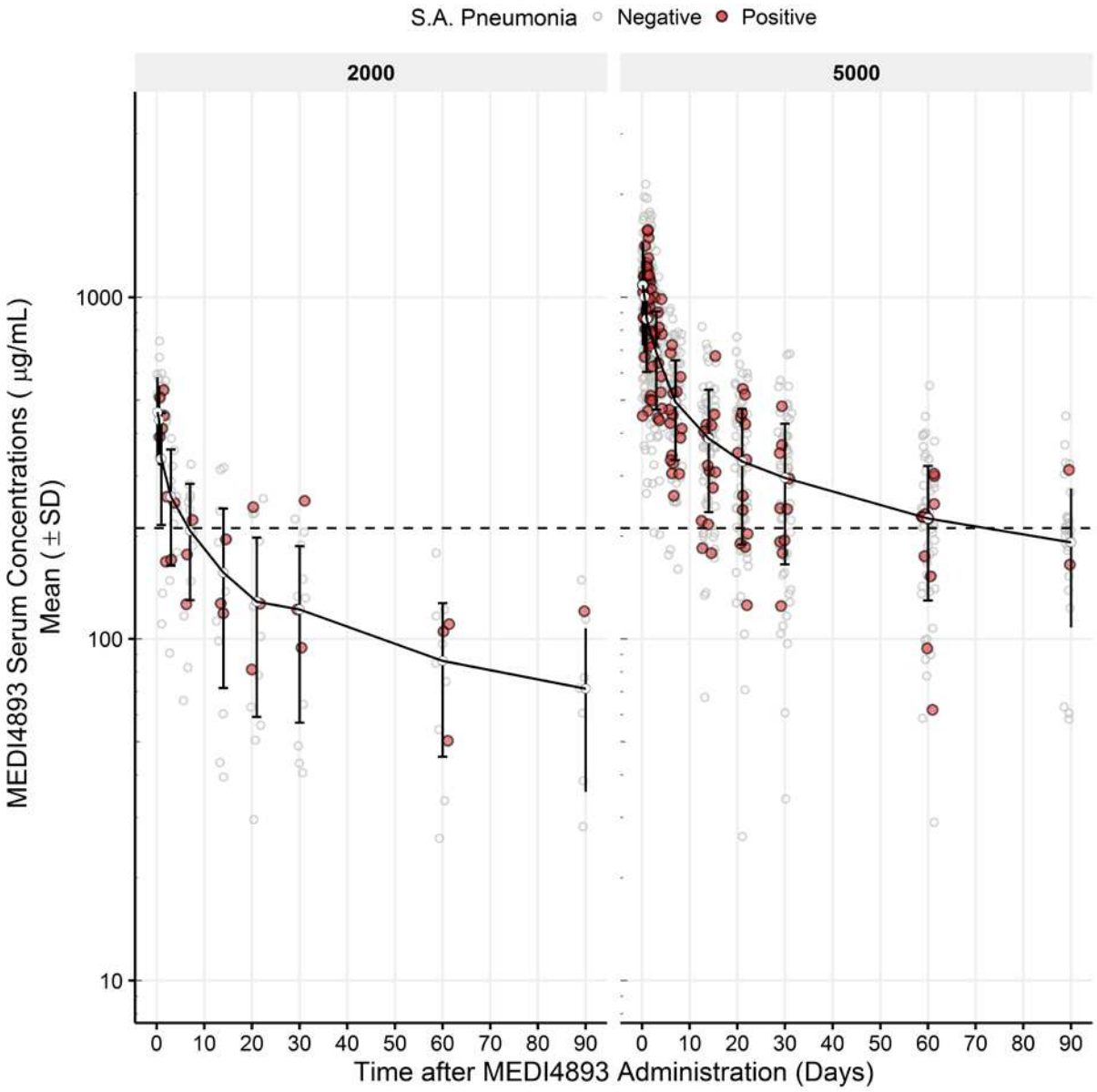
Figure S2. Kaplan–Meier Estimate of Time to EAC-determined S. aureus Pneumonia Through Study Day 31.



Placebo							
No. at risk	100	82	71	68	62	61	60
No. of events	0	17	24	25	26	26	26
Suvratoxumab 5000 mg							
No. at risk	96	81	75	71	70	69	68
No. of events	0	12	15	17	17	17	17

EAC endpoint adjudication committee,

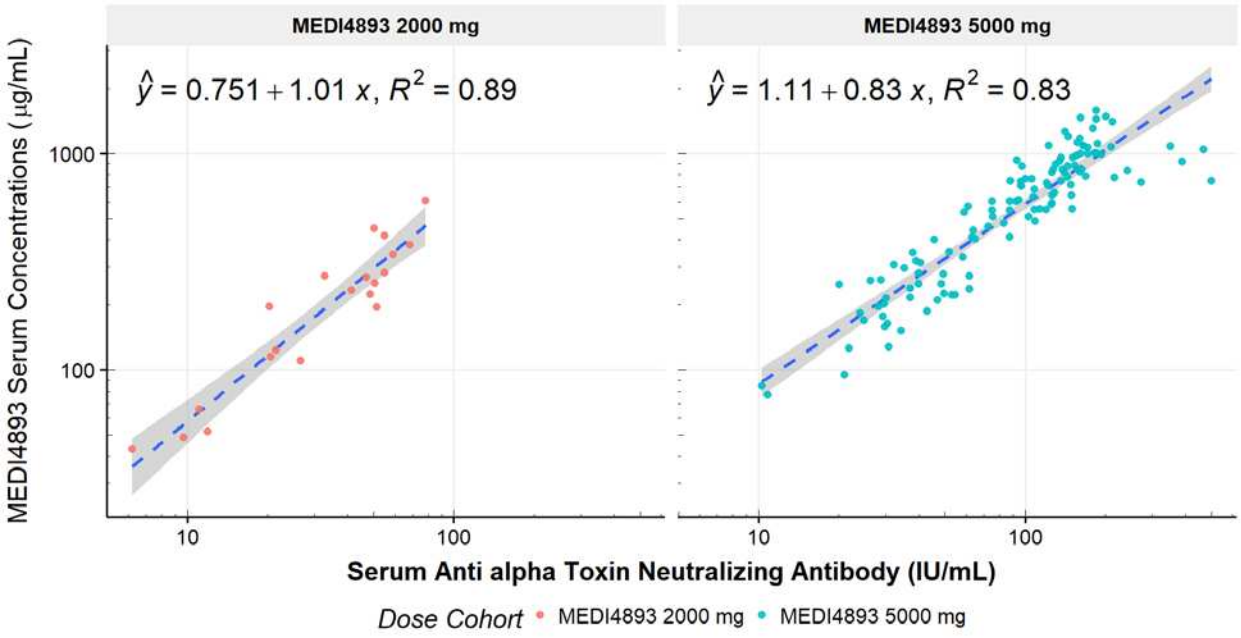
Figure S3. Concentration of Suvratoxumab in Serum in Subjects With and Without S. aureus Pneumonia through 90 Days Post Dose.



Following a single 5000 mg infusion of survratoxumab, mean (SD) serum concentration was 296 (131) µg/mL at 30 days and 192 (84) at 90 days post dose. For the 2000 mg cohort, mean (SD) serum concentration was 122 (65) µg/mL and 72 (36) µg/mL at 30 and 90 days post dose, respectively. At 30 days post dose, most (73·5%) subjects treated with the 5000 mg suvratoxumab dose had mean serum concentrations of antibody above the targeted concentration of 211 µg/mL[1] (indicated by the dashed line). In contrast, only 1 out 13 (7·7%) subjects with quantifiable PK treated with the 2000mg

dose had serum concentrations above the PK target. Subjects positive for *S. aureus* pneumonia at any time are indicated by red circles.

Figure S4. Correlation of Serum Concentrations of Suvratoxumab and Alpha-toxin-Neutralizing Activity.



There was a linear correlation of suvratoxumab concentration and anti-alpha-toxin neutralizing antibody concentration in serum.

Additional References

1. Yu XQ, Robbie GJ, Wu Y, et al. Safety, tolerability, and pharmacokinetics of MEDI4893, an investigational, extended-half-life, anti-*Staphylococcus aureus* alpha-toxin human monoclonal antibody, in healthy adults. *Antimicrob Agents Chemother* 2017;**61**:1–9.