CLINICAL STUDY REPORT SYNOPSIS

Vaccine Name and Compound Number: *Staphylococcus aureus* 4-Antigen Vaccine, Compound Number: PF-06290510

Report Title: Final Report: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of *Staphylococcus Aureus* 4 Antigen Vaccine (SA4Ag) in Adults Undergoing Elective Open Posterior Spinal Fusion Procedures With Multilevel Instrumentation

Protocol Number: B3451002

Sponsor: Pfizer, Inc.

Phase of Development: Phase 2b

First Subject First Visit: 02 July 2015

Last Subject Last Visit: 27 June 2019

Serology Completion Date: 23 August 2019

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Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): This study was undertaken by Pfizer and conducted at 138 sites in Austria, Bulgaria, Canada, France, Germany, Hungary, Japan, Romania, Spain, Sweden, the United Kingdom, and the United States, including 9 that were shipped investigational product but did not enroll any subjects. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Date of Current Version: 30 April 2020

Date(s) of Previous Report(s): Not applicable.

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OBJECTIVES

Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Objective	Endpoint
Primary Efficacy	
• To assess the efficacy of SA4Ag in the prevention of postoperative *Staphylococcus aureus* BSI[a] and/or deep incisional or organ/space SSI[b] occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults aged 18 to <86 years.	• The number of subjects in each vaccine group with postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, as confirmed by the EAC.
Primary Safety	

• To describe the safety and tolerability of a single vaccination of SA4Ag in adults aged 18 to <86 years undergoing elective open posterior spinal fusion procedures with multilevel instrumentation, by measuring local reactions, systemic events, and AEs.	• Number and proportion of subjects in each vaccine group with local reactions (redness, swelling, and pain) occurring within the 10-day period following study vaccination.
	• Number and proportion of subjects in each vaccine group with systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle, or joint pain) occurring within the 10-day period following study vaccination.
	• Number and proportion of subjects in each vaccine group with AEs reported during the following time periods:
	  • From vaccination until the day of surgery
	  • From vaccination until the Day 42 postoperative evaluation
	  • From the day of surgery until the Day 42 postoperative evaluation
	  • From the Day 42 postoperative evaluation until the Day 180 postoperative evaluation (newly diagnosed chronic medical disorders)
	• Number and proportion of subjects in each vaccine group with SAEs reported during the following time periods:
	  • From vaccination until the Day 180 postoperative evaluation

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Table S1. Study Objectives and Endpoints

Objective	Endpoint
	• From vaccination until the day of surgery • From the day of surgery until the Day 180 postoperative evaluation
Secondary Efficacy	
• To assess the efficacy of SA4Ag in the prevention of postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age.	• The number of subjects in each vaccine group with postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation.
• To assess the efficacy of SA4Ag in the prevention of postoperative *S aureus* SSI occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age.	• The number of subjects in each vaccine group with postoperative *S aureus* SSI occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation.
• To assess the efficacy of SA4Ag in the prevention of postoperative *S aureus* SSI occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age.	• The number of subjects in each vaccine group with postoperative *S aureus* SSI occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation.
Exploratory Efficacy	
• To assess the efficacy of SA4Ag in the prevention of postoperative ISA disease[c] occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age.	• The number of subjects in each vaccine group with postoperative ISA disease occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation.
• To assess the efficacy of SA4Ag in the prevention of postoperative ISA disease occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age.	• The number of subjects in each vaccine group with postoperative ISA disease occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation.
• To assess the efficacy of SA4Ag in the prevention of postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 90 days of elective open posterior spinal fusion procedures with	• The number of subjects in each vaccine group with postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 90 days of elective open posterior spinal fusion procedures with

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Table S1. Study Objectives and Endpoints

Objective	Endpoint
multilevel instrumentation, in adults 18 to <86 years of age, based on baseline *S aureus* colonization status.	multilevel instrumentation, based on baseline *S aureus* colonization status.
• To assess the efficacy of SA4Ag in the prevention of postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age, based on baseline *S aureus* colonization status.	• The number of subjects in each vaccine group with postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 180 days of elective open posterior spinal fusion procedures with multilevel instrumentation, based on baseline *S aureus* colonization status.
Exploratory Immunogenicity	
• To describe the immunogenicity of SA4Ag in adults aged 18 to <86 years undergoing elective open posterior spinal fusion procedures with multilevel instrumentation.	• The proportion of subjects at each time point who achieve specific antibody thresholds in antibody assays that assess functional activity. These may include, for example, OPA assays using an *S aureus* CP5-expressing strain and a CP8-expressing strain, and cLIA for ClfA and MntC. Additional exploratory assays to measure immune responses may also be conducted on all 4 antigens. • The proportion of subjects at each time point who achieved specific antibody thresholds to all 4 antigens both individually and combined using immunological assays.
Exploratory Colonization	
• To describe *S aureus* colonization in adults aged 18 to <86 years undergoing elective open posterior spinal fusion procedures with multilevel instrumentation, before and after SA4Ag administration.	• The number of subjects in each vaccine group determined to be colonized with *S aureus* on each occasion swab samples were collected. • From subjects with *S aureus* infection, the association between *S aureus* strain or strains identified as colonizing the subject and the *S aureus* strain or strains recovered from the infection.
Exploratory Healthcare-Utilization	
• To compare healthcare-utilization data between vaccine groups.	• Healthcare-utilization data, including days in hospital, days in an ICU, discharge disposition, inpatient days in rehabilitation facilities or skilled nursing facility after discharge, number of hospital readmissions and reoperations, days of antibiotic use, and number of rehabilitation/physical therapy outpatient visits.

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Table S1. Study Objectives and Endpoints

Objective	Endpoint
Abbreviations: AE = adverse event; BSI = bloodstream infection; ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; EAC = event adjudication committee; ICU = intensive care unit; ISA = invasive *Staphylococcus aureus*; MntC = manganese transporter C; OPA = opsonophagocytic activity; PDI = protocol-defined infection; SAE = serious adverse event; SA4Ag = *Staphylococcus aureus* 4-antigen vaccine; SSI = surgical-site infection. a. BSI: clinical infection involving a recognized pathogen (eg, *S aureus*) cultured from 1 or more blood cultures, or a commensal organism cultured from 2 or more blood cultures, whether primary or secondary to infection at another site. b. SSI: infection at a surgical incision, whether involving the primary posterior incision or a secondary (eg, anterior) incision associated with the spinal fusion procedure itself or with the harvesting of autologous bone graft material. SSI was further classified as: • Superficial SSI: infection involving only skin and subcutaneous tissue of the incision. • Deep incisional SSI: infection involving deep soft tissues of the incision (eg, fascia and muscle layers). • Organ/space SSI: infection involving any part of the body, excluding the skin incision, fascia, or muscle layers, that was opened or manipulated during the operative procedure. Specific to spinal fusion surgery, osteomyelitis, vertebral disc space infection, meningitis, and spinal abscess without meningitis when directly attributable to a surgical incision were classified as organ/space SSIs. Likewise, intra-abdominal infection, when directly attributable to a secondary anterior intra-abdominal incision, and joint and bursa infection, when directly attributable to a surgical incision (eg, harvesting autologous bone), were considered organ/space SSIs. c. ISA disease: defined as culture of *S aureus* from a normally sterile location, with clinical evidence of disease. With the exception of superficial SSI, all microbiologically confirmed *S aureus* PDIs were considered ISA disease.	

To maintain the scientific integrity, this study used an independent event adjudication committee (EAC) for adjudication of all primary and secondary efficacy endpoints, exploratory endpoints of invasive *S aureus* (ISA) disease, multiple-organ failure (MOF) events, and deaths in accordance with the EAC charter. The EAC's assessment of these events represented the final confirmed classification of the event.

The primary and/or secondary efficacy-related events for adjudication included all reported bloodstream infection (BSI) and surgical-site infection (SSI) events. Furthermore, the EAC was responsible for adjudicating all other reported protocol-defined infection (PDI) events, including any other invasive infection (irrespective of the causative pathogen).

METHODS

Study Design:

This was a Phase 2b, multicenter, parallel-group, placebo-controlled, randomized, double-blind study to evaluate *Staphylococcus aureus* 4-antigen vaccine (SA4Ag) safety and efficacy in the prevention of postoperative *S aureus* disease in adults aged 18 to <86 years who were undergoing elective open posterior spinal fusion procedures with multilevel instrumentation.

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This was an event-driven study with a total target of 48 primary endpoint *S aureus* cases. It was anticipated that approximately 6000 subjects were to be enrolled globally to accumulate these 48 cases. However, the total enrollment number could have varied based on the incidence rate of the primary endpoint, true underlying vaccine efficacy (VE), and a potential early stop for efficacy or futility. The study enrollment was terminated for futility at the time of the interim analysis after the accrual of 24 per-protocol primary endpoint cases.

There were 5 scheduled study visits and 1 scheduled telephone contact during 6 to 8 months of subject participation. Study-eligible subjects who provided consent were randomized in a 1:1 ratio to receive either a single dose of SA4Ag or placebo at Visit 1, which occurred 10 to 60 days prior to undergoing elective open posterior spinal fusion procedures with multilevel instrumentation (index surgical procedure). Visit 2 was a longitudinal visit and was to monitor the index hospital admission period from the day of surgery (Day 1) until the day of hospital discharge. A telephone contact with the subject occurred on Day 21, while postoperative evaluation study visits occurred on Day 42, Day 90, and Day 180 after surgery. The Day 180 postoperative evaluation could be conducted by telephone provided that arrangements were made for blood and colonization sample collection (eg, home nursing visit).

Unscheduled telephone contacts were conducted for assessment of severe local reactions, severe fever, and severe systemic events after vaccination. Severe fever or a severe local reaction warranted an unscheduled assessment visit.

Following the index hospital admission, unscheduled visits were conducted for assessment of suspected BSI and/or SSI events, and to assess re-hospitalization(s) subsequent to the index hospital admission.

VE was evaluated by monitoring and assessing the occurrence of PDIs. All BSIs, SSIs, and other ISA infections underwent adjudication by the EAC. Subjects with EAC-confirmed postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 90 days after the index surgical procedure contributed to the primary efficacy endpoint analysis.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Subjects must have met all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subjects personally signed and dated the informed consent document indicating that the subjects had been informed of all pertinent aspects of the study.

2. Subjects were aged 18 to <86 years at the time of enrollment.

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3. Subjects were scheduled to undergo an elective open posterior spinal fusion procedure with multilevel instrumentation 10 to 60 days after study vaccination.

4. Subjects were available for the entire duration of the study, and were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures, including completion of the electronic diary (e-diary) for 10 days after study vaccination (if surgery occurred on Day 10, then the e-diary did not need to be completed for that day).

5. Subjects were able to be contacted by telephone during study participation.

6. Male subjects and female subjects of childbearing potential and at risk for pregnancy agreed to use a highly effective method of contraception throughout the study.

Exclusion Criteria

Subjects presenting with any of the following were not included in the study:

1. Planned spinal fusion procedure requiring separate operations performed on separate days (ie, staged procedure).

2. Single-level spinal fusions without insertion of multilevel instrumentation (ie, surgical implantation of prosthetic material involving 2 or more motion segments).

3. Surgical indication of malignancy, infection, or acute or emergency trauma (ie, related to a traumatic incident occurring within 6 months prior to study enrollment).

4. History of major surgery (specifically, an open procedure that enters a body cavity, organ, or joint space) within 3 months prior to enrollment, or anticipated major surgery other than the index surgical procedure between study enrollment and completion of study participation.

5. History of any spinal surgery performed within 6 months prior to study enrollment.

6. History of any previous spinal surgery resulting in postoperative BSI or SSI.

7. Congenital or AIDS, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, within the year prior to enrollment or the use of systemic corticosteroids (equivalent of ≥10 mg/day of prednisone) for >14 days within 30 days prior to study enrollment.

8. History of leukemia, lymphoma, or underlying bone marrow disorder (eg, myelodysplasia, myeloma, myeloproliferative disorder) or history of bone marrow transplant.

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9. Malignancy that required treatment with chemotherapy, immunotherapy, radiation therapy, or other antineoplastic target therapies within 24 months prior to study enrollment.

10. Any known or suspected malignancy to the spine.

11. Congenital, functional, or surgical asplenia.

12. End-stage renal disease (defined as requiring or anticipating requirement for hemodialysis, peritoneal dialysis, or renal transplant) or nephrotic syndrome.

13. Any contraindication to vaccination or vaccine components, including history of anaphylactic reaction to any vaccine or vaccine-related component.

14. Receipt of blood products or immunoglobulins (including monoclonal antibodies) within 6 months prior to study enrollment OR anticipated receipt of blood products or immunoglobulins (including monoclonal antibodies) prior to the index hospital admission.

15. Previous administration of *S aureus* vaccine or *S aureus*/*Candida* vaccine.

16. Antibiotic therapy for microbiologically confirmed ISA disease within 12 months prior to enrollment.

17. Participation in other studies involving investigational drug(s) (Phases 1-4) within 30 days before the current study begins and/or anticipated participation during the study.

18. Pregnant females, breastfeeding females, and males and females of childbearing potential who were unwilling or unable to use a highly effective method of contraception, for the duration of the study.

19. Presence of a colostomy, urostomy, tracheostomy, percutaneous gastrostomy tube, indwelling vascular or urinary catheter, central nervous system shunt, central nervous system implanted device, or spinal cord stimulator; or anticipated presence of a colostomy, urostomy, tracheostomy, percutaneous gastrostomy tube, indwelling vascular or urinary catheter, central nervous system shunt, central nervous system implanted device, or spinal cord stimulator prior to the index hospital admission.

20. Other severe acute or chronic medical or psychiatric condition (including drug and alcohol dependencies) or laboratory abnormality that increased the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subjects inappropriate for entry into this study.

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21. Subjects who were investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who were Pfizer employees directly involved in the conduct of the study.

Vaccines Administered:

Study subjects received a single 0.5-mL dose of investigational product (SA4Ag or placebo) into the deltoid muscle in the nondominant arm at Visit 1. As a standard practice of vaccination, administration occurred in the nondominant arm unless medically contraindicated.

Efficacy Evaluations:

All subjects who underwent the per-protocol or modified intent-to-treat (mITT) surgery procedure were monitored for any PDI after surgery until the Day 180 postoperative evaluation. All PDIs that did not constitute primary or secondary endpoints were simultaneously reported to the EAC and reported as an adverse event (AE)/serious adverse event (SAE).

Immunogenicity Evaluations:

Blood samples for immunogenicity assessments were collected from all subjects prior to vaccination, prior to the index surgery and at hospital discharge, at each postoperative clinic visit, and at each unscheduled BSI/SSI assessment visit and unscheduled hospitalization visits if the subject had MOF. Immunoassays were performed at select time points and may have included opsonophagocytic activity (OPA) assays using *S aureus* capsular polysaccharide serotype 5 (CP5)- and capsular polysaccharide serotype 8 (CP8)-expressing strains, and competitive Luminex immunoassays (cLIAs) for clumping factor A (ClfA) and manganese transporter C (MntC). A subset of cases and noncases was tested for immunogenicity at 3 select time points (day of index surgery, hospital discharge, and Day 90 postoperative evaluation) following the futility analysis.

Colonization Evaluations:

Oropharyngeal and nasal swabs for *S aureus* colonization were collected from all subjects prior to study vaccination, as specified at each postvaccination visit, and at each BSI/SSI assessment visit.

Healthcare-Utilization Evaluations:

Upon hospital discharge following the index hospital admission, for each subsequent hospitalization, and for each postoperative follow-up visit, a healthcare-utilization assessment was conducted.

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Safety Evaluations:

Starting on the day of vaccination, local reactions (redness, swelling, and pain at the injection site) systemic events (fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain), and fever were recorded in the e-diary for 10 days by the subject. Fever was defined as an oral temperature of ≥38.0°C (100.4°F) and analyzed as a systemic event.

AEs were collected and analyzed from the day of vaccination until the day of surgery, from the day of vaccination until Day 42 postoperative evaluation, from the day of surgery until Day 42 postoperative evaluation. Newly diagnosed chronic medical disorders (defined as a disease or medical condition, not previously identified, that was expected to be persistent or otherwise long-lasting in its effects) were collected and analyzed from the Day 42 postoperative evaluation until the Day 180 postoperative evaluation. SAEs were collected and analyzed from vaccination until the day of surgery, from vaccination until the Day 180 postoperative evaluation, and from the day of surgery until the Day 180 postoperative evaluation.

Preoperative and perioperative subject status were evaluated using:

- Charlson Comorbidity Index (CCI): a validated prognostic indicator for which factors, individually or in combination, may increase the risk of short-term mortality for patients enrolled in longitudinal studies. The sum of the values for each comorbid condition (score range of 1 to 6) was added to the subject's value for age (score range of 0 to 5) to obtain the CCI. Both the CCI and the Charlson probability (10-year survival) was derived programmatically.

- American Society of Anesthesiologists (ASA) physical status classification system: utilized by anesthesiologists to assess the fitness of surgical patients prior to undergoing surgery. The ASA score (scale of 1 [healthy patient] to 5 [moribund patient]) correlates with patient morbidity and postoperative infection risk.

Organ failure (OF) events were monitored for subjects who underwent the index surgical procedure, from after surgery to Day 180, as follows: during the index hospital admission from after surgery until discharge, and during any subsequent hospitalization(s) that occurred over the course of the study, including, where possible, those that occurred at any outside hospital.

A protocol definition for OF was established for each of the 6 organ systems (respiratory, cardiovascular, renal, hematological, neurological, and hepatic) on the basis of prospective sequential organ failure assessment (SOFA) scores (range of 0 to 4). OF was defined as a SOFA score ≥3 for any 1 organ system, while MOF was defined as OF in 2 or more organ systems simultaneously. Each MOF was classified as an AE or SAE and appeared in the appropriate analysis.

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Statistical Methods:

Analysis Populations

Per-Protocol Efficacy Population: The per-protocol efficacy population included subjects who met all eligibility criteria, were vaccinated as randomized, underwent the index surgery 9 to 90 days (inclusive) after vaccination, underwent surgery consistent with study-defined criteria for the index surgery, did not have the index surgery modified to be a staged procedure on separate days, had no major protocol violations before reporting of the suspected *S aureus* infection, and had no infection or malignancy identified during the index surgical procedure. Subjects were analyzed according to the investigational product to which they were randomized (SA4Ag or placebo).

Modified Intent-to-Treat (mITT) Efficacy Population: The mITT efficacy population included subjects who were vaccinated and underwent spinal surgery. Subjects were analyzed according to the investigational product to which they were randomized (SA4Ag or placebo).

Restricted Modified Intent-to-Treat (mITT) Efficacy Population: The restricted mITT efficacy population was a subset of the mITT efficacy population. It excluded subjects with a pre-existing infection, or malignancy, or acute or emergency trauma, at any time from enrollment up to and including the time of the index surgery.

Safety Population: All subjects who received investigational product were included in the safety population. Subjects were analyzed according to the investigational product they actually received.

Modified Intent-to-Treat (mITT) Immunogenicity Population: The mITT immunogenicity population comprised all subjects who were vaccinated and had at least 1 valid and determinate postvaccination immunogenicity result. Subjects were analyzed according to the investigational product to which they were randomized.

Modified Intent-to-Treat (mITT) Colonization Population: The mITT colonization population included all randomized subjects who had at least 1 valid colonization swab sample result.

Methods for Efficacy Endpoint Analysis

Efficacy endpoint evaluations included:

- Incidence of postoperative *S aureus* BSI and/or deep incisional or organ/space SSI occurring within 90 and 180 days after index surgery.
- Incidence of postoperative *S aureus* SSI occurring within 90 and 180 days after index surgery.

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- Incidence of postoperative ISA disease occurring within 90 and 180 days after index surgery.

VE was defined as VE = 1 – RR, where RR was the relative risk in SA4Ag compared to placebo (ie, the proportion of SA4Ag recipients who met the primary endpoint relative to the proportion of placebo recipients who met the primary endpoint).

A sequential analysis was performed on the primary endpoint for the per-protocol efficacy population, in which early stopping boundaries were based on a group-sequential design. An interim analysis was performed after the accrual of 24 cases that met the primary efficacy endpoint.

There were pre-specified futility checks after approximately 10 and 15 cases had accrued. Only the primary endpoint was examined. The power of the study to reject the original null hypothesis, conditional upon the results accumulated so far, was calculated. Futility would be declared and the study ceased enrollment if the conditional power fell below 20%.

An interim analysis was to be performed after the accrual of 24 cases that met the primary efficacy endpoint as confirmed by the EAC. Only the primary endpoint was to be examined. The Data Monitoring Committee (DMC) was to make a recommendation for study continuation with or without modification unless 1 of the following criteria was fulfilled at the interim analysis, in which case recommendations may have been made as follows:

- Futility criterion was met (ie, conditional power <50%); a recommendation to stop enrollment for futility may have been made.

- Clinically significant efficacy was demonstrated (ie, lower limit of the 99.7% confidence interval [CI] exceeded 20%); a recommendation to continue the study with modification to an open label design may have been made.

Methods for Immunogenicity Endpoint Analysis

Immunogenicity endpoint evaluations included:

1. The proportion of subjects who achieved specific antibody thresholds at each scheduled time point, compiled separately for each antigen/assay.

2. The proportion of subjects who achieved specific antibody thresholds to all 4 antigens simultaneously at each scheduled time point, limited to CP5/OPA, CP8/OPA, ClfA/cLIA, and MntC/cLIA.

3. Geometric mean titer (GMT) at each time point.

4. Geometric mean fold rise (GMFR) from Visit 1 to Visit 2 admission.

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5. Increases of 2-, 4-, 8-, 16-, and 32-fold from Visit 1 to Visit 2 admission.

Methods for Colonization Endpoint Analysis

Colonization endpoint evaluations, based on colonization results from scheduled visits, were:

1. Colonization, defined as the number and proportion of subjects in each vaccine group determined to be colonized with *S aureus* at each scheduled visit where swab samples were collected.

2. Subject carriage status, characterized across visits as persistent, indeterminate, intermittent, or noncarrier as described below.

    - Persistent: positive at 4 of 5, 5 of 5, 5 of 6, or 6 of 6 visits.

    - Indeterminate: 3 or 4 visits, regardless of combination of positive/negative results.

    - Intermittent: positive at 1 or 2 visits if 2 visits are available, positive at 1 to 3 visits if 5 visits are available, positive at 1 to 4 visits if 6 visits are available.

    - Noncarrier: no positive results at any visit, minimum of 5 visits.

3. Acquisition, defined as a positive swab at any visit after the index surgery, given that the results at the time of vaccination and prior to surgery were both negative.

4. Clearance, defined as 2 consecutive postbaseline negative swabs, given that all preceding swabs were positive.

Colonization, carriage status, acquisition, and clearance were compiled for "any *S aureus*," methicillin-resistant *S aureus* (MRSA), and methicillin-sensitive *S aureus* (MSSA).

Methods for Healthcare-Utilization Endpoint Analysis

For healthcare utilization endpoint evaluations, variables whose units were days (eg, number of days in an intensive care unit [ICU]) were summarized by sample size, mean, standard deviation, median, minimum, and maximum. Categorical variables (eg, interventional procedures, discharge disposition) were summarized by frequency counts and proportion of subjects in each category. The number of service visits and the number of rehabilitation/physical therapy visits were summarized by sample size, mean, standard deviation, median, minimum, and maximum.

Methods for Safety Endpoint Analysis

Local reactions and systemic events reported in the e-diary were summarized by the maximum severity across the 10-day observation period.

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AEs (including newly diagnosed chronic medical disorders from Day 42 until Day 180, SAEs, and deaths) were summarized by AEs with ≥1% incidence in either vaccine group in either the preoperative or postoperative period, and by all remaining AEs. For AEs with ≥1% incidence, incidence proportions, the differences between vaccine groups in proportions, and 95% CIs for the differences were provided. For all remaining AEs, only incidence proportions and the differences between vaccine groups in proportions were summarized.

Events of MOF were compared across vaccine groups using the using the Fisher exact test, 2-sided, for each organ system.

Methods for Handling of Missing Values

Missing values were not imputed for any immunogenicity, safety, demographic, or colonization variables. However, immunogenicity values less than the lower limit of quantitation (LLOQ) were set as 0.5 × LLOQ for the analysis.

RESULTS

Subject Disposition and Demography:

In this event-driven study with a total target of 48 primary endpoint *S aureus* cases, it was anticipated that 6000 subjects would be enrolled globally to accumulate these 48 cases. Upon the DMC interim analysis of the primary endpoint after accrual of 24 primary endpoint cases, enrollment in the study was terminated upon the DMC's recommendation that futility criteria had been met. A total of 3450 subjects were randomized in the study, with 3417 (99.0%) completing vaccination, 3311 (96.0%) completing index surgery, and 3193 (92.6%) completing the study.

Most (3091 [89.6%]) randomized subjects were included in the per-protocol efficacy population: 1544 (89.5%) in the SA4Ag group and 1547 (89.7%) in the placebo group. Exclusion from the per-protocol efficacy population was similar for SA4Ag and placebo subjects (10.4% overall), and most often because the subject did not undergo spinal surgery (4.0%).

Overall, 55.3% of subjects were female, most (75.5%) were white, and the mean age at vaccination was 62.7 years (range: 18 to 85 years). Demographics were generally similar across the SA4Ag and placebo groups.

Overall, comorbidities and physical status for subjects in the safety population were generally similar for the SA4Ag and placebo groups at the time of surgery. The vast majority of subjects in both groups had CCI scores ≤4, with mean scores of 3.4 and 3.5 in the SA4Ag and placebo groups, respectively, indicating that subjects had limited significant co-morbidities. The Charlson 10-year survival probabilities were comparable in both groups, with mean probabilities of 75.5% and 74.4% and median probabilities of 90.1% and 77.5% for the SA4Ag and placebo groups, respectively. At the time of surgery,

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approximately two-thirds of subjects in both groups had an ASA physical status classification of 1 or 2, indicating they were assessed to be healthy or had mild systemic disease with no functional limitation. The mean observed ASA physical classification status was 2.3 for both the SA4Ag and placebo groups. No subjects had an ASA physical status classification of 5 (moribund patient likely to die within 24 hours), and 0.9% of all subjects had a classification of 4 (severe systemic disease that is a constant threat to life).

The characteristics of the index surgeries and related hospitalizations for subjects in the per-protocol efficacy population were similar for the SA4Ag and placebo groups. Key characteristics in each group in this surgical population include days from vaccination to surgery (mean of approximately 23 days), use of decolonization measures (approximately 56%), motion segments fused (mean of approximately 4 motion segments), surgical duration (mean duration of >250 minutes), blood loss (mean of >600 mL), and units of blood products transfused (mean of approximately 4 units of blood products). Almost all subjects (approximately 97% in each group) received prophylactic antibiotics within 1 hour prior to incision, and approximately 56% in each group received intrawound antibiotics. The majority of index procedures were initial spinal fusions (>70%) and were performed by orthopedic surgeons (>70%).

The key surgical reoperation characteristics, including motion segments fused, blood loss, and blood transfusions, were similar in for the SA4Ag and placebo groups in the per-protocol efficacy population. Subjects may have had multiple indications for reoperations, including debridement, loose hardware, and decompression. Overall, 66.1% and 67.5% of those in the SA4Ag and placebo groups, respectively, had “other” reasons, for example other hardware related issues, wound explorations and infection related reasons. There was evidence of infection in 29.9% and 34.2% of subjects having a reoperation in the SA4Ag and placebo groups, respectively. Accordingly, a higher proportion of subjects had surgical wound classifications for reoperations compared with index surgeries that were clean-contaminated, contaminated, or dirty/infected. Compared to the index surgeries, reoperations were a shorter duration (mean durations of 148.2 and 129.3 minutes in the SA4Ag and placebo groups, respectively), had less intraoperative blood loss (mean blood loss of 315.2 mL and 336.8 mL in the SA4Ag and placebo groups, respectively), and fewer motion segments were fused (mean of 3.6 and 3.2 motion segments fused in the SA4Ag and placebo groups, respectively).

The numbers of subjects in the per-protocol efficacy population readmitted after index surgery included 206 subjects in the SA4Ag group and 211 subjects in the placebo group were readmitted after index surgery. Characteristics of the hospital admissions for subjects readmitted to the hospital were comparable in the SA4Ag and placebo groups. Readmissions were related to complications of the index surgery for 46.1% and 41.7% of subjects in the SA4Ag and placebo groups, respectively. For subjects readmitted for complications of the index surgery, 69.5% and 75.0% of subjects in the SA4Ag and placebo groups, respectively, required additional surgery. Durations of readmissions and ICU stays were similar for the SA4Ag and placebo groups.

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The mean duration of any antibiotic use from the day of index surgery until study completion or withdrawal was similar in the SA4Ag and placebo groups (11.9 and 12.3 days, respectively) in the mITT efficacy population.

Efficacy Results:

- For the primary efficacy analysis, the VE of SA4Ag in the prevention of postoperative *S aureus* BSI and/or deep incisional or organ/space SSI within 90 days of the index surgery was 0.0% (14 of 28 cases in the SA4Ag group and 14 of 28 cases in the placebo group) with 95% CI of -126.30% to 55.81% in the per-protocol efficacy population. Of note, the majority of subjects with BSI also had *S aureus* deep or organ/space SSIs. There were only 2 additional cases included in the restricted mITT analysis of the primary efficacy endpoint (both in the placebo group), therefore the overall conclusion of no VE remains the same. The case split for BSI slightly favored the vaccine in the per-protocol population, with 7 cases of BSI in the SA4Ag group compared with 11 in the placebo group (VE = 36.36% [95% CI: -79.76, 79.08%]). This trend was more prominent in the mITT efficacy population (7 SA4Ag/13 placebo). Of note, the primary efficacy endpoint infection rate of 0.9% in the placebo group was lower than the anticipated ~1.4%.

- There was only 1 additional deep or organ/space SSI (in the SA4Ag group) reported between Day 90 and Day 180 in the per-protocol efficacy population; therefore, the secondary efficacy endpoint through 180 days after index surgery showed similar results to the primary efficacy endpoint.

- The secondary efficacy analysis of *S aureus* SSI through 90 days after index surgery also showed no efficacy, with 24 cases of SSI in the SA4Ag group compared with 22 cases in the placebo group for the per-protocol efficacy population.

- Only 2 more cases of *S aureus* SSI, 1 in each group, were reported between Day 90 and Day 180 in the per-protocol efficacy population, therefore this additional secondary endpoint showed similar results as through 90 days after index surgery.

- For the 15 and 19 cases of ISA disease occurring in the SA4Ag and placebo groups, respectively, within 90 days after index surgery, and 1 additional case in the placebo group occurring between Day 90 and Day 180 (mITT efficacy population), SA4Ag showed no meaningful efficacy in the prevention of postoperative ISA disease occurring within 90 or 180 days after index surgery.

- For the 14 cases of BSI and/or deep incisional or organ/space SSI occurring in each group within 90 and 180 days after index surgery in the per-protocol efficacy population, further analysis of cases in the SA4Ag and placebo groups by baseline *S aureus* colonization status did not show VE.

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- Summaries of efficacy by *S aureus* colonization status, number of motion segments fused, race, ethnicity, age, sex, smoking status, country, and CCI score were limited by small numbers of cases in each group; however, they did not show any trends towards efficacy.

- There was no indication that SA4Ag increased the risk or invasiveness of *S aureus* infection or infection of any etiology.

Immunogenicity Results:

- SA4Ag elicited substantial functional immune responses to CP5, CP8, ClfA, and MntC at all time points after vaccination and GMTs were generally similar in cases and noncases. GMTs generally peaked on the day of index surgery or hospital discharge and then declined, but were still at higher levels on the day of hospital discharge and Day 90 compared to the day of vaccination.

- On the day of index surgery, the CP5 GMTs for the SA4Ag group were 22,417.1 (95% CI: 13,536.1, 37,125.0) and 22,095.3 (95% CI: 18,858.8, 25,887.4) for cases and noncases, respectively; for the placebo group, they were 414.3 (95% CI: 256.5, 668.9) and 262.0 (95% CI: 205.9, 333.4) for cases and noncases, respectively. The CP8 GMTs for the SA4Ag group were 18,286.5 (95% CI: 11,221.9, 29,798.6) and 23,281.5 (95% CI: 19,374.9, 27,975.8) for cases and noncases, respectively; for the placebo group, they were 689.9 (95% CI: 378.6, 1257.3) and 609.2 (95% CI: 449.0, 826.5) for cases and noncases, respectively.

- On the day of index surgery, the ClfA GMTs for the SA4Ag group were 2831.4 (95% CI: 1487.5, 5389.3) and 3053.8 (95% CI: 2518.6, 3702.8) for cases and noncases, respectively; for the placebo group, they were 216.5 (95% CI: 165.5, 283.3) and 190.7 (95% CI: 163.4, 222.5) for cases and noncases, respectively. The MntC GMTs for the SA4Ag group were 4231.9 (95% CI: 2468.9, 7253.8) and 2926.1 (95% CI: 2452.3, 3491.5) for cases and noncases, respectively; for the placebo group, they were 338.6 (95% CI: 242.1, 473.5) and 272.7 (95% CI: 232.7, 319.6) for cases and noncases, respectively.

- The percentage of subjects achieving a ≥4-fold increase in titers from baseline was highest on the day of hospital discharge in the SA4Ag group for both case and noncase subjects. Overall, on the day of index surgery the majority of both case and noncase subjects achieved a ≥4-fold increase from baseline in CP5 and CP8 OPA titers (≥91% of subjects) and in ClfA and MntC titers (≥73.5% of subjects).

- For CP8, on the day of index surgery a lower proportion of cases achieved ≥16-fold rises in titers (48.1%; 95% CI: 28.7, 68.1%) compared with noncases (72.9%; 95% CI: 58.2, 84.7%). No substantial differences between cases and noncases were observed for the other antigens.

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- On the day of index surgery the majority (≥73.5%) of SA4Ag subjects (both cases and noncases) achieved the defined OPA titer thresholds (CP5 ≥1000, CP8 ≥2000) and cLIA titer thresholds (≥4-fold rise from baseline for MntC and ClfA). For both cases and noncases, the majority (66.7%) of SA4Ag subjects achieved defined titers for all 4 assays on the day of index surgery.

- Surgical subjects in this study had lower CP5 (estimated ratio 0.5) and CP8 (estimated ratio 0.6) titers than the healthy subjects in previous studies (B3451015 and B3451003). However, the magnitude of the immune responses in surgical subjects was still high for both cases and noncases. Also, surgical subjects in this study had comparable titers for ClfA (estimated ratio 0.9) and MntC (estimated ratio 0.8) relative to the healthy subjects in previous studies. The results of these analyses for subjects across studies, however, should be interpreted with caution.

Colonization Results:

- *S aureus* colonization rates in either the nose or throat were similar among the SA4Ag and placebo groups at each visit through Day 180 after index surgery. At baseline (prior to vaccination), 34.9% and 33.4% of subjects in the SA4Ag and placebo groups, respectively, were colonized. The proportion colonized decreased through the hospital discharge visit but returned close to baseline by the Day 180 visit, with no notable differences in the percentage colonized between the SA4Ag and placebo groups.

- *S aureus* colonization was mostly due to MSSA, with 31.1% of all subjects colonized with MSSA in the nose or throat at baseline compared with 3.3% colonized with MRSA.

- For cases including subjects with adjudication-confirmed *S aureus*-related SSI and/or BSI, the majority (63.8%) of all subjects were positive at either site at baseline; for noncases, 35.8% of all subjects were positive at either site at baseline.

- Colonization analysis by age group (18 to <50 years, 50 to <65 years, and 65 to <86 years) was consistent with trends observed in previous studies, with the youngest age group having the highest proportion of subjects with *S aureus* colonization at any visit.

- Persistent colonization by any *S aureus* was similar for the SA4Ag (13.1%) and placebo (15.1%) groups. In both groups, persistent MRSA colonization occurred in ≤1% of subjects.

- Acquisition of any *S aureus* was similar for the SA4Ag (11.1%) and placebo (10.1%) groups.

- Conclusions for analyses of colonization by primary endpoint were generally limited by few subjects meeting the primary endpoint.

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Healthcare-Utilization Results:

- Overall, healthcare utilization relating to hospitalization, hospital discharge, and outpatient rehabilitation/physical therapy after index surgery was similar for subjects in the SA4Ag and placebo groups.

- The median duration of index hospitalization was 7.0 days for subjects in both groups.

- Readmissions after index surgery occurred in 13.7% and 13.8% of subjects in the SA4Ag and placebo groups, respectively. Readmissions were related to complications of index surgery in 46.1% and 40.5% of subjects in the SA4Ag and placebo groups, respectively. Among subjects with readmissions related to complications of index surgery, an additional surgery occurred in 69.3% and 75.3% of subjects in the SA4Ag and placebo groups, respectively. The median number of days in the ICU from readmissions due to complications of index surgery were 2.0 and 3.0 days in the SA4Ag and placebo groups, respectively.

Safety Results:

- Reporting of any local reaction within 10 days after vaccination was significantly more common in the SA4Ag group than the placebo group (28.9% compared to 9.8%, respectively; $p < 0.001$). Local reactions reported in either group were mostly mild in severity. In the SA4Ag group, <1% of subjects reported severe redness, severe swelling, or severe pain at the injection site. Pain at the injection site was the most frequently reported local reaction in both groups.

- Reporting of systemic events within 10 days after vaccination was similar in the SA4Ag and placebo groups (62.3% and 60.4% reported any systemic event, respectively). Systemic events reported were mostly mild or moderate in severity. Fatigue was the most frequently reported systemic event in both groups, and there were no significant differences in the percentages of subjects reporting each of the systemic events including fever. The reported use of antipyretic or pain medication was similar in the SA4Ag (39.4%) and placebo (38.9%) groups.

- There were no substantial differences in the proportion of subjects in either group reporting any AEs or SAEs from vaccination to day of index surgery or after index surgery. Overall, 72.2% of subjects reported an AE and 24.3% of subjects reported an SAE. Of the 1334 SAEs reported, only 2 were considered related to the investigational product by the investigator (chills and rheumatoid arthritis). The majority of AEs and SAEs were reported after index surgery.

- Newly diagnosed chronic medical disorders were reported in 1.7% of subjects in the SA4Ag group and 2.4% of subjects in the placebo group; none of these were related to the investigational product.

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- Most related AEs were reported from vaccination until day of index surgery (1.2% and 0.2% in the SA4Ag and placebo group), the majority of which were from the general disorders and administration site conditions system organ class (SOC) for SA4Ag group subjects.

- A total of 8 (0.2%) subjects (3 SA4Ag group, 5 placebo group) with AEs leading to discontinuation reported 9 AEs, with only 1 event (rheumatoid arthritis) in the SA4Ag group being assessed as related by the investigator.

- The occurrence of EAC-confirmed MOFs was similar in the SA4Ag and placebo groups: 10 (0.59%) and 9 (0.53%) subjects, respectively.

- Deaths were reported in <1% of subjects in either group between vaccination and Day 180: 13 (0.8%) and 10 (0.6%) subjects in the SA4Ag and placebo groups, respectively. None of the deaths were assessed as related to the investigational product. Two additional deaths were reported: 1 subject died prior to vaccination and 1 subject died after completing the study. For the 10 SA4Ag and 9 placebo group subjects with MOF, there were 7 deaths (5 SA4Ag group, 2 placebo group) including 1 subject in the placebo group who had a microbiologically-confirmed *S aureus* infection.

- Overall, SA4Ag was well tolerated with an acceptable safety profile in adults undergoing elective open posterior spinal fusion procedures with multilevel instrumentation.

Conclusions:

This was an event-driven study to evaluate SA4Ag safety and efficacy in the prevention of postoperative *S aureus* disease in adults undergoing elective open posterior spinal fusion procedures with multilevel instrumentation. Enrollment in the study was terminated prior to the accrual of the planned final number of primary endpoint cases based on a scheduled assessment of the prespecified futility criteria by the external DMC, which noted no safety concerns in their review of the safety data.

The results of all randomized subjects presented in this report confirm that SA4Ag was safe and well tolerated. However, despite substantial antibody responses to each vaccine antigen, SA4Ag was not efficacious in preventing *S aureus* BSI or deep or organ/space SSI, *S aureus* SSI, or other ISA disease in patients undergoing elective orthopedic surgical procedures.