Efficacy and Safety Profile of Suvratoxumab, a Novel Anti-*Staphylococcus aureus* Monoclonal Antibody: Results of the SAATELLITE Study in Mechanically Ventilated, Intensive Care Unit Patients

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This research project receives support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115523 | 115620 | 115737 resources of which are composed of financial contribution from the European Union Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

Disclosures

Dr. FRANCOIS reports personal fees from AstraZeneca-Medimmune, during the conduct of the study; personal fees from Asahi-Kasaï, personal fees from Ferring, personal fees from Aridis, personal fees from Inotrem, personal fees from Biomerieux, personal fees from Combioxin, personal fees from AM-Pharma, personal fees from Polyphor, outside the submitted work.

Funding Statement

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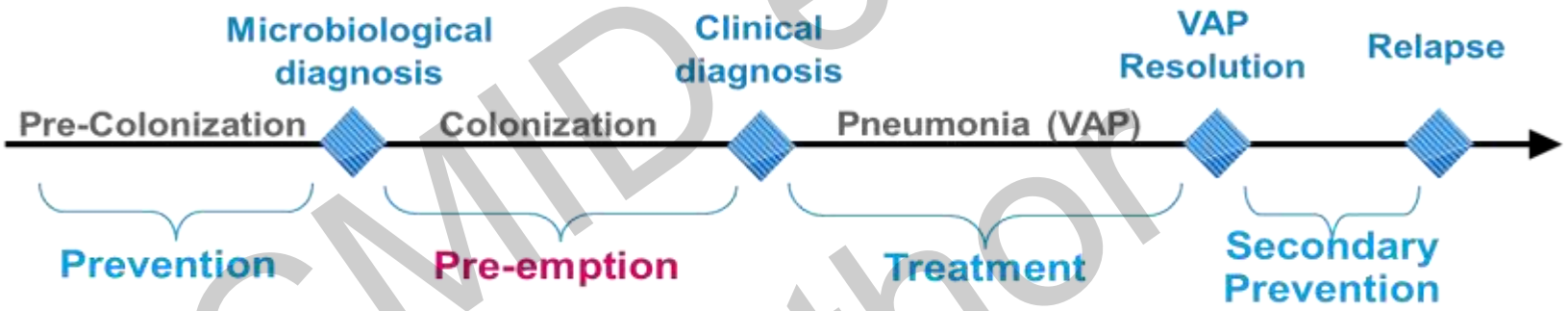
Burden of *Staphylococcus aureus* ICU Pneumonia

- Mechanical ventilation (MV) is a lifesaving intervention in millions of critically ill patients each year globally
- ICU patients of all ages are at high risk for pneumonia and poor outcomes, including death[1]
- *Staphylococcus aureus* remains one of the most common causes of pneumonia in ICU patients, occurring early and requiring rapid intervention[2-4]

1. Blot S et al. *Crit Care Med.* 2014;42:601-609. 2. ATS/IDSA. *Amer J Respir Crit Care Med.* 2005;171:388-416. 3. Restrepo MI et al. *Respir Care.* 2013;58:1220-1225. 4. Weiner LM et al. *Infect Control Hosp Epidemiol.* 2016;1-14.

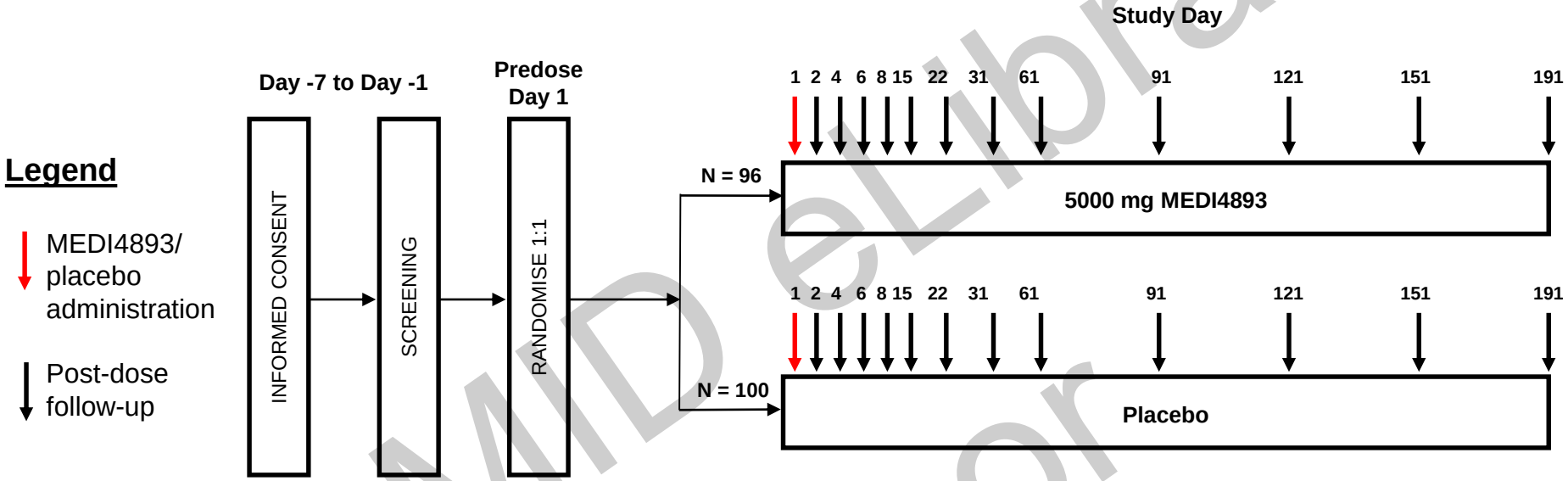
Study Rationale

- Respiratory tract colonization precedes ventilator-associated pneumonia in 94 % of cases

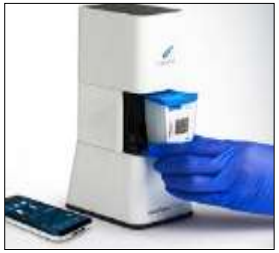


- Suvratoxumab (MEDI4893) is an extended half-life, human monoclonal antibody targeting the pore-forming alpha toxin (AT) of *S. aureus*

SAATELLITE Phase 2 Study



- Critically ill patients without pneumonia, requiring prolonged ventilation were enrolled and tested by PCR to identify *S aureus* colonization in the lower respiratory tract
  - PCR: Fast (<2 hrs), easy to perform (<2 mins hands-on time)
  - PCR-positive subjects randomized to receive single IV infusion of either placebo or suvratoxumab
  - Followed closely for development of *S aureus* pneumonia (Primary Endpoint), adjudicated by an independent panel of blinded HAP/VAP experts and radiologists



Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Age ≥18 years
- Tracheal or bronchial sample positive for *S aureus*
- Currently intubated, on mechanical ventilation in the ICU
- Expected to remain intubated and mechanically ventilated for ≥3 days
- No diagnosis of new-onset pneumonia

Exclusion criteria:

- Acute confirmed or suspected Staphylococcal disease
- Anti-*S aureus* antibiotics for > 48 hours within 72 hours prior to randomisation
- CPIS of ≥6, or SOFA score ≥9, or APACHE-II score ≥25
- Active pulmonary disease that would impair the ability to diagnose pneumonia

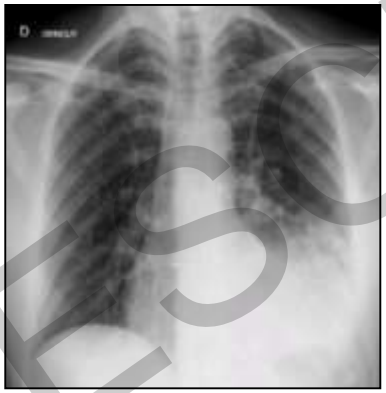
Primary Endpoint: Incidence of *S aureus* Pneumonia Within 30 Days Post Dose

In Mechanically Ventilated Subjects:

- Intubated with endotracheal or nasotracheal tube and receiving positive pressure ventilation support, or
- Not intubated but requires >8 hours positive pressure ventilation in the past 24 hours

In Extubated Subjects:

- Subject is not intubated with an endotracheal or nasotracheal tube, and
- Subject requires positive pressure ventilation support for <8 hours



Must meet ALL 3 criteria to satisfy Primary Endpoint:

- Radiographic
- Clinical
- Microbiologic

Adjudicated by an independent panel of blinded HAP/VAP experts and radiologists

Subject Characteristics

Parameter	Placebo	Suvratoxumab
Enrolment		
• Screened = 797		
• Number subjects randomised (ITT)	102	96
• Number subjects dosed (mITT)	100	96
Patient characteristics, n (%) (mITT)		
• Female	45 (45.0)	37 (38.5)
• Male	55 (55.0)	59 (61.5)
• Age ≤65	69 (69.0)	59 (61.5)
• Age >65	31 (31.0)	37 (38.5)
Clinical severity score, mean (SD)		
• APACHE-II[a]	15.2 (5.2)	15.1 (5.2)
• SOFA[b]	4.5 (2.0)	4.8 (2.0)
• CPIS[c]	3.0 (1.5)	3.0 (1.3)
Pre-dose anti-*S aureus* antibiotic stratum, n (%)		
• Yes	13 (13.0)	12 (12.5)
• No	87 (87.0)	84 (87.5)

[a]APACHE II: Acute Physiology and Chronic Health Evaluation II
[b]SOFA: Sepsis-related Organ Failure Assessment
[c]CPIS: Clinical Pulmonary Infection Score

[a]Subjects ≤65 years of age represented over 65% of the overall population.

Efficacy against multiple pneumonia definitions in mITT population

Pneumonia Definition	Placebo N=100	Suvratoxumab N=96	RRR (90% CI)[a]	NNT[b]
***S aureus* Pneumonia**[c]	26 (26.0%)	17 (17.7%)	**31.9%** (-7.5%,56.8%)	12
All Cause Pneumonia	30 (30.0%)	20 (20.8%)	**30.6%** (-4.9%,54.0%)	11
All Cause Pneumonia or Death	42 (42.0%)	31 (32.3%)	**23.1%** (-4.9%,43.6%)	10

Efficacy in subjects age ≤65 years (mITT population)

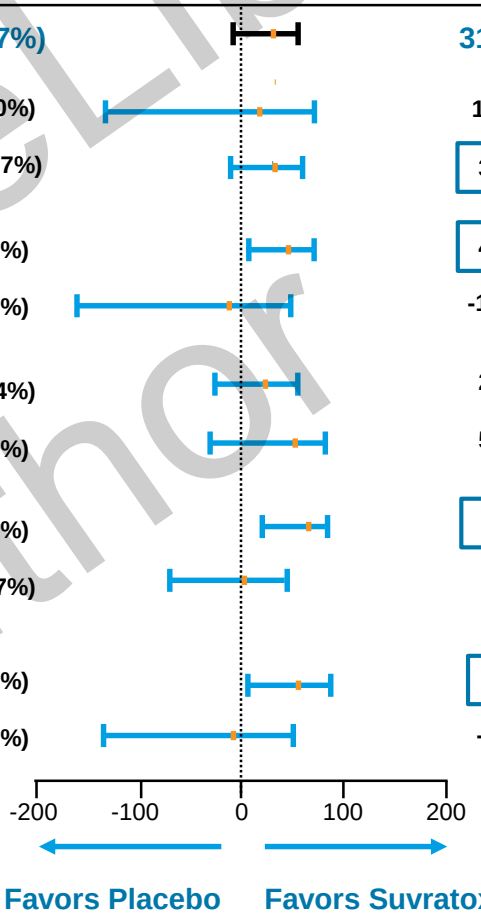
Characteristic	Placebo N=69	Suvratoxumab N=59	RRR (90% CI)[a]	NNT[b]
***S aureus* Pneumonia**[c]	20 (29.0%)	9 (15.3%)	**47.4%** (3.5%, 71.4%)	7
All Cause Pneumonia	22 (31.9%)	10 (16.9%)	**46.8%** (6.3%, 69.9%)	7
All Cause Pneumonia or Death	29 (42.0%)	17 (28.8%)	**31.4%** (-5.4%, 55.2%)	8

[a] Relative risk reduction (MEDI4893 5000 mg versus placebo), 90% confidence interval (CI), and p-value based on Poisson regression with robust variance.
[b] NNT = number needed to treat.
[c] Primary efficacy analysis for the Incidence of EAC-Determined S aureus pneumonia through study day 31, mITT population.

[a]Incidence rate reduction and 90% confidence interval (CI) based on Poisson regression with robust variance. [b]NNT was calculated as the inverse of the absolute risk reduction (1/rate percent placebo minus rate percent suvratoxumab). [c]Primary Endpoint; causative pathogens include *S aureus* with or without other pathogens

Prevention of *S. aureus* Pneumonia in Certain Subgroups

Subgroup	Placebo n/N (%)	Suvratoxumab n/N (%)	RRR (90% CI)
Overall	**26/100 (26.0%)**	**17/96 (17.7%)**	**31.9% (-7.5%, 56.8%)**
Pre-dose anti-*S aureus* Abx Stratum			
Yes	4 / 13 (30.8%)	3 / 12 (25.0%)	18.8% (-133.2%, 72.9%)
No	22 / 87 (29.0%)	14 / 84 (16.7%)	34.1% (-11.6%, 60.4%)
Age (years)			
≤ 65	20 / 69 (29.0%)	9 / 59 (15.3%)	47.4% (3.5%, 71.4%)
> 65	6 / 31 (19.4%)	8 / 37 (21.6%)	-11.7% (-160.4%, 49.3%)
BMI (kg/m^2)			
≤ 30	19 / 73 (26.0%)	14 / 72 (19.4%)	25.3% (-26.0%, 55.6%)
> 30	7 / 26 (26.9%)	3 / 24 (12.5%)	53.6% (-31.1%, 83.2%)
Staph colonisation load (PCR CT value)			
Low Bacterial Load	12 / 36 (33.3%)	4 / 36 (11.1%)	66.7% (21.3%, 86.2%)
High Bacterial Load	14 / 63 (22.2%)	13 / 60 (21.7%)	2.5% (-70.4%, 45.3%)
VAP prevention			
5 bundles	19 / 59 (32.2%)	9 / 52 (17.3%)	46.3% (2.2%, 70.5%)
< 5 bundles	7 / 41 (17.1%)	8 / 44 (18.2%)	-6.5% (-135.1%, 51.1%)



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Suvratoxumab Associated With Shorter HRU Duration Through 90 Days Post-Dose

Health Resource	Overall Study Population			Subjects ≤65 Years of Age		
	Placebo N=69	Suvratoxumab N=59	Days Saved/ Subject	Placebo N=69	Suvratoxumab N=59	Days Saved/ Subject
Hospital duration						
Mean hospitalisation duration (days)	37.9	35.2	**2.7**	39.1	30.3	**8.8**
Hospitalisation duration adjusted for 90 days study follow-up	45.2	42.2	**3.0**	45.7	35.6	**10.1**
Mean hospital-free days	37.5	39.4	**1.9**	37.7	46.2	**8.5**
ICU duration						
Mean ICU duration (days)	20.5	18.5	**2.0**	20.0	16.7	**3.3**
ICU duration adjusted for 90 days study follow-up	24.5	22.1	**2.4**	23.4	19.7	**3.7**
Mean ICU-free days	53.9	54.6	**0.7**	55.9	58.5	**2.6**
MV duration						
Mean MV duration (days)	15.3	14.2	**1.1**	14.6	12.7	**1.9**
MV duration adjusted for 90 days study follow-up	18.2	17.0	**1.2**	17.1	14.9	**2.1**
Mean MV-free days	58.9	58.7	**-0.2**	60.9	62.1	**1.2**

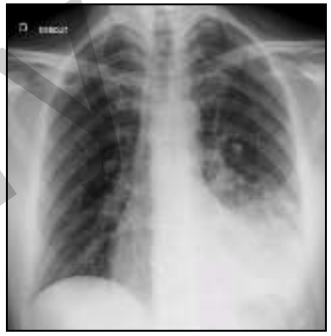
TEAEs and SAEs (mITT population)

Subjects with[a], n (%)	30 Days Post-Dose		90 Days Post-Dose	
	Placebo N=100	Suvratoxumab N=96	Placebo N=100	Suvratoxumab N=96
At least one event	90 (90.0)	87 (90.6)	92 (92.0)	89 (92.7)
At least one investigational product related TEAE	2 (2.0)	6 (6.3)	2 (2.0)	6 (6.3)
At least one event of ≥ grade 3 severity[b]	51 (51.0)	50 (52.1)	54 (54.0)	55 (57.3)
Death (Grade 5)[b]	16 (16.0)	15 (15.6)	20 (20.0)	21 (21.9)
At least one investigational product related SAE[c]	0	1 (1.0)	0	1 (1.0)
At least one investigational product related AESI	0	2 (2.1)	0	2 (2.1)

SAE = Serious Adverse Event; AESI = Adverse Event of Special Interest.

[a] Subjects are counted once for each category regardless of the number of events.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal
[c] Serious adverse event 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).

Conclusions



- PCR-based enrichment strategy successfully identified an intubated population with 26% ICU *S aureus* pneumonia attack rate
- Suvratoxumab prevented *S aureus*-associated pneumonia using multiple pneumonia case definitions, with greater efficacy in subjects ≤ 65 years
  - *S aureus* pneumonia (32%; 47% ≤65 years)
  - All-cause pneumonia (30%; 47% ≤65 years)
- Efficacy was observed even when VAP bundles were optimised
- Potential cost savings: shorter duration of hospitalisation, ICU stay, and ventilator utilisation
- As expected, 30 and 90-day mortality was balanced
- Suvratoxumab demonstrated an acceptable safety profile

Acknowledgements

The authors wish to thank all patients and supporting family members for their participation in this clinical study. We also wish to thank the WP6B team and all study site investigators and staff members for their outstanding work on this challenging study.

Backup Slides

Other Endpoints

- **Primary safety endpoints**
  - Treatment-emergent adverse events (TEAEs) through 30 and 90 days
  - Treatment-emergent serious adverse events (TESAEs) and adverse events of special interest (AESIs) through 190 days (30 and 90 days post dose presented)
- **Secondary endpoints**
  - Suvratoxumab serum PK parameters and anti-drug antibodies (ADA) response through 90 days post dose
- **Exploratory endpoints**
  - Incidence of all-cause mortality and all-cause pneumonia through 30 days post dose
  - Magnitude of healthcare utilisation (HRU) through 30 days (per protocol) and 90 days (ad hoc) post dose

Health Resource Utilization (HRU) Savings Through 90 Days Post-Dose

- **Key HRUs**
  - Duration of hospitalisation
  - Duration of ICU stay
  - Duration of mechanical ventilation
- **Analyzed 3 ways**
  - Mean HRUs
  - Mean HRUs adjusted for duration of study participation through 90 days
  - Mean HRU-free days

Suvratoxumab PK and ADAs

- Serum PK was sustained above the 211 µg/mL target for up to 60 days
  - Terminal half-life: 72±33 days
- In the placebo group, ADAs were detected post-dose in:
  - 4/74 (5.4%) at 30 days
  - 2/66 (3.0%) at 60 days, and
  - 1/60 (1.7%) at 90 days post dose
- In the suvratoxumab group, no subjects had ADAs detected post-dose