Safety, Tolerability, and Immunogenicity of a Novel 4-Antigen *Staphylococcus aureus* Vaccine (SA4Ag) in Healthy Adults: Results of a Randomised, Placebo-Controlled, First-in-Human Phase 1/2 Study

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INTRODUCTION AND PURPOSE

- *Staphylococcus aureus* is a major cause of healthcare-associated infections[1,2]
- Given the burden of disease, a 4-antigen *S. aureus* vaccine (SA4Ag) has been developed to protect against a range of clinical *S. aureus* isolates and includes:
  - Capsular polysaccharide serotypes 5 and 8 (CP5 and CP8) conjugated to the nontoxic mutant form of diphtheria toxin, CRM_{197};
  - recombinant surface protein clumping factor A (r*m*ClfA); and
  - recombinant manganese transporter protein C (rP305A)
- SA4Ag antigens target *S. aureus* virulence factors that facilitate immune evasion (CP5 and CP8), adhesion (ClfA), and nutrient transport (P305A)[3]
- The current study evaluates the immunogenicity, safety, and tolerability of SA4Ag in healthy adults

METHODS

Study Design

- Healthy subjects aged 18 to <65 years were enrolled in this Phase 1/2a placebo-controlled, double-blind, parallel group dose-ranging study in 2 equally sized age strata (18 to <50 years and 50 to <65 years)
- Subjects were randomised (1:1:1:1) to receive a single, intramuscular injection of placebo or 1 of 3 formulations of SA4Ag containing fixed doses of CP5-CRM_{197}, CP8-CRM_{197}, and r*m*ClfA and either low-, mid-, or high-dose level rP305A (**Figure 1**)

Figure 1. SA4Ag Dose Levels

	SA4Ag dose levels		
Antigen	Low dose	Mid dose	High dose
CP5-CRM_{197}	30 µg	30 µg	30 µg
CP8-CRM_{197}	30 µg	30 µg	30 µg
r*m*ClfA	60 µg	60 µg	60 µg
rP305A	30 µg	60 µg	200 µg

- Primary objectives
  - Evaluate safety and tolerability of SA4Ag
  - Evaluate immunogenicity 28 days after vaccination with SA4Ag
- Secondary objective
  - Describe kinetics of immune response for 12 months following SA4Ag vaccination

Assessments

Safety

- Immediate reactions
- Reactogenicity
  - Local reactions: redness, swelling, and pain at the injection site
  - Systemic events: fever, vomiting, diarrhoea, headache, new/worsening muscle and/or joint pain
- Adverse events (AE) collected through Day 29; serious AE (SAE) collected through Month 6
- Laboratory assessments (Phase 1 subjects only): haematology, coagulation, and biochemistry parameters

Immunogenicity

- Assessed at baseline and at postvaccination Days 8, 11, 15, and 29, and Months 3, 6, 9, and 12
- Measured by a functional opsonophagocytic activity (OPA) assay using clinical *S. aureus* strains expressing CP5 and CP8. Responses to each antigen were measured using a 4-plex competitive Luminex® immunoassay (cLIA)
- A Fibrinogen Binding Inhibition (FBI) assay measured functional ability of anti-ClfA antibodies to inhibit fibrinogen-dependent binding of *S. aureus*

Statistical Analysis

- Geometric mean titres (GMT) and associated confidence intervals (CI) (95.2% CI at Day 29; 95% elsewhere) were calculated for each assay in each vaccine group

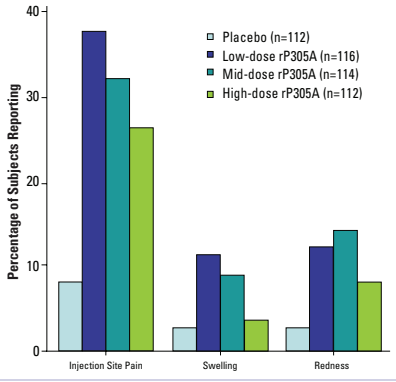
RESULTS

- 456 subjects were randomised; 454 were vaccinated (low dose, n=117; mid dose, n=114; high dose, n=113; placebo, n=112)
  - 18 to <50 years (SA4Ag, n=172; placebo, n=59)
  - 50 to <65 years (SA4Ag, n=170; placebo, n=53)
- Mean age of subjects 45 years (18-64); 57% female; 74% white
- 87.5% of subjects completed the study

Safety

- SA4Ag vaccine was generally well tolerated across all rP305A dose levels tested
- Local reactions were reported more frequently with SA4Ag than with placebo (**Figure 2**)
  - Most reactions were mild in severity

Figure 2. Local Reactions



- Systemic events were comparable across vaccine and placebo groups
- AEs considered related to the vaccine were reported in 3.6%, 6.0%, 4.4%, and 10.7% of subjects receiving placebo, low-, mid-, and high-dose rP305A, respectively
- No vaccine-related SAE or deaths were reported

Immunogenicity

- Substantial increases in OPA and FBI GMT relative to baseline were observed at Days 15 and 29 (**Figure 3**)
- A rapid increase in cLIA GMT for all 4 antigens was observed (**Figure 4**)
  - cLIA GMT were sustained, with a gradual wane through Month 12
- cLIA GMT for rP305A was dose dependent (**Figure 4**)
- Responses to CP5, CP8, or ClfA at Days 15 and 29 were not dependent on dose of rP305A

Figure 3. OPA, cLIA, and FBI GMTs at Baseline, Day 15, and Day 29 – Subjects Aged 18 to <65 Years (Evaluable Population)

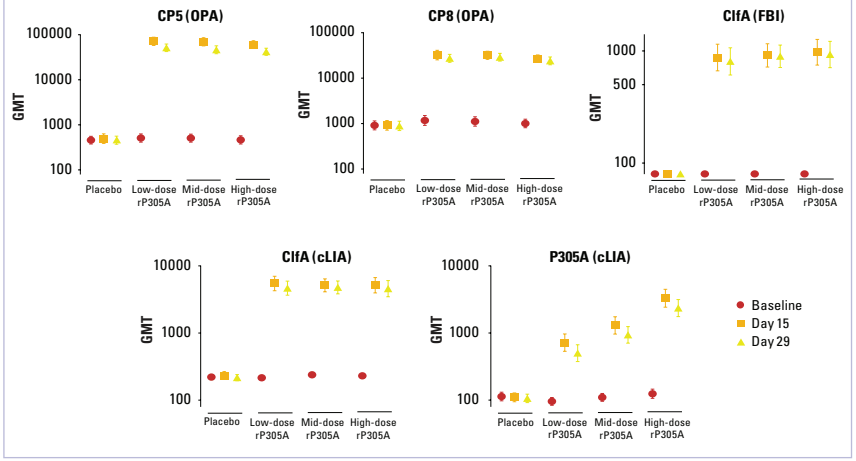
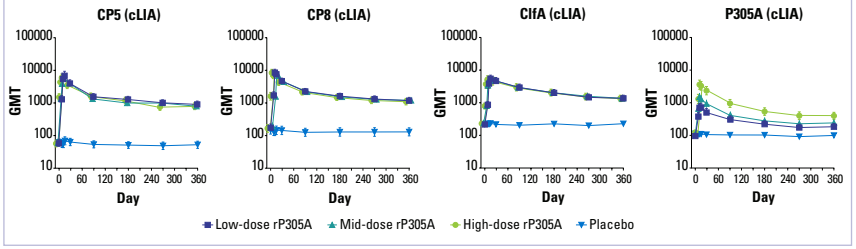


Figure 4. cLIA GMTs for Each Antigen Through Month 12 – Subjects Aged 18 to <65 Years (Evaluable Population)



CONCLUSIONS

- SA4Ag was well tolerated and induced rapid and robust functional antibody responses
- The immune responses to rP305A antigen were dose-dependent
- rP305A dose level did not affect the immune response to the other 3 antigens in the vaccine
- Marked antibody response is present by Day 15, indicating the potential for vaccine administration prior to a period of risk
- Antibody titres persisted through Month 12, the last time point measured
- Results support further development of SA4Ag for the prevention of invasive *S. aureus* disease in at-risk adults

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