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


1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; 2Vanderbilt University School of Medicine and Monroe Carell Jr. Children’s Hospital at Vanderbilt, Nashville, TN, USA; 3Miami Research Associates Clinical Research, Overland Park, KS, USA; 4Pfizer Inc, Sydney, NSW, Australia; 5Pfizer Inc, Collegeville, PA, USA; 6Pfizer Inc, Pearl River, NY, USA

INTRODUCTION AND PURPOSE

• Staphylococcus aureus is a major cause of healthcare-associated infections.
• 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 P6-agglutinin, CRM197
  − Clumping factor A (ClfA, Cp305A)
• SA4Ag antigens target S. aureus virulence factors that facilitate immune evasion (CP5 and CP8, adhesion, ClfA, and nutrient transport rP305A)
• 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 CPS-CRM197, CP5-CRM197, and rCpfA and either low-, mid-, or high-dose level rP305A (Figure 1)
• Primary objectives
  − Evaluate safety and tolerability of SA4Ag
  − Evaluate immunogenicity 28 days after vaccination with SA4Ag

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

Assessments

• Secondary objective
  − Describe kinetics of immune response for 12 months following SA4Ag vaccination

Immunogenicity

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

Statistical Analysis

• Geometric mean titres (GMT) and associated confidence intervals (CI) (95% 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=117; placebo, n=112)
  − 50 to <65 years (SA4Ag, n=114; placebo, n=113)
• Mean age of subjects 45 years (18-64)
• 87.5% of subjects completed the study

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 12 months following SA4Ag vaccination
• No vaccine-related SAE or deaths were reported

REFERENCES


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Figure 1. SA4Ag Dose Levels

Figure 2. Local Reactions

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)

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