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Vaccine development

SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A NOVEL 4-ANTIGEN STAPHYLOCOCCUS AUREUS VACCINE (SA4AG) IN HEALTHY ADULTS: RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED FIRST-IN-HUMAN PHASE 1/2 STUDY

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Objectives: *Staphylococcus aureus* is a major cause of serious healthcare- and community-associated infections in all age groups. Due to increasing antibiotic-resistance, other means to control *S. aureus* infections, including vaccines, are critically needed. A novel 4-antigen *S. aureus* vaccine (SA4Ag) is being developed containing capsular polysaccharide serotypes 5 and 8 (CP5 and CP8) individually conjugated to CRM_{197}, a recombinant surface protein clumping factor A (r*m*ClfA), and a recombinant manganese transport protein C (MntC) (referred to as rP305A). The main objectives of the study were to evaluate the immunogenicity, safety and tolerability of SA4Ag vaccine in healthy adults.

Methods: Adults aged 18 to <65 years were enrolled in this Phase 1/2 placebo-controlled, double-blind, parallel-group trial. Subjects were randomized to receive placebo or one of three formulations of SA4Ag vaccine containing fixed doses of CP5-CRM_{197}, CP8-CRM_{197}, and r*m*ClfA (30 µg, 30 µg, and 60 µg respectively), and either low (20 µg), mid (60 µg), or high (200 µg) dose level rP305A. Immunogenicity was measured at multiple time points through Month 12 using antigen-specific competitive Luminex® immunoassays (cLIAs) and opsonophagocytic activity (OPA) assays. Blood chemistry, hematology and coagulation parameters were assessed in Phase 1 subjects, and local reactions and systemic events were evaluated through Day 14 following vaccination in all subjects. All adverse events (AEs) were collected through Day 29 and serious AEs (SAEs) through Month 6. This study is registered under NCT01364571 at ClinicalTrials.gov.

Results: 456 healthy adults were enrolled (112 placebo, 117 low dose, 114 mid dose, 113 high dose SA4Ag vaccine). A single dose of SA4Ag vaccine resulted in a rapid increase in cLIA geometric mean titers (GMTs) for all 4 antigens, and a dose-dependent response was observed for rP305A. cLIA geometric mean fold rises at Day 29 were 62.6–69.3 for CP5, 21.2–27.0 for CP8, 19.9–21.9 for ClfA, and 5.3, 8.4, and 18.3 for low, mid and high dose levels of rP305A, respectively. While cLIA GMTs gradually waned, they remained substantially greater than baseline through Month 12. The SA4Ag vaccine also elicited substantial increases in OPA GMTs at Day 15 and Day 29, demonstrating functional (bacterial killing) antibody responses. The SA4Ag vaccine was well tolerated with local reactions mostly reported as mild or moderate. Systemic events were comparable among SA4Ag vaccine and placebo recipients. AEs and SAEs were also similar among vaccine and placebo groups. Phase 1 clinical laboratory evaluations were similar, pre- and post-vaccination among SA4Ag vaccine and placebo recipients.

Conclusions: Single dose SA4Ag vaccination was well tolerated in adults aged 18 to <65 years and induced rapid and robust functional antibody responses maintained through post-vaccination Month 12. These results support continuing development of SA4Ag vaccine for the prevention of invasive *S. aureus* infection in at-risk adult populations including patients undergoing elective surgery.