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

Compound:	PF-06290510
Compound Name:	*Staphylococcus aureus* 4-Antigen Vaccine
United States (US) Investigational New Drug (IND) Number:	BB-IND #14705
European Clinical Trials Database (EudraCT) Number:	2014-002644-40
Protocol Number:	B3451002
Phase:	2b

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 4	05 February 2018	– Protocol Summary-Study Design, Section 3.1 and Section 9.1: Changed the expected number of enrolled subjects from 2600 to 6000 and target number of endpoint cases changed from 42 to 48. Added a statement that the final enrollment numbers may be varied. *Rationale*: Lower than predicted post-operative SA infection rate and undetermined vaccine efficacy. – Table of Contents: Updated to reflect changes. – Section 1.2.4.3: Removed the reference to study B3451011 data being preliminary and added a statement regarding persistence of immune response through Month 12 after vaccination. *Rationale*: B3451011 study results are now available. – Section 1.2.4.4: Added results for study B3451014. *Rationale*: Results now available. – Section 1.2.5: Appendix 7 (Country-Specific Appendix – Required for Sweden) has been incorporated into the body of the protocol under the title: Benefit-Risk Assessment. Ethics Committees were notified of the addition of Appendix 7 via a Protocol Administrative Clarification Letter in November 2016. Minor editorial updates were also made to this section. *Rationale*: Satisfies an earlier commitment to the Swedish Authorities to incorporate this text into Amendment 4. – Section 3.2.1: Expanded the definition of spinal fusion to include occiput and clarified that vertebrae must be adjacent. Expanded the definition of multilevel instrumentation. *Rationale*: Added specificity and clarity. – Section 3.2.2.1: Amended the indication of compression to spinal cord compression for clarity. *Rationale*: Added clarity. – Section 4.2: Amended an exclusion criterion (No. 3) to define the exclusionary period associated with the surgical indication of trauma. Amended an exclusion criterion (No. 7) to clarify that subjects with rheumatologic disorders that are not being treated

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		with immunosuppressant medications can enter the study. Amended an exclusion criterion (No. 19) to include spinal cord stimulators as exclusionary devices. *Rationale*: Added specificity and clarity. – Section 4.4: Added an additional clause to define the sub-population expected to use contraception during the study. *Rationale*: Added specificity and clarity. – Section 6.3.1.1: Clarified the timing of visit 2 procedures for early admissions to hospital. *Rationale*: Allows for subjects admitted to hospital more than 1 day prior to surgery. – Section 6.3.1.2.1, Section 6.4.3, and Section 7.2.3: Clarified requirements for assessment and reporting when a subject is suspected of having organ dysfunction or failure. *Rationale*: Added specificity and clarity. – Table 8: Clarified requirements for reporting nondefined infections. *Rationale*: Added clarity. – Table 14: Clarified measurements for the assessment of respiratory failure and amended the reference for the use of a modified SOFA score. *Rationale*: Added clarity. – Section 7.3.3: Modified surgical site wound culture requirements. *Rationale*: Added inclusivity. – Table 14: Changed bilirubin level from >12 to ≥12. – Section 8.6: Added statement to define deep venous thrombosis as important medical events for this study. *Rationale*: Added specificity and clarity. – Section 8.6.1: Added reference to Study Reference Manual for additional reporting requirements. *Rationale*: Added clarity. – Protocol Summary and Section 9.1: Modified interim analysis case count from 21 to 24; removed all references to hierarchical testing of proof of principle/high-level efficacy; clarified rules for including cases based on time of entry into adjudication system; clarified success criteria if additional cases are included. *Rationale*: Added statistical clarity and refinement based on changes to

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		enrollment numbers and case count. – Section 9.2: Modified sample size and power calculations based on increased sample size, primary endpoint case count, vaccine efficacy and incidence rates. Updated vaccine efficacy Figure 3. *Rationale*: Lower than predicted post-operative SA infection rate and undetermined vaccine efficacy. – Section 9.3: Clarified that primary and secondary endpoint analyses will be repeated for subgroup analyses. *Rationale*: Added clarity. – Section 9.3.1: Made a minor editorial change. – Table 15: Updated to reflect the number of cases required for the interim and final analyses. *Rationale*: Internal statistical consistency based on changes in primary endpoint case counts.
Amendment 3	01 June 2016	– Throughout document: • Changed *S. aureus* to *S aureus* (style change). – Section 1.2.4.4. Noted that clinical study B3451014 was completed in April 2016. – Section 2.5: Clarified the remit of the endpoint adjudication committee (EAC); ie, the remit of the EAC is not restricted to *S aureus* infections. – Section 3.2.1: Amended the index surgery definition. Made changes throughout the protocol to reflect the update. These include: • Protocol title; • Primary, secondary, and exploratory objectives and associated endpoints; • Study design; • Inclusion criteria. – Table 2, Section 6.3.1.2.1, Section 6.4.2, Section 7.1.1, Section 7.2.3: Refined evaluation periods for protocol-defined infections and organ failure events. – Table 4: Added perioperative data collection for index surgery reoperation and revision. – Section 4.2: Added a new exclusion criterion (No. 2) to specify single-level spinal fusions that are

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		exclusionary. – Section 4.2: Amended an exclusion criterion (No. 19) to exclude subjects with indwelling central nervous system shunts and implanted devices. – Section 6.1: Clarified subject participation in the event that the index surgery is not conducted according to the index study procedure definitions. – Section 6.2.1: Clarified the timing of the subject number being provided by the interactive voice response system/interactive Web response. – Section 6.4.2: Added instruction that tissue and fluid samples for suspected bloodstream and surgical-site infections, where possible, should be taken prior to commencing administration of antibiotics. – Section 6.4.3, Table 4: Added requirement to record details of any reoperation and revision of the index surgery, and to culture hardware or tissue if removed during the reoperation or revision surgery. – Section 6.5: Separated the Subject Withdrawal and Safety Follow-up section into 2 subsections for clarity. – Section 7.2.1.3, Section 7.2.1.4, Section 8.8: Added clarification regarding the management of Grade 4 local reactions and systemic events and the application of the adverse event severity scale for these reactions/events. – Table 14: Added phenylephrine to the criteria for hypotension. – Section 8.14.1: Removed duplicate text. – Protocol Summary, Section 9, Section 5.2: Added details of periodic checks for study futility that will be performed prior to the interim analysis. This includes the data monitoring committee's role in these assessments. – Section 9.1: Revised to clarify the rules for inclusion of events in case-driven study analyses. Reference added (credit to source). – Section 9: Revised wording to clarify that there is

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		more than 1 mITT population. – Section 9.3.1: Updated to allow vaccinated subjects who undergo spinal surgery that does not meet the index study procedure definition to be included in a modified intent-to-treat population. – Table 15: Revised the examples of the estimated efficacy and associated CIs for a selected number of SA4Ag cases. – Section 9.3.2.1: Clarified the management of cases identified after the primary analysis. – Section 3.1, Section 6.3.1.2.1, Section 7.1.1, Section 7.2.1.3, Section 7.2.1.4, Section 7.2.2.1, Section 7.2.3.1, Section 9.1, Section 9.3, Section 9.3.2, Section 9.6, Section 15, Section 16: Made editorial changes. – Single-page Appendix 6 added to the last page of the protocol and is applicable to Japan only. Addresses consent/assent issues for minors, and postvaccination temperature management.
Amendment 2	15 September 2015	– Protocol Summary, Section 2.4.1, Section 7.4, Section 9.3.4.1: Exploratory endpoint immunogenicity assays revised from a 4-plex to a 2-plex assay (requested by Pfizer Vaccine Research & Development [VRD]). – Table 1, Section 4.3, Section 6.3.1.3, Section 9.3.4.1: Visit windows added to swab and blood sample collections (negates the need to repeat sample collection if discharge is postponed or vaccination is delayed). – Section 2.5, Section 7.1.1.2: All invasive infections will now be adjudicated by the event adjudication committee (EAC); previously only those associated with *S aureus* were to be adjudicated (change requested by the EAC). – Section 3.2, Section 9.2: Assumptions regarding subject numbers removed (text was confusing). – Section 3.3.2.1: Indications for surgery amended (requested by principal investigator). – Section 3.3.2.3: Any preexisting spinal

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		instrumentation or tissue removed during a revisional surgical procedure, must be cultured (to detect preexisting pathogens) – Section 4.1, Section 7.2.1.1: In the event that surgery occurs on Day 10 after vaccination, the e-diary does not need to be completed for that day (clarification). – Section 4.3: Temporary delay criteria clarified with respect to the use of systemic steroids (clarification). – Section 5.4: Spinal steroids added to concomitant medications (may have an effect on the immune response). – Section 5.4.1: Minor editorial changes. – Section 6.2.1: Added text on inclusion of the spinal condition in the medical history; noted that surgery may occur on Day 10 after vaccination (clarification). – Table 1, Section 6.2.1, Section 7.2.4: Noted that serum samples may be used for pregnancy (clarification). – Section 6.4.1.1.1: Pain at the injection site added (previous omission). – Section 7.1.1: Revision of text in the last bullet point (clarification). – Figure 1: Legend added (previous omission). – Section 7.1.1.2: Added text and Table 8 regarding the EAC adjudication of other invasive infections (EAC request). – Section 8.2, Section 8.4, Section 8.5, Section 8.6.1: Minor editorial changes (Pfizer protocol template language updates). – Section 8.10, Section 8.11: Minor revisions (Pfizer protocol template language updates). – Table 9: Severe pain added to footnote (previous omission). – Table 12: Revision of mathematical symbol (correct typographical error). – Table 13: Reference added (give credit to source).

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		– Table 14: Vasopressin added to the scoring system for categorizing hypotension; dialysis added to the scoring system for categorizing renal failure (requested by the EAC). – Section 9.2: Figure 3 added with explanatory text (displays power vs true efficacy). – Section 9.3.2: Added Table 15 showing estimated efficacy and CI by analysis stage (additional clarification). – Section 9.5: Safety analysis and association with *S aureus* reworded (clarification). – Section 15: Text revisions (Pfizer protocol template language updates). – Appendix 1: Added missing text to criteria for vertebral disc space infection and superficial SSI (previous omissions). – Appendix 3: Added collection of data regarding composition of implanted devices (request by investigators).
Amendment 1	13 May 2015	Single-page Appendix 5 added to the last page of the protocol and is applicable to France only. Addresses contractual agreements not covered in the French Contrat Unique. Administrative letter: Section 8.6.2: Added Hy's law language for reporting changes in liver function. This protocol addition was communicated to investigators via an administrative letter on 12 April 2015. (This mandatory text is applicable to all Pfizer interventional clinical trials, irrespective of whether or not liver function tests are monitored in the study. There are no known or suspected negative associations between SA4Ag and liver function.)
Original protocol	07 November 2014	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
ASA	American Society of Anesthesiologists
BMI	body mass index
BSI	bloodstream infection
CBER	Center for Biologics Evaluation and Research
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
ClfA	clumping factor A
cLIA	competitive Luminex immunoassay
CP5	capsular polysaccharide serotype 5
CP5-CRM_{197}	capsular polysaccharide serotype 5 conjugated to cross-reactive material 197 (nontoxic mutant form of diphtheria toxin)
CP8	capsular polysaccharide serotype 8
CP8-CRM_{197}	capsular polysaccharide serotype 8 conjugated to cross-reactive material 197 (nontoxic mutant form of diphtheria toxin)
CRF	case report form
CRM_{197}	cross-reactive material 197 (nontoxic mutant form of diphtheria toxin)
CRP	C-reactive protein
CSA	clinical study agreement
CSF	cerebrospinal fluid
CT	computed tomography
CTA	clinical trial application
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EAC	event adjudication committee
EACC	event adjudication committee charter
ECG	electrocardiographic
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
ESR	erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FIH	first-in-human
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale

Abbreviation	Term
GMFR	geometric mean fold rise
GMT	geometric mean titer
HAI	healthcare-associated infection
HAP	hospital-acquired pneumonia
IB	investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	institutional review board
ISA	invasive *Staphylococcus aureus*
IST	independent statistical team
IUD	intrauterine device
IVRS	interactive voice response system
IWR	interactive Web response
LP305A	lipoprotein 305A
LRT	lower respiratory tract
LS	least squares
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MntC	manganese transporter C
MOF	multiple-organ failure
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NHSN	National Health Surveillance Network
NIS	Nationwide Inpatient Sample
OF	organ failure
OPA	opsonophagocytic activity
PaO_2	partial pressure of oxygen in arterial blood
PCD	primary completion date
PDA	personal digital assistant
PDI	protocol-defined infection
PMN	polymorphonuclear neutrophil
RCDC	reverse cumulative distribution curve
rClfA*m*	recombinant clumping factor A mutant (a component of the initial formulation of SA3Ag)
r*m*ClfA	recombinant clumping factor A mutant (a component of SA4Ag)
rP305A	recombinant protein 305A

Abbreviation	**Term**
RR	relative risk
SA3Ag	*Staphylococcus aureus* 3-antigen vaccine
SA4Ag	*Staphylococcus aureus* 4-antigen vaccine
S aureus	*Staphylococcus aureus*
SAE	serious adverse event
SAP	statistical analysis plan
SCIP	Surgical Care Improvement Project
SOFA	Sequential Organ Failure Assessment
SpO_2	saturation of peripheral oxygen
SRM	study reference manual
SRSD	single reference safety document
SSI	surgical-site infection
SSTI	skin and soft tissue infection
Tdap	tetanus, diphtheria, and acellular pertussis
VE	vaccine efficacy
WBC	white blood cell

PROTOCOL SUMMARY

INTRODUCTION

Staphylococcus aureus is among the most prevalent pathogens responsible for healthcare-associated infections (HAIs) in numerous healthcare settings. Based on data from the Nationwide Inpatient Sample (NIS), from 2000 to 2001 approximately 0.8% of all US hospitalizations involved *S aureus* infections, and in 2001, 1.1% of US surgical hospitalizations involved *S aureus* infections. Inpatients with *S aureus* infection have an estimated 3 times the length of hospital stay and 5 times the risk of in-hospital death as patients without *S aureus* infection. The risk of developing *S aureus* infection is dependent on factors related to both the patient and the type of healthcare exposure. At-risk populations include patients undergoing surgery, patients with end-stage renal disease, patients in intensive care units (ICUs), transplant recipients, and other immunocompromised individuals. Medically or surgically managed conditions associated with increased exposure to the healthcare system place individuals at further risk of acquiring healthcare-associated *S aureus* infection.

S aureus has been demonstrated to be the leading cause of bloodstream infection (BSI), responsible for 20% to 26% of infections overall among North American, European, and Latin American countries, and for 19% of infections among developing countries globally. *S aureus* is the leading cause of both hospital-acquired (34%) and ventilator-associated (27%) pneumonia, and is commonly identified as the predominant organism isolated among intensive care patients and hospitalized pediatric patients.

The incidence of postoperative *S aureus* disease in surgical patients has led to vigorous efforts to develop specific preventive and therapeutic measures directed against this pathogen, including intranasal administration of mupirocin and chlorhexidine bathing to eliminate carriage, and the administration of prophylactic antibiotics prior to surgery. Despite these efforts, postoperative *S aureus* infection remains a common and serious occurrence. Unlike the long-term risk of healthcare-associated invasive *S aureus* (ISA) disease in patients with chronic medical conditions, postoperative ISA disease in the elective surgery population is usually directly attributable to the surgical incision. In this setting, high ISA disease incidence and burden are encountered during a relatively brief and predictable time frame. Elective surgery therefore presents an appropriate setting for evaluation of the safety and efficacy of investigational vaccine for prevention of ISA disease among immunocompetent patients.

Among elective surgery populations and procedures, investigational vaccine efficacy (VE) is ideally evaluated in a clearly defined elective surgery population with well-characterized patient demographics and comorbidities, and procedural characteristics that are highly representative of a broad array of elective surgery populations with respect to risk factors and mechanisms of pathogenesis of postoperative *S aureus* disease. The elective spinal surgery population is similar to other elective surgical populations with regard to both patient and procedural characteristics. Elective spinal surgery is largely performed in patients with low overall morbidity, as demonstrated by Charlson comorbidity index scores.

Elective spinal surgery patients generally require a brief index hospitalization and experience a low incidence of postoperative morbidity and mortality in the absence of postoperative infection, facilitating evaluation of *Staphylococcus aureus* 4-antigen vaccine (SA4Ag) safety.

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective

- To assess the efficacy of SA4Ag in the prevention of postoperative *S aureus* BSI and/or deep incisional or organ/space surgical-site infection (SSI) occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults aged 18 to <86 years.

Primary Efficacy Endpoint

- 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 event adjudication committee (EAC).

Primary Safety Objective

- 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 adverse events (AEs).

Primary Safety Endpoints

- 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 serious adverse events (SAEs) reported during the following time periods:
  - From vaccination until the Day 180 postoperative evaluation
  - From vaccination until the day of surgery
  - From the day of surgery until the Day 180 postoperative evaluation

Secondary Efficacy Objectives

- 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.
- 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.
- 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.

Secondary Efficacy Endpoints

- 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.
- 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.
- 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 Objectives

- To assess the efficacy of SA4Ag in the prevention of postoperative ISA disease occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age.
- 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.

- 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 multilevel instrumentation, in adults 18 to <86 years of age, 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.

- To describe the immunogenicity of SA4Ag in adults aged 18 to <86 years undergoing elective open posterior spinal fusion procedures with multilevel instrumentation.

- 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.

- To compare healthcare utilization data between vaccine groups.

Exploratory Endpoints

- 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.

- 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.

- 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,, 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.

- 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, opsonophagocytic activity (OPA) assays using an *S aureus* capsular polysaccharide serotype 5 (CP5)-expressing strain and a capsular polysaccharide serotype 8 (CP8)-expressing strain, and competitive Luminex immunoassays (cLIAs) for clumping factor A (ClfA) and manganese transporter C (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 achieve specific antibody thresholds to all 4 antigens both individually and combined using immunological assays.

- The number of subjects in each vaccine group determined to be colonized with *S aureus* on each occasion that swab samples are 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.

- 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.

STUDY DESIGN

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

This is an event-driven study with a total target of 48 primary endpoint *S aureus* cases (meeting the case definition described in Section 9.1); it is anticipated that approximately 6,000 subjects will be enrolled globally to accumulate these 48 cases. However, the total enrollment number may vary based on the incidence rate of the primary endpoint, true underlying VE, and a potential early stop for efficacy or futility. In the event that efficacy is demonstrated at the interim analysis, enrollment may continue in order to complete the safety evaluations in this surgical population.

There are 5 scheduled study visits and 1 scheduled telephone contact during 6 to 8 months of subject participation. Study-eligible subjects who provided consent will be randomized in a 1:1 ratio to receive a single dose of SA4Ag or placebo at Visit 1, which occurs 10 to 60 days prior to undergoing elective open posterior spinal fusion procedures with multilevel instrumentation (index surgical procedure). Visit 2 is a longitudinal visit and is to monitor the index hospital admission period from the day of surgery (Day 1) until the day of discharge. A telephone contact with the subject will occur on Day 21, while postoperative evaluation study visits will occur on Day 42, Day 90, and Day 180 after surgery.

Unscheduled telephone contacts will be conducted for assessment of severe local reactions, severe fever, and severe systemic events after vaccination. Severe fever and severe local reactions may warrant an unscheduled severe local reaction or fever assessment visit.

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

VE will be evaluated by monitoring and assessing the occurrence of protocol-defined infections (PDIs). All BSIs, SSIs, and other ISA infections will undergo 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 will contribute to the primary efficacy endpoint analysis.

INVESTIGATIONAL PRODUCTS

SA4Ag comprises CP5 and CP8 individually conjugated to a nontoxic mutant form of diphtheria toxin, cross-reactive material 197 (CRM_{197}) (CP5-CRM_{197} and CP8-CRM_{197}); a recombinant form of clumping factor A (r*m*ClfA), a surface-expressed protein antigen; and rP305A, a recombinant protein derived from an *S aureus* manganese transporter C (MntC).

CCI [redacted]

A 0.5-mL dose contains 30 µg each of CP5-CRM_{197} and CP8-CRM_{197}, 60 µg of r*m*ClfA, and 200 µg of rP305A.

Placebo is a lyophile match to the vaccine, consisting of excipients of SA4Ag formulation minus the active ingredients.

The reconstituted solutions of SA4Ag and placebo appear identical, being clear, colorless, and free of particulate.

Subjects will be administered a single intramuscular 0.5-mL dose of SA4Ag or placebo into the deltoid muscle of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

STATISTICAL METHODS

VE is defined as VE = 1 - RR, where RR is the relative risk in SA4Ag compared to placebo, ie, the proportion of SA4Ag recipients meeting the primary endpoint relative to the proportion of placebo recipients meeting the primary endpoint. An interim analysis will be performed after accumulating 24 per-protocol cases. Only the primary endpoint will be examined. If the number of vaccine cases is 3 or fewer, then the null hypothesis of no difference between treatments will be rejected in favor of the vaccine. There will be additional periodic assessments for futility.

Once 48 per-protocol cases have accumulated, SA4Ag will be deemed efficacious if it has 14 cases or fewer out of a total of 48 cases (point estimate of VE = 58.8%).

Immunogenicity: Geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) relative to baseline, and corresponding 95% confidence intervals (CIs), will be descriptively summarized at each visit by vaccine group.

- AEs will be summarized in each vaccine group for the following intervals:
- From the day of vaccination (Day -60 to Day -10) until the day of surgery (Day 1)
- From the day of surgery (Day 1) until the Day 42 postoperative evaluation
- From the day of vaccination (Day -60 to Day -10) until the Day 42 postoperative evaluation
- From the Day 42 postoperative evaluation until the Day 180 postoperative evaluation (newly diagnosed chronic medical disorders)
- From the day of vaccination (Day -60 to Day -10) until the Day 180 postoperative evaluation (SAEs)

AEs will be summarized using 3-tier methodology. Local reactions and systemic events reported in the electronic diary (e-diary) will be summarized by the maximum severity across the 10-day observation period.

SCHEDULE OF PRIMARY ACTIVITIES

The Schedule of Primary Activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed below in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Schedule of Primary Activities

Visit ID	**1**	**2**			**3**	**4**	**5**	**6**
Protocol Activity	**Study Enrollment and Day of Vaccination**	**Index Hospital Admission[a]**			**Day 21 Telephone Contact**	**Day 42 Post-operative Evaluation**	**Day 90 Post-operative Evaluation**	**Day 180 Post-operative Evaluation[c]**
		Day of Surgery	**Day After Surgery**	**Day of Discharge[b]**				
Study Stage	**Vaccination Stage**	**Surgery Stage**						
Study Day	**Day -60 to Day -10**	**Day 1**	**Day 2**	**(Day Variable)**	**Day 21**	**Day 42**	**Day 90**	**Day 180**
Visit Window	**Day -60 to Day -10**	**N/A**	**N/A**	**N/A**	**Day 18 to Day 26**	**Day 35 to Day 49**	**Day 83 to Day 97**	**Day 178 to Day 192**
Informed consent[d]	X							
Demography	X							
Medical and surgical history	X							
Smoking/alcohol use	X							
Record concomitant vaccinations and medications[e]	X	X		X	X	X	X	X
Record height and weight	X							
Vital signs[f]	X							
Blood glucose[g]		X	X					
Physical examination[h]	X							
Pregnancy test[i]	X							
Contraceptive use discussion	X							
Inclusion and exclusion criteria	X							

Table 1. Schedule of Primary Activities

Visit ID	**1**	**2**			**3**	**4**	**5**	**6**
Protocol Activity	**Study Enrollment and Day of Vaccination**	**Index Hospital Admission[a]**			**Day 21 Telephone Contact**	**Day 42 Post-operative Evaluation**	**Day 90 Post-operative Evaluation**	**Day 180 Post-operative Evaluation[c]**
		Day of Surgery	**Day After Surgery**	**Day of Discharge[b]**				
Study Stage	**Vaccination Stage**	**Surgery Stage**						
Study Day	**Day -60 to Day -10**	**Day 1**	**Day 2**	**(Day Variable)**	**Day 21**	**Day 42**	**Day 90**	**Day 180**
Visit Window	**Day -60 to Day -10**	**N/A**	**N/A**	**N/A**	**Day 18 to Day 26**	**Day 35 to Day 49**	**Day 83 to Day 97**	**Day 178 to Day 192**
Record planned index surgical procedure[j]	X							
Record actual index surgical procedure[j]			X					
Charlson comorbidity score	X							
Temporary vaccination delay criteria	X							
Immunogenicity blood draw[k]	24 mL	24 mL		24 mL		24 mL	24 mL	24 mL
Nasal and oropharyngeal *S aureus* colonization swab collection[k]	X	X		X		X	X	X
Randomization	X							
Investigational product administration	X							
Postvaccination observation (30 minutes), assessment of acute reactions	X							
E-diary training, baseline data entry by subject; dispense measuring device (eg caliper), thermometer, study participant/emergency contact card	X							
Review subject reminders & instructions[l]	X			X	X	X	X	
Schedule next study visit	X			X		X	X	
Daily event monitoring[m]			----------X----------					
Monitor for protocol-defined infections			See Daily event monitoring		X	X	X	X
Review e-diary data, collect e-diary[n]		----------X----------						
Preoperative data collection		X						
Perioperative data collection			X	X				

Table 1. Schedule of Primary Activities

Visit ID	1	2			3	4	5	6
Protocol Activity	Study Enrollment and Day of Vaccination	Index Hospital Admission[a]			Day 21 Telephone Contact	Day 42 Post-operative Evaluation	Day 90 Post-operative Evaluation	Day 180 Post-operative Evaluation[c]
		Day of Surgery	Day After Surgery	Day of Discharge[b]				
Study Stage	Vaccination Stage	Surgery Stage						
Study Day	Day -60 to Day -10	Day 1	Day 2	(Day Variable)	Day 21	Day 42	Day 90	Day 180
Visit Window	Day -60 to Day -10	N/A	N/A	N/A	Day 18 to Day 26	Day 35 to Day 49	Day 83 to Day 97	Day 178 to Day 192
Healthcare utilization data collection[o]				X	X	X	X	X

Abbreviations: AE = adverse event; e-diary = electronic diary; N/A = not applicable; PDI = protocol-defined infection; *S aureus* = *Staphylococcus aureus*.

a. Index hospital admission: The day of admission is either prior to or the day of surgery. In either case, the day of surgery is defined as Day 1.
b. If the index hospital admission day of discharge coincides with the day after surgery (Day 2), Visit 3, Visit 4, or Visit 5, the study procedures may be performed as a single visit. Procedural windows are described in Section 6.3.1.3.
c. May be conducted by telephone provided that arrangements are made for blood and colonization sample collection (eg, home nursing visit).
d. Informed consent must be obtained before the conduct of any study procedures.
e. Includes nonstudy vaccines, antibiotics, systemic and intraspinal steroids, and blood products. Refer to Section 5.4.
f. Vital signs include temperature (°C or °F), pulse rate, respiratory rate, and blood pressure.
g. Serum or capillary; fasting value required preoperatively.
h. Physical examination includes general appearance; musculoskeletal; skin; head, eyes, ears, nose, and throat; heart; lungs; abdominal; neurological; and lymph nodes.
i. Only applicable for women of childbearing potential. Pregnancy testing may be performed on urine or serum samples.
j. Record the surgical indication and the planned index surgical procedure. Postoperatively, record the actual index surgical procedure.
k. Immunogenicity blood draw and colonization swabs must be collected before vaccination at Visit 1 (window: 7 days) and before surgery at Visit 2.
l. Refer to the respective study visit as detailed in Section 6.
m. Daily observation for PDIs, AEs, and organ failure events as detailed in Section 6.3.1.2.1.
n. The e-diary should be collected and AE data reviewed with the subject prior to surgery.
o. Refer to Appendix 4.

SCHEDULE OF ACTIVITIES FOR ADVERSE AND STUDY EVENT REPORTING

The Schedule of Activities for Adverse and Study Event Reporting table provides an overview of the protocol safety reporting requirements. Refer to the Study Procedures (Section 6.1) and Assessments (Section 7) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Table 2. Schedule of Activities for Adverse and Study Event Reporting

<table>
<tr><th>Visit ID</th><th>1</th><th colspan="3">2</th><th>3</th><th>4</th><th>5</th><th>6</th></tr>
<tr><th>Protocol Activity</th><th rowspan="2">Enrollment and Day of Vaccination</th><th colspan="3">Index Hospital Admission</th><th rowspan="2">Day 21 Telephone Contact</th><th rowspan="2">Day 42 Postoperative Evaluation</th><th rowspan="2">Day 90 Postoperative Evaluation</th><th rowspan="2">Day 180 Postoperative Evaluation</th></tr>
<tr><th>Day of Surgery</th><th>Day After Surgery</th><th>Day of Discharge</th></tr>
<tr><td>Study Day</td><td>Day -60 to Day -10</td><td>Day 1</td><td>Day 2</td><td>(Day Variable)</td><td>Day 21</td><td>Day 42</td><td>Day 90</td><td>Day 180</td></tr>
<tr><td>Visit Window</td><td>Day -60 to Day -10</td><td>N/A</td><td>N/A</td><td>N/A</td><td>Day 18 to Day 26</td><td>Day 35 to Day 49</td><td>Day 83 to Day 97</td><td>Day 178 to Day 192</td></tr>
<tr><td>Local reactions and systemic events collected in the e-diary</td><td>From the day of vaccination for a total of 10 days[a]</td><td colspan="7"></td></tr>
<tr><td rowspan="2">Adverse events</td><td colspan="5">AEs from informed consent to the Day 42 postoperative evaluation</td><td colspan="3"></td></tr>
<tr><td colspan="5"></td><td colspan="3">Newly diagnosed chronic medical disorders from the Day 42 postoperative evaluation to the Day 180 postoperative evaluation</td></tr>
<tr><td>Serious adverse events</td><td colspan="8">SAEs from informed consent to the Day 180 postoperative evaluation</td></tr>
<tr><td>Protocol-defined infection events</td><td></td><td colspan="7">PDI events from after surgery to the Day 180 postoperative evaluation</td></tr>
<tr><td>Organ failure events</td><td></td><td colspan="7">Organ failure events from after surgery to Day 180 (applicable during any hospitalization)</td></tr>
</table>

Abbreviations: AE = adverse event; N/A = not applicable; PDI = protocol-defined infection; SAE = serious adverse event.
a. If surgery occurs on Day 10 after vaccination, the e-diary need not be completed on the day of surgery.

UNSCHEDULED STUDY VISITS, CONTACTS, AND SURVEILLANCE PERIODS

Table 3 shows the list of unscheduled visits that are to occur when certain conditions are met. Refer to Table 4 for unscheduled visit procedures.

Table 3. Unscheduled Study Visits, Contacts, and Surveillance Periods

Visit ID	1	2			3	4	5	6
Protocol Activity	**Enrollment and Day of Vaccination**	**Index Hospital Admission**			**Telephone Call** ☎	**Day 42 Postoperative Evaluation**	**Day 90 Postoperative Evaluation**	**Day 180 Postoperative Evaluation**
		Day of Surgery	**Day After Surgery**	**Day of Discharge**				
Study Day	Day -60 to Day -10	Day 1	Day 2	(Day Variable)	Day 21	Day 42	Day 90	Day 180
Visit Window	Day -60 to Day -10	N/A	N/A	N/A	Day 18 to Day 26	Day 35 to Day 49	Day 83 to Day 97	Day 178 to Day 192
UNSCHEDULED VISITS AND CONTACTS								
Severe local reaction or fever telephone contact ☎ (Section 6.4.1.1.1)	May occur within 10 days after vaccination							
Severe systemic event telephone contact ☎ (Section 6.4.1.1.2)	May occur within 10 days after vaccination							
Severe local reaction or fever assessment visit (Section 6.4.1.2)	May occur within 10 days after vaccination							
BSI/SSI assessment visit (Section 6.4.2)		• May occur postoperatively during the index hospital admission • May occur after discharge from the index hospital						
Hospitalization visit (Section 6.4.3)					May occur at any time after discharge from the index hospital			

Abbreviations: BSI = bloodstream infection; N/A = not applicable; SSI = surgical-site infection.

STUDY PROCEDURES ASSOCIATED WITH UNSCHEDULED STUDY VISITS

The Study Procedures Associated With Unscheduled Study Visits table provides an overview of the unscheduled visit requirements. Refer to the Study Procedures (Section 6.4) and Assessments (Section 7) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Table 4. Study Procedures Associated With Unscheduled Study Visits

Protocol Procedure	Severe Local Reaction or Fever Telephone Contact	Severe Systemic Event Telephone Contact	Severe Local Reaction or Fever Assessment Visit	BSI/SSI Assessment Visit	Hospital-ization Visit
Determine whether a severe local reaction or fever assessment visit is required	X				
Determine whether the severe systemic event meets Grade 4 and/or SAE criteria		X			
Measure temperature (°C or °F)			X		
Measure redness and swelling			X		
Grade pain			X		
Assess lymphadenopathy			X		
Collect colonization swab samples from the nose and throat				X	
Collect blood culture samples				X	
For an SSI that is operatively incised and/or spontaneously draining, collect a wound culture swab				X	
Collect a blood sample for immunogenicity				24 mL	24 mL[a]
Record antibiotic therapy				X	X
Adverse event collection as appropriate				X	X
Collect healthcare utilization data					X
If a PDI event is suspected, complete PDI event requirements[b]				X	X
If a BSI and/or SSI is identified or suspected, complete all procedures for a BSI/SSI assessment visit[c]					X
Assess for organ failure[d]					X
Perioperative data collection for index surgery reoperation and revision					X

Abbreviations: BSI = bloodstream infection; PDI = protocol-defined infection; SAE = serious adverse event; SSI = surgical-site infection.

a. Collect only if subject has multiple-organ failure.
b. Refer to Section 7.1.1 for PDI events.
c. Refer to Section 6.4.2 for the BSI/SSI assessment visit.
d. Refer to Section 7.2.3 for assessment of organ failure.

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1. INTRODUCTION

Staphylococcus aureus (*S aureus*) is a gram-positive coccus and a commensal organism that colonizes the nares, axillae, pharynx, and other mucosal and skin surfaces of approximately 20% to 50% of humans.[1,2] *S aureus* is an opportunistic pathogen[2] and a leading cause of healthcare-associated infections (HAIs), including bloodstream infection (BSI), surgical-site infection (SSI), and hospital-acquired pneumonia (HAP),[2,3] and is an increasingly common cause of community-associated infections in the United States (US), Europe, and globally. Among North American, Latin American, European, and Western Pacific nations, *S aureus* is recognized as the leading cause of HAIs.[4] In the United States, *S aureus* is estimated to represent 15% of all HAIs.[5] In the outpatient setting, *S aureus* has been estimated to be responsible for 11.6 million skin and soft tissue infections (SSTIs) annually in the United States, affecting 411/10,000 persons.[6] Likewise, globally *S aureus* is the predominant cause of SSTI, representing 45% of North American, 34% of Latin American, and 38% of European isolates.[7]

The widespread disease manifestations of *S aureus* and its substantial burden to the healthcare system present a serious unmet medical need. Infections due to methicillin-sensitive *S aureus* (MSSA) as well as those due to methicillin-resistant *S aureus* (MRSA) contribute to disease morbidity, mortality, and economic burden, as well as the increasing need for more rigorous infection control practices. Despite the availability of antibiotics indicated for the prevention and treatment of *S aureus* infections, outcomes remain suboptimal for many patients.[2] Given the failure of the current standards of care to address the global epidemic of *S aureus* disease, the need for a preventive vaccine is clear.

1.1. Mechanism of Action/Indication

S aureus 4-antigen vaccine (SA4Ag) is intended for active immunization for the prevention of postoperative invasive disease caused by *S aureus* in adults 18 years of age and older who are undergoing elective surgery.

1.2. Background and Rationale

1.2.1. Healthcare-Associated *S aureus* Disease

S aureus is among the most prevalent pathogens responsible for HAIs in numerous healthcare settings. Based on data from the Nationwide Inpatient Sample (NIS), from 2000 to 2001 approximately 0.8% of all US hospitalizations involved *S aureus* infections,[8] and in 2001, 1.1% of US surgical hospitalizations[9] involved *S aureus* infections. Inpatients with *S aureus* infection have an estimated 3 times the length of hospital stay and 5 times the risk of in-hospital death as patients without *S aureus* infection.[8] The risk of developing *S aureus* infection is dependent on factors related to both the patient and the type of healthcare exposure. At-risk populations include patients undergoing surgery, patients with end-stage renal disease, patients in intensive care units (ICUs), transplant recipients, and other immunocompromised individuals.[10,11,12] Medically or surgically managed conditions associated with increased exposure to the healthcare system place individuals at further risk of acquiring healthcare-associated *S aureus* infection.[13,14]

S aureus has been demonstrated to be the leading cause of BSI, responsible for 20% to 26% of infections overall among North American, European, and Latin American countries,[15] and for 19% of infections among developing countries globally.[16] A large international study recently estimated the population incidence of *S aureus* BSI to be 26.1/100,000 among several developed nations.[17] *S aureus* is the leading cause of both hospital-acquired (34%) and ventilator-associated (27%) pneumonia,[18] and is commonly identified as the predominant organism isolated among intensive care patients[12,19] and hospitalized pediatric patients.[20]

1.2.1.1. Postoperative *S aureus* Disease

SSI is an important cause of patient morbidity and healthcare cost, representing approximately 38% of infectious complications among surgical patients in the United States.[21] Based on 2012 US dollars, each SSI is estimated to result in overall healthcare costs of $20,785. Collectively, SSIs account for 34% of the estimated $9.8 billion burden of US HAIs.[22] About 2% to 5%[23] of US surgeries are complicated by SSI, of which *S aureus* is estimated to be responsible for at least 20% overall.[21,22,23,24,25] SSI can result in secondary BSI which places the patient at substantially greater risk of postoperative morbidity and mortality. *S aureus* SSI is far more likely to result in secondary BSI, representing 66% of such cases.[26]

1.2.1.1.1. Patient Risk Factors for Postoperative Infection

The individual risk of acquiring postoperative *S aureus* infection, while directly attributable to the surgical incision itself, can be influenced by both patient and procedural factors across the spectrum of surgical practice. Advanced age,[27,28] diabetes mellitus,[29] obesity,[30-33] and tobacco use[34] are among the most relevant of numerous patient risk factors for acquiring postoperative infection. The incidence of healthcare-associated *S aureus* infection correlates directly with age, as demonstrated by an overall MRSA incidence of 31.8/100,000 for the general US population but 127.7/100,000 for those aged 65 years and older.[35] Advanced age is likewise a well-established risk factor for postoperative infection.[27,28] Hyperglycemia has been shown to negatively impact neutrophil chemotactic, phagocytic, and bactericidal activity[29] and is associated with increased risk of postoperative infection among cardiothoracic[36] and noncardiothoracic[37,38] surgery populations. Obesity is associated with comorbidities such as insulin resistance, hyperglycemia, and metabolic syndrome, and has substantial direct impacts on the surgical wound, such that obese patients undergoing spinal, arthroplasty, general, cardiothoracic, and vascular surgeries are at substantial risk of postoperative infection relative to nonobese patients.[27,30-33,39,40] Tobacco use is a well-established risk factor for postoperative infectious as well as noninfectious complications across a broad range of surgeries. The profound multisystem effects of tobacco use result in higher rates of SSI, wound dehiscence and rupture, and delayed wound healing, in addition to greater risk of pulmonary infection.[34,41]

1.2.1.1.2. Procedural Risk Factors for Postoperative Infection

Across the spectrum of surgical practice, wound-related factors such as wound class, operative duration, suture length, implantation of prosthetic material, and insertion of drains may increase the risk of SSI.[42-45]

Based on the large body of evidence that supports preoperative shaving, patient hypothermia, and hyperglycemia as consistent risk factors for infection across surgical practice, the Surgical Care Improvement Project (SCIP), an initiative of the US Centers for Disease Control and Prevention (CDC), recommends preoperative hair removal using clippers and avoidance of shaving, and maintenance of patient normothermia and euglycemia during the first 48 postoperative hours.[46] Perioperative hypothermia is associated with significantly increased SSI risk thought to result from a decrease in subcutaneous tissue perfusion mediated by vasoconstriction.[47] For both diabetic and nondiabetic patients, perioperative hyperglycemia is associated with increased length of hospital and ICU stay, increased risk of bloodstream, respiratory, and urinary tract infections, and increased risk of death.[48]

1.2.2. Rationale for Evaluation of SA4Ag Efficacy in the Prevention of Postoperative *S aureus* Disease in Patients Undergoing Elective Surgery

The incidence of postoperative *S aureus* disease in surgical patients has led to vigorous efforts to develop specific preventive and therapeutic measures directed against this pathogen, including intranasal administration of mupirocin and chlorhexidine bathing to eliminate carriage, and the administration of prophylactic antibiotics prior to surgery.[46,49] Despite these efforts, postoperative *S aureus* infection remains a common and serious occurrence. Unlike the long-term risk of healthcare-associated invasive *S aureus* (ISA) disease in patients with chronic medical conditions, postoperative ISA disease in the elective surgery population is usually directly attributable to the surgical incision. In this setting, high ISA disease incidence and burden are encountered during a relatively brief and predictable time frame. Elective surgery therefore presents an appropriate setting for evaluation of the safety and efficacy of investigational vaccine for prevention of ISA disease among immunocompetent patients.

Among elective surgery populations and procedures, investigational vaccine efficacy (VE) is ideally evaluated in a clearly defined elective surgery population with well-characterized patient demographics and comorbidities, and procedural characteristics that are highly representative of a broad array of elective surgery populations with respect to risk factors and mechanisms of pathogenesis of postoperative *S aureus* disease. The elective spinal surgery population is similar to other elective surgical populations with regard to both patient and procedural characteristics. Elective spinal surgery is largely performed in patients with low overall morbidity, as demonstrated by Charlson comorbidity index (CCI) scores.[50] Elective spinal surgery patients generally require a brief index hospitalization and experience a low incidence of postoperative morbidity and mortality in the absence of postoperative infection,[51] facilitating evaluation of SA4Ag safety.

The demographics and comorbidities associated with postoperative infection among elective spinal surgery patients are similar to those reported among other orthopedic and plastic surgery populations and among patients undergoing clean, general surgery.[50] Spinal surgery involves surgical violation of anatomical layers, including the dermis, soft tissue, and fascial layers, as well as bony structures, frequently involving the implantation of prosthetic materials and bone grafting. These procedural characteristics are common to arthroplasty and other elective orthopedic surgeries. Clean abdominal, general, and plastic surgical procedures also involve the violation of dermal, soft tissue, and fascial planes where bacterial

inoculation leading to postoperative infection is most likely to occur, and often involve the implantation of prosthetic material (eg, hernia repair, breast reconstruction). Despite these similar demographic and procedural characteristics, the incidence of postoperative ISA disease in patients undergoing elective spinal surgery is relatively high[51,52] compared with other procedures such as arthroplasty.[53] As such, this higher incidence of ISA disease will facilitate evaluation of SA4Ag efficacy in a clinical trial setting.

1.2.3. Vaccine Antigen Composition

Pfizer's investigational SA4Ag is designed to be protective across the range of clinical *S aureus* disease isolates, including MSSA and MRSA, regardless of their antibiotic resistance profiles or geographical origin.

SA4Ag contains the following 4 antigens, each of which elicits immune responses targeting surface-expressed, conserved, and globally represented *S aureus* components that are used by *S aureus* to facilitate infection:

- **CP5-CRM$_{197}$** and **CP8-CRM$_{197}$**: capsular polysaccharide serotype 5 (CP5) and serotype 8 (CP8), each conjugated to the nontoxic mutant form of diphtheria toxin, cross-reactive material 197 (CRM$_{197}$);
- **r*m*ClfA**: a truncated recombinant form of clumping factor A (ClfA) with a single amino-acid substitution (Y338A) that abolishes human fibrinogen binding; and
- **rP305A**: a recombinant form of the manganese transporter C (MntC) or lipoprotein 305A (LP305A); the recombinant protein is a nonlipidated form of MntC.

The quantities of each vaccine antigen are shown in Table 5:

Table 5. *Staphylococcus aureus* Vaccine Antigen Levels

	Antigen			
	CP5-CRM$_{197}$	**CP8-CRM$_{197}$**	**r*m*ClfA**	**rP305A (MntC)**
Volume in 0.5 mL water	30 µg	30 µg	60 µg	200 µg

Abbreviations: CP5-CRM$_{197}$ = capsular polysaccharide serotype 5 conjugated to cross-reactive material 197; CP8-CRM$_{197}$ = capsular polysaccharide serotype 8 conjugated to cross-reactive material 197; r*m*ClfA = recombinant clumping factor A mutant; rP305A = recombinant protein 305A; MntC = manganese transporter C.

1.2.4. Clinical Experience

1.2.4.1. First-in-Human Trial of SA3Ag (Phase 1, Study B2251002)

Study B2251002, conducted in Australia, was a first-in-human (FIH) Phase 1 study evaluating the safety and immunogenicity of a preliminary *S aureus* 3-antigen vaccine (SA3Ag). In this completed study, 406 healthy subjects aged 18 to 24 or 50 to 85 years received 1 of 3 dose levels of SA3Ag (low dose level [10 µg CP5-CRM$_{197}$, 10 µg CP8-CRM$_{197}$, and 20 µg rClfA*m*], mid dose level [30 µg CP5-CRM$_{197}$, 30 µg CP8-CRM$_{197}$,

and 60 µg rClfA*m*], or high dose level [100 µg CP5-CRM_{197}, 100 µg CP8-CRM_{197}, and 200 µg rClfA*m*]) or placebo. SA3Ag was shown to be safe, well tolerated, and capable of eliciting robust functional (bacterial killing) immune responses at postvaccination Day 15 after a single administration of 1 of 3 dose levels of SA3Ag. Substantial antibody titers to each of the 3 SA3Ag antigens were sustained through postvaccination Month 12. Immune responses to CP5-CRM_{197} and CP8-CRM_{197} were comparable for the groups receiving the mid and high dose levels of SA3Ag, with lower responses observed for the low-dose-level group. For rClfA*m*, responses were similar across the dose level groups. While each dose level had an acceptable safety profile, local reactions were reported at an increased incidence and severity in the high-dose-level group; therefore, the mid dose level of SA3Ag (30 µg CP5-CRM_{197}, 30 µg CP8-CRM_{197}, and 60 µg r*m*ClfA) was selected to be included as a fixed dose level in the SA4Ag formulations evaluated in subsequent studies, along with 3 escalating dose levels of rP305A (20 µg, 60 µg, or 200 µg).

1.2.4.2. First-in-Human Trial of SA4Ag (Phase 1/2a, Study B3451001)

Study B3451001, conducted in the United States, was an FIH Phase 1/Phase 2a study evaluating the safety and immunogenicity of SA4Ag. In this completed study, 456 healthy subjects aged 18 to <65 years received either placebo or 1 of 3 formulations of SA4Ag (ie, 3 dose levels of rP305A antigen). SA4Ag formulations used in the study each included the original 3 antigens in SA3Ag at the dose levels selected based on results from Study B2251002 (30 µg CP5-CRM_{197}, 30 µg CP8-CRM_{197}, and 60 µg r*m*ClfA), in addition to rP305A at 1 of 3 dose levels: low (20 µg), mid (60 µg), or high (200 µg).

Safety data demonstrated that SA4Ag was well tolerated at all rP305A dose levels evaluated. Immunogenicity results showed that all 4 vaccine antigens elicited robust immune responses at postvaccination Day 29, which gradually waned but remained substantially above prevaccination levels through Month 12 after vaccination.

1.2.4.3. Trial of SA4Ag in Elderly Subjects (Phase 1/2a, Study B3451011)

Study B3451011, conducted in the United States, was a Phase 1/2a study similarly evaluating safety and immunogenicity of SA4Ag in elderly adults. In this study, 283 healthy subjects aged 65 to <86 years received 1 of the 3 above formulations of SA4Ag, placebo, or SA3Ag (containing the CP5-CRM_{197}, CP8-CRM_{197}, and ClfA components at the same dose levels used in the SA4Ag formulations, without the rP305A component) as a comparator. As with Study B3451001, safety data demonstrated that SA4Ag was well tolerated at all rP305A dose levels evaluated. Likewise, similarly robust immune responses to all 4 vaccine antigens were observed at postvaccination Day 29, and immune responses were sustained through Month 12 after vaccination.

1.2.4.4. Duration-of-Immunogenicity Study (Phase 2, Study B3451014)

Study B3451014, conducted in the United States, was a Phase 2 study evaluating the persistence of the immune responses to SA4Ag antigens in previously vaccinated B3451001 and B3451011 study subjects. Antibody levels to each of the 4 vaccine antigens were measured through 36 months after single-dose SA4Ag administration in the primary study. Results showed persistent functional immune responses to CP5, CP8, and ClfA through

Month 36 after vaccination. Immune responses to rP305A had declined at Month 36, however remained above baseline levels.

1.2.5. Summary of Benefit-Risk Assessment

S aureus is an opportunistic pathogen[2] and a leading cause of healthcare-associated infections, including bloodstream infections, surgical-site infections, and hospital-acquired pneumonia,[3, 4] and is an increasingly common cause of community-associated infections.[4] The widespread disease manifestations of *S aureus* and its substantial burden to the healthcare system present a serious unmet medical need. Despite the availability of antibiotics indicated for the prevention and treatment of *S aureus* infections, outcomes remain suboptimal for many patients; therefore, there is a need to develop a vaccine to prevent *S aureus* infections.

Results from the Phase 1/2a studies of SA3Ag and SA4Ag conducted in healthy adults aged 18 to <86 years demonstrated an acceptable safety profile. Local vaccine reactions (redness, swelling, and pain at the injection site) and systemic events (fever, vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain) were generally mild or moderate in severity and resolved within a few days after vaccination. Similar incidences of adverse events were reported across the study groups (vaccine recipients and placebo recipients) and were consistent with what is expected in adults. The majority of subjects demonstrated normal hematology, biochemistry, and coagulation profiles at baseline, Day 5, and Day 15 after vaccination. There were no notable trends in laboratory abnormalities within or across vaccine or age groups.

Immunogenicity results showed that all 4 vaccine antigens elicited robust immune responses at postvaccination Day 15 and Day 29 as demonstrated by functional assays in all age groups and that the immune response persisted through at least 36 months after vaccination.

For this study, the data monitoring committee meets on a quarterly basis to review safety data (blinded and unblinded) and to date has not identified any safety signal and has recommended to continue the study.

Pfizer considers the available information from Phase 1/2a clinical trials to support a favorable benefit-risk profile for studies administering a single dose of SA4Ag as a potential prevention against invasive *S aureus* disease in adults undergoing elective open, posterior spinal fusion surgery with multilevel instrumentation.

1.3. rP305A Dose Level Selection for SA4Ag Phase 2b Evaluation

Results from the B3451001 and B3451011 studies were used to determine the dose level of rP305A for inclusion in the final formulation of SA4Ag. The highest dose level of rP305A evaluated (200 µg) was selected for further SA4Ag clinical development because (1) immune responses to rP305A were dose dependent, with the high-dose-level group demonstrating highest responses to rP305A, which were sustained out to 12 months (B3451001); (2) increasing the rP305A dose level did not impact the immune response to the other 3 antigens; (3) local reactions and systemic events did not increase with increasing rP305A dose levels; and (4) the incidence of adverse events (AEs) in the high-dose-level group was

similar to that of the placebo group in the younger subjects (26.8% vs 25.9%, respectively), and lower than that of the placebo group in the older subjects (29.8% vs 36.7%, respectively).

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the IB.

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints employ the following definitions:

- **Protocol-defined infection (PDI)**: Postoperative infections that occur following elective spinal surgery, particularly those frequently caused by *S aureus*, will be prospectively evaluated in this study. PDI clinical and microbiological criteria are based upon CDC National Health Surveillance Network (NHSN) criteria; complete case definitions provided in Appendix 1 will be applied for case identification and confirmation. Summaries of the PDIs that, when microbiologically confirmed as being due to *S aureus,* will contribute to study objectives and endpoints are provided below.

    - **Bloodstream infection (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.

    - **Surgical-site infection (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 is further classified as:

        - **Superficial SSI**: Infection involves only skin and subcutaneous tissue of the incision.

        - **Deep incisional SSI**: Infection involves deep soft tissues of the incision (eg, fascial and muscle layers).

        - **Organ/space SSI**: Infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is 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 will be 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), will be considered organ/space SSIs.

    - **Invasive *S aureus* (ISA) disease**: ISA disease is 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 defined in Appendix 1 will be considered ISA disease.

2.1. Primary Efficacy Objective

- 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 multilevel instrumentation, in adults aged 18 to <86 years.

2.1.1. Primary Efficacy Endpoint

- 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 event adjudication committee (EAC).

2.2. Primary Safety Objective

- 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.

2.2.1. Primary Safety Endpoints

- 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 serious adverse events (SAEs) reported during the following time periods:

    - From vaccination until the Day 180 postoperative evaluation

    - From vaccination until the day of surgery

- From the day of surgery until the Day 180 postoperative evaluation

2.3. Secondary Efficacy Objectives

- 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.

- 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.

- 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.

2.3.1. Secondary Efficacy Endpoints

- 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.

- 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.

- 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.

2.4. Exploratory Objectives

- To assess the efficacy of SA4Ag in the prevention of postoperative ISA disease occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults 18 to <86 years of age.

- 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.

- 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 multilevel instrumentation, in adults 18 to <86 years of age, 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.

- To describe the immunogenicity of SA4Ag in adults aged 18 to <86 years undergoing elective open posterior spinal fusion procedures with multilevel instrumentation.

- 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.

- To compare healthcare utilization data between vaccine groups.

2.4.1. Exploratory Endpoints

- 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.

- 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.

- 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, 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.

- 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, opsonophagocytic activity (OPA) assays using an *S aureus* capsular polysaccharide serotype 5 (CP5)-expressing strain and a capsular polysaccharide serotype 8 (CP8)-expressing strain, and competitive Luminex immunoassays (cLIAs) 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 achieve specific antibody thresholds to all 4 antigens both individually and combined using immunological assays.

- The number of subjects in each vaccine group determined to be colonized with *S aureus* on each occasion swab samples are 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.

- 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.

2.5. Endpoint Adjudication

To maintain the scientific integrity, this protocol will use an independent EAC for adjudication of all primary and secondary efficacy endpoints, exploratory endpoints of ISA disease (Section 7.1.1.2), multiple-organ failure (MOF), and death, as summarized below. The EAC's assessment of these events will represent the final confirmed classification of the event.

The primary and/or secondary efficacy-related events for adjudication include all reported BSI and SSI events. The EAC is responsible for adjudicating whether BSI and SSI events fulfill the protocol-defined clinical criteria, and whether the confirmed infections are attributable to microbiologically confirmed *S aureus,* attributable to other pathogen(s), or without microbiological confirmation.

Furthermore, the EAC is responsible for adjudicating all other reported PDI events. As with BSI and SSI events, the EAC will confirm whether these events fulfill the protocol-defined clinical criteria, and whether these events represent microbiologically confirmed *S aureus* infection.

In addition, any other invasive infection (irrespective of the causative pathogen) will be adjudicated by the EAC.

The most adverse outcomes of postoperative infections are MOF and death. Therefore, in addition to the PDI adjudication responsibilities mentioned above, the EAC is also responsible for adjudicating whether reported organ failure (OF) events meet the protocol-defined clinical criteria for OF/MOF, and whether the confirmed OF/MOF events and all reported deaths are attributable to microbiologically confirmed *S aureus,* attributable to other pathogen(s), or without microbiological confirmation (Section 7.2.3).

The detailed event adjudication criteria, documentation requirements, responsibilities, EAC membership requirements, and training are found in the event adjudication committee charter (EACC). The EAC will remain blinded to subject vaccine assignments. To facilitate EAC adjudication, in addition to the data captured in the case report form (CRF), documents that support the clinical and microbiological criteria specified in Appendix 1 will be provided by investigators in conjunction with the sponsor's study team.

Any SAE that is adjudicated by the EAC and determined NOT to meet endpoint criteria is reported back to the investigative site of incidence; the investigator at the study site must

evaluate and report that SAE to Pfizer, in accordance with the time frames described in the Serious Adverse Event Reporting Requirements (Section 8.14.1). The investigator's SAE awareness date in this instance is identified as the date on which the investigative site of incidence receives the determination that the SAE does not meet endpoint criteria back from the EAC. Handling these SAEs in this manner will allow Pfizer to meet its sponsor reporting obligations to regulatory authorities upon receipt of such SAEs.

However, when the investigator has judged an SAE to have a causal relationship with the investigational product, the investigator must additionally report the event to the sponsor as described in the Serious Adverse Event Reporting Requirements (Section 8.14.1), even if that event is a component of the endpoint.

Any events that remain unadjudicated at the annual safety report cutoff date are not to be included in the safety tables of the report.

3. STUDY DESIGN

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

There are 5 scheduled study visits and 1 scheduled telephone contact during 6 to 8 months of subject participation. Study-eligible subjects who provided consent will be randomized in a 1:1 ratio to receive a single dose of SA4Ag or placebo at Visit 1, which occurs 10 to 60 days prior to undergoing elective open posterior spinal fusion procedures with multilevel instrumentation (*index surgical procedure*). Visit 2 is a longitudinal visit and is to monitor the index hospital admission period from the day of surgery (Day 1) until the day of discharge.

A telephone contact with the subject will occur on Day 21 (window: Days 18 to 26), while postoperative evaluation study visits will occur on Day 42 (window: Days 35 to 49), Day 90 (window: Days 83 to 97), and Day 180 (window: Days 178 to 192) after surgery.

Additional reminders will be communicated to study subjects instructing them to contact the investigational site whenever there is a suspicion of a PDI or a severe postvaccination local reaction or fever.

Unscheduled telephone contacts will be conducted for assessment of severe local reactions, severe fever, and severe systemic events after vaccination. Severe fever and severe local reactions may warrant an unscheduled *severe local reaction* or *fever assessment visit*.

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

3.1. Subject Numbers and Duration of Subject Participation

It is anticipated that approximately 6000 subjects will be enrolled globally to accumulate 48 per-protocol cases. As this is an event-driven study, the final enrollment number may vary depending on the incidence rate of the primary endpoint, the true underlying VE, and a potential early stop for efficacy or futility (see Section 9.1). In the event that efficacy is demonstrated at the interim analysis, enrollment may continue in order to complete the safety evaluations in this surgical population.

Each subject is expected to participate in the study for approximately 6 to 8 months.

The end of the study is defined as last subject last visit (LSLV) for the purposes of closing out sites, informing the institutional review board/independent ethics committee (IRB/IEC), and stopping the sending of Council for International Organizations of Medical Sciences (CIOMS) reports; however, for other purposes the end of the study will be defined as the last serology sample assayed or characterization of the last strain isolate.

3.2. Study Population

3.2.1. Index Study Procedure Definitions

Subjects undergoing elective, spinal fusion procedures with multilevel instrumentation performed via an open posterior incision will be considered eligible for participation in this study, where

- An *elective* surgical procedure is defined as a nonemergency inpatient surgical procedure scheduled to occur 10 to 60 days after receiving the study vaccination.

- An *open posterior* incision is defined as a posterior midline, posterolateral, or transverse exposure of the vertebrae to be fused or instrumented. Subjects undergoing procedures involving additional surgical access, whether via open incision, minimally invasive, or laparoscopic technique (eg, anterior or lateral interbody fusion procedures), may be eligible, provided that the procedure involves open posterior exposure. Subjects undergoing staged fusion procedures requiring operations performed on separate days or procedures performed exclusively by a minimally invasive technique are not eligible for inclusion.

- For this study, *spinal fusion* is defined as a surgical arthrodesis procedure that includes at least 2 adjacent intervertebral levels/motion segments, ie, a minimum of:

    - 3 adjacent vertebrae (any region of spine), or

    - 2 adjacent cervical vertebrae plus the occiput, or

    - 2 adjacent lumbar/sacral vertebrae plus the pelvis

- A single fusion that includes 1 intervertebral level/motion segment is permitted only if the instrumentation inserted spans at least 2 adjacent intervertebral levels/motion segments (ie, multilevel instrumentation).

- For this study, *multilevel instrumentation* is defined as the surgical implantation of prosthetic material (eg, rods, screws, plates, hooks, wires, and/or bone cages) involving at least 2 intervertebral levels/motion segments, ie, a minimum of:

  - 3 adjacent vertebrae (any region of spine), or

  - 2 adjacent cervical vertebrae plus the occiput, or

  - 2 adjacent lumbar/sacral vertebrae plus the pelvis

3.2.2. Surgical Indications

3.2.2.1. Permitted Indications for the Index Surgical Procedure

Subjects presenting with 1 or more of the following surgical indications for their index surgery may be eligible for inclusion.

- Intervertebral disc disease (eg, herniation, rupture, postdiscectomy syndrome)

- Facet joint arthritis, facet joint syndrome

- Vertebral instability (eg, spondylolysis, spondylolisthesis, true instability)

- Adjacent segment syndrome

- Transitional lumbosacral anomaly

- Spinal stenosis

- Spinal deformity (eg, scoliosis, kyphosis)

- Spinal cord compression

- Other

3.2.2.2. Prohibited Indications for the Index Surgical Procedure

Subjects presenting with 1 or more of the following surgical indications for their index surgery are not eligible for inclusion. Further details are provided in the study exclusion criteria (Section 4.2).

- Infection

- Malignancy

- Acute or emergency trauma

3.2.2.3. Previous or Revisional Spinal Surgery

Subjects with a history of previous spinal surgery at least 6 months prior to study enrollment, including subjects undergoing previous fusion of the same or adjacent vertebrae, may be eligible for inclusion, provided that other study eligibility criteria are met. Subjects with a history of postoperative BSI and/or SSI following previous spinal surgery are not eligible for inclusion.

If, during a revision surgery, hardware or tissue is removed, the hardware and/or tissue should be cultured.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

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

1. Subject must personally sign and date the informed consent document (ICD) indicating that the subject has been informed of all pertinent aspects of the study.

2. Subject must be aged 18 to <86 years at the time of enrollment.

3. Subject must be scheduled to undergo an elective open posterior spinal fusion procedure with multilevel instrumentation 10 to 60 days after study vaccination. (For additional details, see Section 3.2.1).

4. Subject must be available for the entire duration of the study, and 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 occurs on Day 10, then the e-diary does not need to be completed for that day).

5. Subject must be able to be contacted by telephone during study participation.

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

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be 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). (For additional details, see Section 3.2.1.)

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 acquired immunodeficiency disorder, 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.

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 are unwilling or unable to use a highly effective method of contraception, as outlined in Section 4.4, 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 may increase 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 subject inappropriate for entry into this study.

21. Subjects who are 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 are Pfizer employees directly involved in the conduct of the study.

4.3. Criteria for Temporarily Delaying Vaccine Administration

The following conditions are temporary or self-limiting and a subject may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met, provided that the scheduled surgical procedure remains within the 10- to 60-day window from the day of vaccination to the day of surgery.

- Current febrile illness (oral temperature of ≥38.0°C [100.4°F]) or other acute illness within 48 hours prior to investigational product administration.

- Receipt of any nonlive vaccine within 14 days or any live vaccine within 28 days prior to vaccination; anticipated administration of any nonlive vaccine within 14 days or any live vaccine within 28 days after study vaccination.

- Systemic antibiotic therapy for an acute illness within 72 hours prior to investigational product administration.

- If systemic corticosteroids (equivalent of ≥10 mg/day of prednisone) have been administered short term (≤14 days) for treatment of an acute illness, investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Locally administered (eg, intraspinal), inhaled, or topical steroids do not require temporary delay of investigational product administration.

If a subject meets any delay criteria for vaccination as specified above, study procedures, relating to that visit will be delayed until the rescheduled day of vaccination. Blood and swab samples, however, may be collected up to 7 days prior to vaccination.

4.4. Lifestyle Guidelines

All male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active and at risk for pregnancy with their partner(s), must agree to use a highly effective method of contraception consistently and correctly for the duration of the study. The investigator or his/her designee, in consultation with the subject, will determine the most appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet at least 1 of the selected methods of contraception.

The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

- Established use of oral, inserted, injected, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

- Correctly placed copper-containing or progestin-containing intrauterine device (IUD).

- Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

- Male sterilization with absence of sperm in the postvasectomy ejaculate.

- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study reference manual (SRM).

4.5.1. Study Participant/Emergency Contact Card

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. INVESTIGATIONAL PRODUCTS

5.1. Allocation to Investigational Product

All eligible subjects will be randomized to receive a single injection of investigational product (SA4Ag or placebo) at Visit 1 (-60 to -10 days prior to the day of surgery).

Allocation of subjects to vaccine groups will proceed through the use of an interactive voice response system (IVRS) or interactive Web response (IWR) system. The site personnel are required to enter or select information including but not limited to the user name and password, protocol, and subject number. The site personnel will be provided with a vaccine assignment and container number when the investigational product is being supplied via the IVRS/IWR. The IVRS/IWR will provide a confirmation report containing the subject number and container number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IVRS/IWR help desk available for any questions or issues. The study-specific IVRS/IWR reference manual will provide the contact

information and further details on the use of the IVRS/IWR. The IVRS/IWR is the source of the subject number. The IVRS/IWR will provide the subject number at the end of the first IVRS/IWR subject transaction.

5.2. Breaking the Blind

The study will be subject, investigator, and sponsor blinded.

At the initiation of the study, the study site will be instructed on the method for breaking the blind for individual subjects. The method will be either a manual or an electronic process. Blinding codes are only to be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator will consult with a member of the sponsor's study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented in the source notes.

The EAC will receive, review, and adjudicate blinded subject data only.

The data monitoring committee (DMC) will review blinded and unblinded study summary reports. Unblinded study reports will be prepared by an unblinded, independent statistician under the direction of the blinded study statistician. The DMC will also review unblinded study data at the periodic futility checks and at the interim analysis. Details are provided in the DMC charter.

5.3. Investigational Product Supplies

5.3.1. Formulation and Packaging

The investigational products (SA4Ag, placebo, and diluents) will be provided by the sponsor to each study site, packed and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. Investigational product formulations are described below. For more detailed information on the antigenic components of SA4Ag, please refer to the IB.

In the event of a product quality complaint, which is defined as a report regarding a physical, chemical, microbiological, or other alleged defect of a Pfizer Vaccine Research and Development investigational product, the investigator or designee will telephone the responsible person at Pfizer as detailed in the SRM and follow the instructions therein.

5.3.1.1. *Staphylococcus aureus* 4-Antigen Vaccine

SA4Ag comprises capsular polysaccharide serotypes 5 and 8 (CP5 and CP8) individually conjugated to a nontoxic mutant form of diphtheria toxin, cross-reactive material 197 (CRM_{197}) (CP5-CRM_{197} and CP8-CRM_{197}); a recombinant form of clumping factor A (r*m*ClfA), a surface-expressed protein antigen; and rP305A, a recombinant protein derived from an *S aureus* manganese transporter C (MntC).

CCI [redacted]

CCI [redacted] A 0.5-mL dose contains 30 µg each of CP5-CRM$_{197}$ and CP8-CRM$_{197}$, 60 µg of r*m*ClfA, and 200 µg of rP305A. On reconstitution, the SA4Ag solution appears clear, colorless, and free of particulate.

A single intramuscular 0.5-mL dose will be prepared as described in the SRM, and administered into the deltoid muscle of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

5.3.1.2. Placebo

Placebo is a lyophile match to the vaccine, consisting of excipients of SA4Ag formulation minus the active ingredients. CCI [redacted] On reconstitution, the placebo solution appears clear, colorless, and free of particulate.

A single 0.5-mL intramuscular dose will be prepared as described in the SRM, and administered into the deltoid muscle of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

5.3.2. Preparation and Dispensing

See the SRM for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.3. Administration

Subjects will receive 1 dose of SA4Ag or placebo at Visit 1. A single 0.5-mL intramuscular dose will be prepared as described in the SRM, and administered into the deltoid muscle of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction will be available in accordance with local guidelines for standard immunization practices.

Investigational products must be administered by an appropriately qualified, Good Clinical Practice (GCP)-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Investigational product administration details (eg, kit number, date of administration, volume, route, and site of administration) will be recorded in the CRF.

5.3.4. Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigative site.

5.3.5. Investigational Product Storage

The investigational product will be shipped at +2°C to +8°C to each study site after required regulatory and legal documents have been received by the sponsor. Upon receipt at the study site, the investigational product should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage. The refrigerator where the investigational product is stored must be secure and have limited access.

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products, are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the vaccine label.

Storage conditions stated in the SRSD (IB) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions described on the product label, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

5.3.6. Investigational Product Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies (SA4Ag and placebo).

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

5.4. Concomitant Medication(s), Vaccinations, and Blood Products

The following concomitant medications, vaccinations, and blood products will be recorded in the CRF:

- Antibiotics, including all antibiotic use from study enrollment until completion of study participation, start and stop dates, name of antibiotic, dose, route, and frequency.
- Systemic steroids, from study enrollment until completion of study participation, start and stop dates, medication name, dose, units, route, frequency, and indication for use.
- Intraspinal steroids, from 6 months prior to study enrollment until completion of study participation, including medication name and date administered.
- Nonstudy vaccines administered from 6 months prior to study enrollment until completion of study participation, including name of vaccine and date administered.
- Blood products, including number of units and type (eg, whole blood, red blood cells, platelets, clotting factors, cryoprecipitate, white blood cells, immunoglobulins, albumin, and plasma). In addition, whole blood and red blood cells should be identified as heterologous or autologous donations. If a cell saver is used to return the subject's red blood cells during the index surgical procedure, this information will be recorded. All blood product use should be recorded from study vaccination through study completion.

5.4.1. Restrictions to Concomitant Vaccinations and Medications

- Prophylactic use of antipyretic medications at the time of study vaccination will be discouraged.
- Licensed vaccines may be given if, in the opinion of the investigator, they are medically appropriate and necessary (eg, seasonal influenza vaccine; age-appropriate pneumococcal vaccine; tetanus, diphtheria, and acellular pertussis [Tdap] vaccine; or postexposure tetanus vaccine). When possible, concomitant administration of licensed vaccines should be avoided during the periods specified in Section 4.3.
- Where possible, systemic corticosteroid therapy of >14 days (equivalent of ≥10 mg/day prednisone) should not be used during the study. Short-term systemic steroids (≤14 days) and inhaled, topical, or localized injections of corticosteroids are permitted.
- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration or ongoing conditions is permitted, unless otherwise stated.

- The use of medications required for treatment of stable preexisting conditions is permitted, unless otherwise stated.

6. STUDY PROCEDURES

6.1. Scheduled Study Visits

An overview of the study stages, visits, and procedures is presented in the Schedule of Primary Activities in Table 1. An overview of activities for Adverse Event and Study Event Reporting is presented in Table 2.

Before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the subject. Each signature on the ICD must be personally dated by the signatory. A copy of the signed and dated ICD must be given to the subject. The source data must reflect that the informed consent was obtained before commencement of subject participation in the study.

Before randomization, the investigator or a medically qualified designee will review the subject's medical history and medications to ensure that the subject meets all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria.

In the event that the subject's index surgery is not conducted according to the index study procedure definitions (Section 3.2.1), the subject will continue to participate in all study procedures.

The procedures required at each visit are detailed below.

6.2. Stage 1: Vaccination Stage

The vaccination stage of the study covers the period from Visit 1 (day of vaccination) through the period **prior to** admission to hospital for the index surgical procedure. It does not include Visit 2.

6.2.1. Visit 1, Day of Vaccination (Day -60 to Day -10)

- Obtain written informed consent prior to performing any protocol-required procedures.
    - Enter the subject into the IVRS/IWS and obtain a subject number.
    - Record the subject's demography (including date of birth, sex, race, and ethnicity).
    - Record significant medical history including chronic medical conditions, all conditions requiring hospital admission, including the spinal condition precipitating the index surgery, and all previous documented *S aureus* infections, including antibiotic treatments if known.
    - Record previous surgical procedures (excluding outpatient dermatological procedures).

- Record smoking status (smoker, past smoker, never smoked).
- Record alcohol use status (drinker, nondrinker) and number of standard drinks per week.
- Record nonstudy vaccinations received in the previous 6 months and concomitant medications as described in Section 5.4.
- Record height and weight.
- Perform vital sign measurements including blood pressure, pulse rate, respiratory rate, and temperature (°C or °F). When multiple measurements are taken at the same time (eg, blood pressure is measured twice), the most out-of-range (eg, highest or lowest) value must be reported.
- Perform a physical examination noting any clinically significant abnormalities within the following body systems: general appearance; musculoskeletal; skin; head, eyes, ears, nose, and throat; heart; lungs; abdominal; neurological; and lymph nodes.
- Conduct a urinary (or serum) pregnancy test on all women of childbearing potential.
- Discuss contraceptive use and record discussion in source documents.
- Ensure that all inclusion criteria and none of the exclusion criteria are met (Section 4).
- Record the indication for the index surgical procedure, and the planned surgical procedure, including anatomical approach and vertebral levels to be fused. The planned date of surgery is to be recorded in the source documents.
- Determine the Charlson comorbidity score (Section 7.2.2.1).
- If the subject meets the temporary delay criteria, vaccination may be rescheduled, provided that rescheduling will not encroach upon the 10-day minimum window between the day of vaccination and the day of surgery. Surgery may occur on Day 10 after vaccination.
- Collect a blood sample of approximately 24 mL for immunogenicity assessments. This sample must be collected prior to vaccination
- Collect colonization swab samples from the nose and throat.
- After all eligibility criteria are confirmed, the investigator or designee will use the IVRS/IWS to obtain the subject's randomization number and investigational product kit assignment. Refer to the SRM for further instructions and requirements for recording screen failure subjects.

- Issue a subject e-diary, and provide instructions on its completion. After completing e-diary training and setup, ensure that the subject records a baseline assessment in the e-diary **prior to vaccination**. Ask the subject to record systemic events, local reactions, and fever in the e-diary each evening from the day of vaccination for 10 consecutive days.

- Administer a single 0.5-mL intramuscular injection of the assigned investigational product into the deltoid muscle of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

- Observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any events observed within the 30 minutes as immediate AE(s) on the CRF. Capture date and time of vaccination and date and time of onset of the event (if any) in the CRF. Record and report AEs (relative to the time of vaccination) as described in Section 8 and in the Schedule of Activities for Adverse and Study Event Reporting (Table 2).

- Issue a measuring device (caliper) and a digital thermometer and provide instructions on their use.

- Issue a study participant/emergency contact card.

- Instruct the subject to contact the site staff or investigator immediately if he or she experiences fever ≥39.0°C (≥102.1°F), redness or swelling at the injection site measuring greater than 10 cm (≥21 caliper units), or severe pain at the injection site, within 10 days following vaccination, to determine if a severe local reaction or fever assessment visit is required (Section 6.4.1.2).

- Instruct the subject to contact the site staff or investigator immediately if any medically attended illness or hospitalization occurs prior to the index hospital admission.

- Remind the subject to bring the e-diary with them when they are admitted to hospital for their spinal surgery.

- Schedule the next study visit to occur upon commencement of the index hospital admission so that preoperative study procedures required **prior to surgery** are conducted. Instruct the subject to contact the site staff or investigator in the event that their surgery is rescheduled.

- Report study participation and study details to the subject's primary care physician, if applicable.

- Complete the source documents and the investigational product accountability record.

- Complete the CRF.

6.3. Stage 2: Surgery Stage

The surgery stage of the study covers the period from Visit 2 (index hospital admission) to Visit 6 (Day 180 postoperative evaluation).

6.3.1. Visit 2, Index Hospital Admission

6.3.1.1. Day of Surgery (Day 1)

The day of admission may occur prior to or on the day of surgery. In either case, the day of surgery (the day on which the index surgical procedure is performed) is defined as Day 1 of the study.

If the subject is admitted to hospital prior to the day of surgery, the visit procedures may be performed on the day prior to surgery. If the subject is admitted to hospital on the day of surgery and time is limited, the procedures noted below as "**prior to surgery**" must be performed before the surgical procedure. Other requirements (eg, preoperative assessment and concomitant medication review) may be completed in the postoperative recovery period.

- **Prior to surgery**, collect a blood sample of approximately 24 mL for immunogenicity assessments.
- **Prior to surgery**, collect colonization swab samples from the nose and throat.
- **Prior to surgery**, obtain the subject's fasting blood glucose level (eg, glucose meter or serum).
- **Prior to surgery,** collect and review e-diary data and follow up on any ongoing symptoms. If the subject has any ongoing symptoms reported on the last day of e-diary reporting, record the stop date(s).
- **Prior to surgery,** determine whether any AEs or SAEs have occurred or require updating since the last study visit. Record and report AEs as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).
- Record nonstudy vaccinations and concomitant medications as described in Section 5.4.
- Record the information required for the preoperative assessment as shown in Appendix 2.
- Complete the source documents and CRF.

6.3.1.2. Day After Surgery (Day 2)

- Record the actual index surgical procedure. Record excursions from the planned index surgical procedure, taking into account the study protocol inclusion and exclusion criteria.
- Obtain the subject's postoperative blood glucose level (eg, glucose meter or serum).

- Record the information required for the perioperative assessment as shown in Appendix 3.

- Determine whether any AEs or SAEs have occurred since the last subject assessment. Record and report AEs as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).

- Complete the source documents and CRF.

6.3.1.2.1. Daily Monitoring During the Index Hospitalization

- Following surgery, on each day of hospitalization through the day of discharge, the following assessments will be conducted:

    - Determine whether any AEs or SAEs have occurred or require updating since the last review. Record and report AEs as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).

    - Determine whether the subject has a suspected PDI; if so, record and report the PDI event as described in Section 7.1.1, and

    - If the suspected PDI represents BSI and/or SSI, perform the procedures required for a BSI/SSI assessment visit described in Section 6.4.2.

    - If the suspected PDI does not represent a BSI and/or SSI, the BSI/SSI assessment visit procedures are not required.

- Determine whether the subject meets the protocol-defined criteria for organ failure (eg, via review of medical and nursing records, clinical findings, and laboratory results) as described in Section 7.2.3. When a subject is identified as having organ dysfunction:

    - Record a daily Sequential Organ Failure Assessment (SOFA) score on the SOFA worksheet, as described in Section 7.2.3, until the event is resolved (normal or baseline), or for the duration of the hospitalization if not resolved.

    - When a SOFA score of ≥3 is recorded for any single organ, record the SOFA score in the CRF on a daily basis until the failing organ system(s) returns to normal/baseline or stabilizes.

    - Record the OF events (SOFA ≥3) as AEs/SAEs as appropriate. SOFA Scores <3 should be assessed to determine if AE reporting is required as per Section 8.

    - If the subject develops MOF, ie, OF in 2 or more body systems concurrently, collect a 24-mL blood sample for immunogenicity.

    - Complete a MOF event report and submit the event for adjudication as detailed in the SRM.

6.3.1.3. Day of Hospital Discharge (Day Variable)

If discharge is scheduled for a weekend/holiday, visit procedures may be conducted within 3 days prior to discharge.

If discharge procedures are conducted and the subject's discharge is subsequently postponed by more than 3 days, blood and swab samples must be re-collected.

- If the day of hospital discharge coincides with the timing of the day after surgery (Day 2), the Day 21 telephone contact, or the Day 42 or Day 90 postoperative evaluation, coincident study procedures (eg, collection of the 24-mL blood sample for immunogenicity, colonization swabs) may be combined as a single visit.
- Record nonstudy vaccinations and concomitant medications as described in Section 5.4.
- Collect and process a blood sample of approximately 24 mL for immunogenicity assessments.
- Collect colonization swab samples from the nose and throat.
- Determine whether any AEs or SAEs have occurred or require updating since the last subject assessment. Record and report AEs as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).
- Review the subject's medical record for any new or additional perioperative information described in Appendix 3.
- Record the information (where applicable) contained in the healthcare-utilization assessment described in Appendix 4.
- Remind the subject to contact the investigator immediately if he or she develops signs and symptoms of postoperative infection (eg, fever, chills, increased pain, redness, swelling, or discharge at the wound) or is hospitalized or treated with antibiotic therapy.
- Schedule the next study appointment within the allowed visit window.
- Complete the source documents and CRF.

6.3.2. Visit 3, Day 21 Telephone Contact (Window: Days 18-26)

- Record nonstudy vaccinations and concomitant medications as described in Section 5.4.
- Determine whether any AEs or SAEs have occurred or require updating since the last subject assessment. Record and report AEs as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).
- Determine whether the subject has or has had a suspected PDI; if so, record and report the PDI event as described in Section 7.1.1, and

- If the suspected PDI represents BSI and/or SSI, arrange an unscheduled visit and perform the procedures required for a BSI/SSI assessment visit described in Section 7.1.1.1.
    - If the suspected PDI does not represent a BSI and/or SSI the BSI/SSI assessment visit procedures are not required.
- Record the number of visits to a physical or rehabilitation specialist or days in a skilled nursing home or rehabilitation hospital (Appendix 4).
- Remind the subject to contact the investigator immediately if he or she develops signs and symptoms of postoperative infection (eg, fever, chills, increased pain, redness, swelling, or discharge at the wound) or is hospitalized or treated with antibiotic therapy.
- Complete the source documents and CRF.

6.3.3. Visit 4, Day 42 Postoperative Evaluation (Window: Days 35-49)

- Record nonstudy vaccinations and concomitant medications as described in Section 5.4.
- Collect and process a blood sample of approximately 24 mL for immunogenicity assessments.
- Collect colonization swab samples from the nose and throat.
- Determine whether any AEs or SAEs have occurred or require updating since the last subject assessment. Record and report any events as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).
- Determine whether the subject has or has had a suspected PDI; if so, record and report the PDI event as described in Section 7.1.1, and
    - If the suspected PDI represents BSI and/or SSI, perform the procedures required for a BSI/SSI assessment visit described in Section 6.4.2.
    - If the suspected PDI does not represent a BSI and/or SSI the BSI/SSI assessment visit procedures are not required.
- Perform a healthcare-utilization assessment as specified in Appendix 4.
- Remind the subject to contact the investigator immediately if he or she develops signs and symptoms of postoperative infection (eg, fever, chills, increased pain, redness, swelling, or discharge at the wound) or is hospitalized or treated with antibiotic therapy.
- Schedule the next study appointment within the allowed time window.
- Complete the source documents and CRF.

6.3.4. Visit 5, Day 90 Postoperative Evaluation (Window: Days 83-97)

- Record nonstudy vaccinations and concomitant medications as described in Section 5.4.
- Collect and process a blood sample of approximately 24 mL for immunogenicity assessments.
- Collect colonization swab samples from the nose and throat.
- Determine whether any SAEs or newly diagnosed chronic medical disorders have occurred since the last subject assessment. Record and report any events as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).
- Determine whether the subject has or has had a suspected PDI; if so, record and report the PDI event as described in Section 7.1.1, and
    - If the suspected PDI represents BSI and/or SSI, perform the procedures required for a BSI/SSI assessment visit described in Section 6.4.2.
    - If the suspected PDI does not represent a BSI and/or SSI, the BSI/SSI assessment visit procedures are not required.
- Perform a healthcare-utilization assessment as specified in Appendix 4.
- Remind the subject to contact the investigator immediately if he or she develops signs and symptoms of postoperative infection (eg, fever, chills, increased pain, redness, swelling, or discharge at the wound) or is hospitalized or treated with antibiotic therapy.
- Schedule the next study appointment within the allowed time window.
- Complete the source documents and CRF.

6.3.5. Visit 6, Day 180 Postoperative Evaluation (Window: Days 178-192)

The Day 180 postoperative evaluation visit may be conducted at the study site or may be conducted via telephone interview, with collection of blood and colonization samples by a home nursing visit or by other arrangement. If it is suspected that the subject has a BSI/SSI, a site visit will be required.

- Record nonstudy vaccinations and concomitant medications as described in Section 5.4.
- Collect and process a blood sample of approximately 24 mL for immunogenicity assessments.
- Collect colonization swab samples from the nose and throat.

- Determine whether any SAEs or newly diagnosed chronic medical disorders have occurred since the last subject assessment. Record and report any events as described in Section 8 and the Schedule of Activities for Adverse and Study Event Reporting (Table 2).

- Determine whether the subject has or has had a suspected PDI; if so, record and report the PDI event as described in Section 7.1.1, and

  - If the suspected PDI represents BSI and/or SSI, perform the procedures required for a BSI/SSI assessment visit described in Section 6.4.2.

  - If the suspected PDI does not represent a BSI and/or SSI the BSI/SSI assessment visit procedures are not required.

- Perform a healthcare-utilization assessment as specified in Appendix 4.

- Complete the source documents and CRF.

6.4. Unscheduled Study Visits

A list of unscheduled visits which are to occur when certain conditions are met is presented in Table 3. A list of procedures for these visits is presented in Table 4.

6.4.1. Assessment of Postvaccination Severe Reactions and Systemic Events

6.4.1.1. Unscheduled Telephone Contacts

6.4.1.1.1. Severe Local Reaction or Fever Telephone Contact (Up to 10 Days After Study Vaccination)

If a severe local reaction (redness, swelling, or pain [at the injection site]) or fever ≥39.0°C (≥102.1°F) is reported in the e-diary within 10 days of study vaccination, a telephone contact between the subject and the investigator will be conducted as soon as possible to assess whether a severe local reaction or fever assessment visit is required. In the event the subject does not call the investigator, the investigator will call the subject.

A severe local reaction or fever assessment visit (Section 6.4.1.2) will be scheduled as soon as possible to assess the extent of the reaction, unless:

- The reaction is no longer present at the time of the telephone contact, or

- The investigator confirms that the data were entered into the e-diary in error, or

- The subject is unable to attend the severe local reaction or fever assessment visit. In this event, reactions (if still present) will be assessed at the next scheduled visit; findings will be documented in the source notes.

This telephone contact will be recorded in the source documents and CRF.

6.4.1.1.2. Severe Systemic Event Telephone Contact (Up to 10 Days After Study Vaccination)

If a severe systemic event (fatigue, headache, muscle pain, and joint pain) is reported in the e-diary within 10 days of study vaccination, the investigator must contact the subject by phone as soon as possible to determine whether the systemic event meets Grade 4 and/or SAE reporting criteria (refer to Section 7.2.1.4 and Section 8.6).

This telephone contact will be recorded in the source documents.

6.4.1.2. Severe Local Reaction or Fever Assessment Visit (Up to 10 Days After Study Vaccination)

At the severe local reaction or fever assessment visit, the following procedures will be conducted by the investigator or medically qualified member of the study staff. For the purpose of severe reaction assessment, a medically qualified member of the study staff is a study physician, physician assistant, or study nurse, as applicable to the investigator's local practice.

- Measure the subject's temperature (°C or °F).
- Measure the minimum and maximum diameter of redness at the site of vaccination.
- Measure the minimum and maximum diameter of swelling at the site of vaccination.
- Assess the subject's pain in accordance with the grades provided in Section 7.2.1.3.
- Assess the subject for lymphadenopathy associated with the reaction.
- Complete the source documents and CRF.

6.4.2. BSI/SSI Assessment Visit

At any time after surgery until completion of study participation, when a subject is suspected of having a BSI and/or SSI, a BSI/SSI assessment visit will be conducted.

If the BSI/SSI assessment visit occurs during the index study admission, or is coincident with the Day 21 telephone contact or the Day 42, Day 90, or Day 180 postoperative assessment visit, the BSI/SSI assessment visit study procedures common to both visits may be combined.

The following procedures will be conducted:

- Complete a PDI event report for BSI and /or SSI, as appropriate for the PDI(s), as described in Section 7.1.1.
- Collect and process a blood sample of approximately 24 mL for immunogenicity assessments.
- Collect colonization swab samples from the nose and throat.

- Collect blood culture sample(s) for any suspected BSI or deep incisional or organ/space SSI and, when clinically indicated, for a superficial SSI.

- For an SSI that is operatively incised and/or spontaneously draining, collect a wound culture swab as per local clinical laboratory guidance. Where possible, tissue and fluid samples are to be taken prior to commencing administration of antibiotics.

- Record antibiotic therapy as concomitant medication(s) as described in Section 5.4.

- Determine whether any AEs or SAEs have occurred or require updating since the last subject assessment. Record and report AEs as described in Section 8 and according to the Schedule of Activities for Adverse and Study Event Reporting (Table 2).

- Complete the source documents and CRF.

In the event that a subject is identified as having a suspected BSI and/or SSI and it is not possible to complete the BSI/SSI assessment visit (eg, in the event that the investigator is made aware of an infection that has already been treated to resolution by medical personnel external to the study team, and where there are no active signs or symptoms of infection), a PDI event report will be completed regardless.

6.4.3. Hospitalization Visit

Hospitalization(s) subsequent to the index hospital admission will be evaluated as hospitalization visit(s).

A hospitalization visit will be required for any admission (including short-stay [<24 hours] admissions) to a hospital or equivalent healthcare facility that occurs subsequent to discharge from the index hospital.

On admission to hospital, the investigator will assess whether the indication for hospitalization represents a postoperative complication of the index surgical procedure (eg, postoperative infection, increased pain at the surgical site, loose or broken hardware) or is coincidental to the index surgical procedure.

On each day of hospitalization, the investigator will assess:

- Whether the subject has or has had a suspected PDI; if so, record and report the PDI event as described in Section 7.1.1, and

    - If the suspected PDI represents BSI and/or SSI, perform the procedures required for a BSI/SSI assessment visit described in Section 6.4.2.

    - If the suspected PDI does not represent a BSI and/or SSI, the BSI/SSI assessment visit procedures are not required.

- Whether the subject meets the protocol-defined criteria for organ failure as described in Section 7.2.3. When a subject is identified as having organ dysfunction:
  - Record daily SOFA scores on the SOFA worksheet, as described Section 7.2.3, until the event is resolved (normal or baseline) or until hospital discharge if the event remains unresolved.
  - When a SOFA score of ≥3 is recorded for any single organ, record the SOFA score in the CRF on a daily basis until the failing organ system(s) returns to normal/baseline or stabilizes.
  - Record the OF events (SOFA ≥3) as AEs/SAEs as appropriate. SOFA Scores <3 should be assessed to determine if AE reporting is required as per Section 8.
  - If the subject develops MOF, ie, OF in 2 or more systems concurrently, collect a 24-mL blood sample for immunogenicity.
  - Complete a MOF event report and submit the event for adjudication as detailed in the SRM.
- If the index surgical procedure requires subsequent spine surgery reoperation and revision (eg, for loose hardware, debridement, decompression, dural tear repair), record the details of the subsequent surgery as listed in the perioperative assessment shown in Appendix 3. If, during a reoperation and revision of the index surgery, hardware or tissue is removed, the hardware and/or tissue should be cultured.
- Determine whether any AEs or SAEs have occurred or require updating since the last subject assessment. Record and report AEs as described in Section 8 and according to the Schedule of Activities for Adverse and Study Event Reporting (Table 2).
- Record antibiotic therapy as concomitant medication(s) as described in Section 5.4.
- At hospital discharge, perform a healthcare-utilization assessment as specified in Appendix 4.
- Complete the source documents and CRF.

6.5. Subject Withdrawal and Safety Follow-up

6.5.1. Subject Withdrawal From the Study

Subjects will be withdrawn from the study under the following circumstances:

- If the subject was enrolled but did not receive the investigational product (SA4Ag or placebo).
- At any time at their own request.

- At the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. Details for contacting lost-to-follow-up subjects are provided in the SRM. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.5.2. Safety Follow-up

Any vaccinated subject who undergoes the index surgical procedure and who withdraws from the study, and provided the subject is agreeable, will receive safety follow-up as follows:

- AEs will be monitored until the Day 42 postoperative evaluation.
- SAEs will be monitored for at least 6 months after vaccination.

Any vaccinated subject who **does not** undergo the index surgical procedure within 6 months after vaccination or any vaccinated subject who withdraws from the study prior to the index surgical procedure, and provided the subject is agreeable, will receive safety follow-up as follows:

- AEs will be monitored for at least 28 days after vaccination.
- SAEs will be monitored for at least 6 months after vaccination.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy Assessments

7.1.1. PDI Events

All subjects who undergo the index surgical procedure will be monitored for PDIs after surgery until the Day 180 postoperative evaluation.

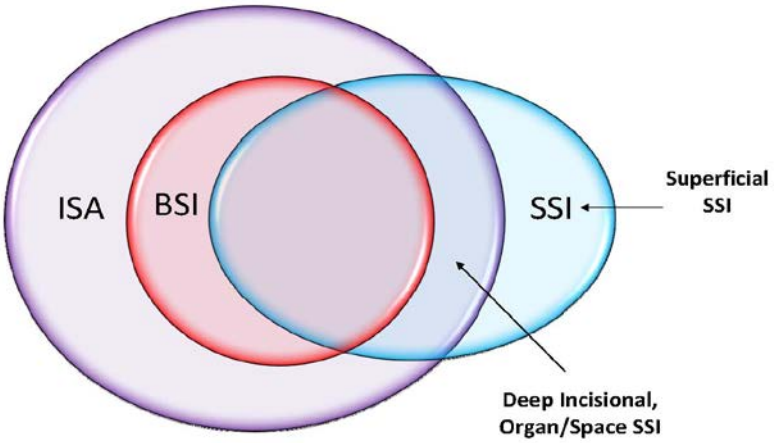
The investigator will review all suspected PDIs against the clinical criteria provided in Appendix 1. Where the clinical criteria are met, the following procedures will be conducted:

- Notify the sponsor that a PDI event has occurred.
- Complete the requirements for a BSI/SSI event (Section 6.4.2) or an ISA event (Section 7.1.1.2).
- Report the PDI event in the CRF.

If an infection occurs after discharge from the index hospital, and the infection is managed or treated by a noninvestigator physician or at a nonstudy hospital, the study investigator will contact the treating noninvestigator physician/hospital to obtain the information required (eg, medical or hospital records, clinical, diagnostic, and microbiological data) to determine whether the infection meets PDI clinical criteria. If the clinical criteria are met, the investigator will complete the PDI event report noted above and notify the sponsor.

For the purposes of this study, PDIs will include all the infections listed in Table 6 and Table 7. As shown in Figure 1, the relationships between ISA, BSI, and SSI overlap, insofar as all BSI and SSI, with the exception of superficial SSI, are considered to be ISA disease.

Figure 1. Protocol-Defined Infections (Venn Diagram)



7.1.1.1. BSI and SSI Events

All BSI and SSI listed in Table 6 require an unscheduled BSI/SSI assessment visit (Section 6.4.2).

Specific to spinal fusion surgery, **osteomyelitis**, **vertebral disc space infection**, **meningitis,** and **spinal abscess without meningitis,** when directly attributable to posterior midline or posterolateral surgical incisions, will be reported as organ/space SSIs. Likewise, **intra-abdominal infection,** when directly attributable to an intra-abdominal incision, and **joint and bursa infection,** when directly attributable to a surgical incision (eg, harvesting autologous bone), will be reported as organ/space SSIs.

The EAC will confirm that the clinical and microbiological criteria shown in Appendix 1 have been met before events are acknowledged as confirmed *S aureus* BSI or SSI cases. Microbiologically confirmed *S aureus* BSI and SSI cases will contribute to the study endpoints.

Table 6. BSI and SSI Events Requiring an Unscheduled Assessment Visit

Bloodstream infection
Superficial SSI
Deep incisional SSI
Organ/space SSI Osteomyelitis[a] Vertebral disc space infection[a] Meningitis[a] Spinal abscess without meningitis[a] Intra-abdominal infection[a] Joint or bursa infection[a]

Abbreviations: BSI = bloodstream infection; SSI = surgical-site infection.

a. Report as organ/space SSI when the infection involves tissue that was opened or manipulated during the index surgical procedure.

7.1.1.2. ISA Events

The PDIs listed in Table 7 do not require an unscheduled assessment visit. However, the investigator will review the clinical and microbiological data listed in Appendix 1 specific for the suspected PDI.

Osteomyelitis, vertebral disc space infections, spinal abscess without meningitis, meningitis, intra-abdominal infections, and joint or bursa infections, will be evaluated as potential ISA events when they do not fulfill the requirements for an organ/space SSI described in Section 7.1.1.1.

All PDIs will be reported for adjudication by the EAC. Designation of an ISA event as "confirmed" is the responsibility of the EAC, based upon defined criteria listed in Appendix 1.

For ISA events, the documentation to support elements of respective PDI criteria as specified in respective PDI definitions in Appendix 1 will be provided for adjudication.

All PDIs in Table 7 should be reported as an AE/SAE irrespective of whether or not the infectious pathogen is shown to be *S aureus* (eg, meningococcal meningitis, *Pseudomonas* pneumonia, *Streptococcus viridans* endocarditis).

Table 7. PDIs Contributing to ISA Disease (in Addition to BSI and Deep Incisional and/or Organ/Space SSI)

Osteomyelitis	Spinal abscess without meningitis
Joint or bursa infection	Pneumonia
Periprosthetic infection	Intra-abdominal infection
Vertebral disc space infection	Endocarditis
Meningitis	

Abbreviations: BSI = bloodstream infection; ISA= invasive *Staphylococcus aureus*; PDI = protocol-defined infection; *S aureus* = *Staphylococcus aureus*; SSI = surgical-site infection.

When osteomyelitis, vertebral disc space infections, spinal abscess without meningitis, meningitis, intra-abdominal infections, and joint or bursa infections **do not** involve tissue that was opened or manipulated during the index surgical procedures (and therefore are organ/space SSI as per Table 6), but are positive for *S aureus*, they are reported as ISA disease using the verbatim term.

When a subject with an *S aureus* BSI develops any of the ISA events shown in this table, the BSI will contribute to the primary or secondary endpoint.

In the event that a subject develops any other invasive infection such as those listed in Table 8 the clinical criteria for the infection should be reviewed against the NHSN criteria provided in the SRM.

All other invasive infections will be reported for adjudication by the EAC. Evidential clinical and microbiological data are to be provided to support the adjudication process.

Table 8. Other Invasive Infections

Intracranial infections (brain abscess, subdural or epidural infection, encephalitis)	Mediastinitis
Myocarditis	Mastoiditis
Pericarditis	Ventilator-acquired pneumonia
Nondefined,[a] eg, necrotizing fasciitis	

a. The nondefined infection category includes any invasive infection that is not defined in Appendix 1 or the study reference manual. For any invasive infection reported under this category, the adjudication criteria and required supportive data will be provided by the event adjudication committee.
- Contact the medical monitor for guidance when reporting under this category.
- Deep SSI unrelated to the index surgery are reported to the EAC and assessed using the NHSN criteria.

7.2. Safety Assessments

Safety parameters will be assessed as described in the Schedule of Primary Activities (Table 1) and below. Any subject who receives the investigational product will be included in the evaluation for safety.

A medical history, physical examination, and measurement of vital signs will be performed on all subjects prior to vaccination to determine subject eligibility and to establish a clinical baseline. Significant medical and surgical history and observations from the physical examination and vital sign measurement will be documented and recorded in the CRF.

The postvaccination safety parameters include assessments of local reactions and systemic events occurring within 10 days following investigational product administration. They will be graded as described in Section 7.2.1.3 and Section 7.2.1.4.

Reactions occurring within 30 minutes after investigational product administration will be documented and recorded in the AE CRF.

AEs, SAEs, and newly diagnosed chronic medical disorders will be collected as described in Table 2 and reported as described in Section 8.14. A newly diagnosed chronic medical disorder is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

7.2.1. Local Reactions and Systemic Events

7.2.1.1. Electronic Diary

The subject will be issued an e-diary, based on a personal digital assistant (PDA) or equivalent technology. Prior to vaccination, a baseline assessment (fatigue, headache, muscle pain, or joint pain over the previous month) will be recorded in the e-diary. Starting on the day of vaccination, the subject will monitor and record local reactions, systemic events, and any antipyretics or pain medication used to treat symptoms, for 10 days.* The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, systemic events, and antipyretics/pain medication used to treat symptoms reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators via an Internet-based portal. At intervals agreed to by the vendor and Pfizer, the data will be transferred electronically into Pfizer's event database for analysis and reporting.

Investigators (or appropriately qualified designee) are required to review the daily e-diary data online at frequent intervals during active vaccination periods, as part of the ongoing safety review.

The investigator or designee will obtain from the subject stop dates for any symptoms ongoing on the last day that the e-diary was completed. The stop dates will be documented in the source documents and the information entered in the CRF.

*In the event that surgery occurs on the 10th day after vaccination, the e-diary data for Day 10 does not need to be completed.

7.2.1.2. Grading Scales for Local Reactions and Systemic Events

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[54]

7.2.1.3. Local Reactions

For 10 consecutive days starting on the day of vaccination, subjects will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary. Redness and swelling will be measured and recorded in caliper units (range: 1 to 21+), and then categorized as mild, moderate, or severe based on the grading scale in Table 9. Caliper units can be converted to centimeters according to the following formula:
1 caliper unit = 0.5 cm.

Pain at the injection site will be assessed by the subject as mild, moderate, or severe according the grading scale in Table 9. A subject with a severe/Grade 3 local reaction will be instructed to contact the investigator to assess the reaction and perform a severe local reaction or fever assessment visit as appropriate. In the event that the subject does not call, the investigator will call the subject.

7.2.1.3.1. Management of Grade 4 Local Reactions

Only an investigator is able to classify a subject's local reaction as Grade 4, after physical examination of the subject or telephone contact with the subject. Confirmed Grade 4 local reactions require immediate notification to the sponsor and include:

- Skin necrosis or exfoliative dermatitis (for redness) or skin necrosis (for swelling):

  Consider whether the reaction is an important medical event (Section 8.6). If yes, report the reaction as an SAE; if no, report it as an AE. Grade the severity of the necrosis or exfoliative dermatitis using the AE severity grading scale in Section 8.8.

- An emergency room visit for management of pain at the injection site:

  Consider whether the reaction is an important medical event (Section 8.6). If yes, report the reaction as an SAE; if no, report it as an AE. Grade the severity of the injection site pain using the AE severity grading scale in Section 8.8.

- Hospitalization for management of pain at the injection site:

  Report the hospitalization for injection site pain management as an SAE and grade the severity of the injection site pain using the AE severity grading scale in Section 8.8.

Table 9. Local Reaction Grading Scale

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Redness	5 to 10 caliper units (or measuring device units) 2.5 to 5.0 cm	11 to 20 caliper units (or measuring device units) 5.5 to 10.0 cm	≥21 caliper units (or measuring device units) ≥10.5 cm	Necrosis or exfoliative dermatitis[b]
Swelling	5 to 10 caliper units (or measuring device units) 2.5 to 5.0 cm	11 to 20 caliper units (or measuring device units) 5.5 to 10.0 cm	≥21 caliper units (or measuring device units) ≥10.5 cm	Necrosis[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization

Abbreviations: AE = adverse event; CRF = case report form; e-diary = electronic diary.

a. Subjects experiencing local reactions ≥21 caliper units (≥10.5 cm) or severe pain at the injection site will telephone the study site. In the event that the subject does not call, the investigator will call the subject.
b. Grade 4 assessment should be made by the investigator and recorded as an AE on the CRF. Manage as shown in Section 7.2.1.3.1 and Section 8.8.

If the size of the redness and/or swelling falls between 2 caliper units, the higher caliper unit number will be recorded in the e-diary.

7.2.1.4. Systemic Events

Prior to vaccination, subjects will consider whether they generally experience fatigue, headache, muscle pain, or joint pain. If so, the symptoms will be graded as mild, moderate, or severe and recorded in the e-diary as baseline symptoms. The Systemic Event Grading Scale in Table 10 will be used.

Starting on the day of vaccination, and for 10 consecutive days, postvaccination systemic events will be assessed by the subject each day, and if present, they will be graded as mild, moderate, or severe and recorded in the e-diary, using the grading scale in Table 10.

A subject with a severe/Grade 3 systemic event will be instructed to contact the investigator who will assess the reaction. In the event that the subject does not call, the investigator will call the subject.

7.2.1.4.1. Management of Grade 4 Systemic Events

Only an investigator is able to classify a subject's systemic event as Grade 4, after physical examination of the subject or telephone contact with the subject. Confirmed Grade 4 systemic events require immediate notification to the sponsor and include:

- An emergency room visit for management of a systemic event:

  Consider whether the systemic event is an important medical event (Section 8.6). If yes, report the event as an SAE; if no, report it as an AE. Grade the severity of the systemic event using the AE severity grading scale in Section 8.8.

- Hospitalization for management of a systemic event:

Report hospitalizations for management of a systemic event as an SAE and grade the severity of the systemic event according to the AE severity grading scale in Section 8.8.

Table 10. Systemic Event Grading Scale

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Fatigue (Tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization

Abbreviations: AE = adverse event; CRF = case report form.

a. Subjects experiencing severe systemic events will telephone the study site. In the event that the subject does not call, the investigator will call the subject.

b. Grade 4 assessment should be made by the investigator and recorded as an AE on the CRF. Manage as shown in Section 7.2.1.4.1 and Section 8.8.

7.2.1.5. Fever

To record fever, a digital thermometer will be given to the subject with instructions on how to measure his or her oral temperature. Starting on the day of vaccination, temperature will be measured each evening for 10 consecutive days and at any time during the 10 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary. In the event of a fever, temperature will be collected daily until fever has resolved (1 day with a temperature less than 38.0°C [100.4°F]). Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 11.

Where a fever ≥39.0°C (≥102.1°F) is recorded, the subject will contact the investigator by telephone and the investigator will assess whether a severe local reaction or fever assessment visit is required (refer to Section 6.4.1.1.1). If the subject does not call the investigator, the investigator will contact the subject.

Table 11. Scale for Fever

38.0 to 38.4°C (100.4 to 101.1°F)
38.5 to 38.9°C (101.2 to 102.0°F)
39.0 to 40.0°C (102.1 to 104.0°F)
>40.0°C (>104.0°F)

7.2.2. Preoperative and Perioperative Subject Status Assessments

7.2.2.1. Charlson Comorbidity Index

The Charlson comorbidity index (CCI) is 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.[55] On completion of the physical examination at Visit 1, the investigator or designee will record the presence of each comorbid condition and age cohort as presented in Table 12 in the CRF.

The sum of the values for each comorbid condition is added to the subject's value for age to obtain the CCI. Both the CCI and the Charlson probability (10-year survival) will be derived programmatically.

CCI = sum of comorbid conditions + value for age (on the date of assessment)

Table 12. Charlson Comorbidity Score

Comorbid Condition	Score	Age Cohort and Value for Age (on the Date of Assessment)
History of prior myocardial infarction (not ECG changes only)	1	Age ≤40 years: 0 points
Congestive heart failure	1	Age 41-50 years: 1 point
Peripheral vascular disease	1	Age 51-60 years: 2 points
Cerebrovascular disease	1	Age 61-70 years: 3 points
Dementia	1	Age 71-80 years: 4 points
Diabetes	1	Age 81-90 years: 5 points
Mild liver disease	1	
Chronic pulmonary disease	1	
Gastric/duodenal ulcer	1	
Connective tissue disease	1	
Hemiplegia	2	
Moderate or severe renal disease	2	
Diabetes with end-organ damage	2	
Tumor	2	
Leukemia	2	
Lymphoma	2	
Moderate or severe liver disease	3	
Metastatic solid tumor	6	
AIDS	6	

Abbreviations: AIDS = acquired immunodeficiency syndrome; ECG = electrocardiographic.

7.2.2.2. American Society of Anesthesiologists (ASA) Physical Status Classification Score

The American Society of Anesthesiologists (ASA) physical status classification system is utilized by anesthesiologists to assess the fitness of surgical patients prior to undergoing surgery. ASA scores correlate with patient morbidity and postoperative infection risk.[56] At Visit 2 and prior to surgery, the subject's physical status will be assessed and classified by the anesthesiologist using the ASA score shown in Table 13.

Table 13. American Society of Anesthesiologists (ASA) Physical Status Classification

Score	Description
1	Healthy patient
2	Mild systemic disease with no functional limitation
3	Severe systemic disease with definite functional limitation
4	Severe systemic disease that is a constant threat to life
5	Moribund patient unlikely to survive 24 hours with or without operation

Adapted from American Society of Anesthesiologists. ASA physical status classification system. Available: http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System. 18 Jun 2014.

7.2.3. Assessment of Organ Failure

All subjects who undergo the index surgical procedure will be monitored for OF events across the following time periods:

- during the index hospital admission from after surgery until discharge
- during any subsequent hospitalization(s) that occur over the course of the study including, where possible, those that occur at any outside hospital

As OF is sequential and progressive, subject monitoring will occur on a daily basis while the subject is hospitalized. There is no protocol requirement to perform the procedures required to calculate a daily SOFA score; rather, the investigator will review the subject's clinical care records (eg, laboratory results, nursing and medical progress notes) to determine whether or not the subject meets the criteria for an OF event. If the data required to score an organ are not available on the day of assessment, by default the score for that variable will be zero (0).

A clinical diagnosis of organ failure will be established for each of the 6 organ systems-respiratory, cardiovascular, renal, hematological, neurological, and hepatic—on the basis of SOFA scores[57] (Table 14). OF is defined as a SOFA score ≥3 in any 1 organ system, while MOF is defined as OF in 2 or more organ systems simultaneously.

If the subject develops organ system dysfunction, daily SOFA scores are recorded on the SOFA worksheet until organ function returns to normal/baseline or until hospital discharge if the event remains unresolved.

When a SOFA score of ≥3 (OF) is recorded for any single organ, SOFA scores will be entered into the CRF on a daily basis until the failing organ system(s) returns to normal/baseline or stabilizes.

Organ dysfunction and OF events will be reported as AEs or SAEs as appropriate.

All MOF events will be adjudicated by the EAC to determine whether the protocol-defined clinical criteria have been met, whether confirmed events are PDI related or due to noninfectious causes, and whether the PDI-related events are attributable to

microbiologically confirmed *S aureus*, attributable to other organism(s), or without microbiological confirmation.

Additional guidance for obtaining and reporting the SOFA scores and reporting MOF is provided in the SRM.

Table 14. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiratory PaO_2/FiO_2, mm Hg ***or*** SpO_2/FiO_2, mm Hg[a]	>400 >400	≤400 ≤400	≤300 ≤315	≤200[b] ≤230	≤100[b] ≤150
Coagulation Platelets x $10^3/\mu L$	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)[c]	Dop >5, epi ≤0.1, or norepi ≤0.1 or phenylephrine ≤0.1[c]; or vasopressin <0.04 U/min	Dop >15 epi >0.1, or norepi >0.1 or phenylephrine >0.1[c]; or vasopressin ≥0.04 U/min
Central nervous system Glasgow Coma Scale (GCS) score[d]	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5 or <200[e]

Abbreviations: dob = dobutamine; Dop = dopamine; epi = epinephrine; FiO_2 = fraction of inspired oxygen; norepi = norepinephrine; PaO_2 = partial pressure of oxygen in arterial blood; SOFA = Sequential Organ Failure Assessment; SpO_2 = saturation of peripheral oxygen.

a. The preferred measurement for the assessment of respiratory failure is the partial pressure of oxygen in arterial blood (PaO_2) from arterial blood gas data. If that is unavailable, respiratory failure may also be evaluated using a modified respiratory SOFA score based on saturation of peripheral oxygen (SpO_2) and available FiO_2 measurements (eg, face mask, bilevel positive airway pressure, continuous positive airway pressure).[58] If the direct FiO_2 measurement is not available (eg, nasal cannula), a respiratory score should not be calculated.
b. Values are with respiratory support.
c. Adrenergic agents administered for at least 1 hour (doses given are in µg/kg per minute).
d. In patients receiving sedation or muscle relaxants, normal brain function will be assumed for neurological assessment unless there is evidence of altered mentation.
e. Or patient is receiving intermittent hemodialysis, peritoneal dialysis, or continuous renal replacement therapy.

7.2.3.1. Assessment of Deaths

Any deaths that occur during the study will be assessed by the EAC for potential relationship to a PDI and/or association with *S aureus*. The DMC will also review deaths during scheduled safety data review meetings, or on an ad hoc basis if required, in accordance with the DMC charter.

Any death that occurs from the day of informed consent to 180 days after surgery will be reported in the CRF and to the sponsor. Any death that occurs from the date of informed consent will be reported as an SAE.

7.2.4. Pregnancy Testing

For female subjects of childbearing potential, a urine or serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of the vaccine/placebo. A negative pregnancy test result is required before the subject may receive the investigational product. After randomization and vaccination, if the subject becomes pregnant during the study, the subject may continue to participate in the study as it remains appropriate to follow a subject who becomes pregnant for the development of postoperative PDI and fetal outcome. Pregnancy tests may be repeated at the request of IRBs/independent ethics committees (IECs) or if required by local regulations.

7.3. Microbiology Assessments

7.3.1. Microbiological Laboratory Procedures

All samples for microbial culture from suspected infections, regardless of the source of the culture material, will be sent to the local microbiology laboratory for isolation of any organisms. Samples for microbiological cultures will be collected as outlined in the study procedure and reference manual. Each pathogen isolated should be identified to the genus and species level, if possible. *S aureus* strains will be tested for methicillin sensitivity.

At the investigational site laboratory, study site personnel are responsible for obtaining all *S aureus* isolates and sending them to the central laboratory for processing and shipment of samples to the sponsor.

If the investigational site laboratory subcontracts with an outside laboratory, study site personnel are responsible for obtaining all *S aureus* isolates from the outside laboratory and sending them to the central laboratory for processing and shipment of samples to the sponsor.

The local or outside microbiology laboratory is expected to retain a duplicate of each isolate (eg, stored at -70°C) until the isolate has been received, tested, and reported by the central laboratory.

The central laboratory will coordinate and provide each study site with shipping supplies and detailed instructions for the shipment and storage of all microbiological isolates. In addition to species verification, *S aureus* cultures may be further evaluated for genotypic and possibly phenotypic markers by the central laboratory.

Sample collection, storage, and shipping information can be found in the laboratory manual.

7.3.2. Blood Cultures

For all suspected BSI, deep incisional SSI, and organ/space SSI, and where clinically indicated for superficial SSI, 2 sets of blood cultures should be obtained and timed according to the local institution's policy using different sampling sites. Anaerobic and aerobic samples should be collected. The timing of the repeat culture(s) is at the discretion of the investigator. Whenever possible, blood should be collected from peripheral veins; blood drawn through an intravascular catheter will be specifically identified as such in the CRF. *S aureus* isolates will be processed as described above.

7.3.3. Operative (Surgical Site) Wound Cultures

Throughout the subject's participation, bacterial cultures will be obtained at any point during the study if the subject undergoes any drainage procedure. Aerobic and anaerobic cultures will be taken from the site of suspected infection during surgical procedures.

7.3.4. Swabs for Colonization

Oropharyngeal and nasal swabs for *S aureus* colonization will be collected from all subjects prior to study vaccination, as specified at each postvaccination visit, and at each BSI/SSI assessment visit. Colonization swabs will be sent to a central laboratory for processing and culture. *S aureus* isolates may be further evaluated by the sponsor or central laboratory for genotypic and phenotypic markers. Colonization by other staphylococcal species isolated from the swab samples may also be described.

7.4. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected from all subjects prior to vaccination, prior to the index surgery and at discharge, at each postvaccination clinic visit, and at each BSI/SSI assessment visit and in the event of MOF. Immunoassays will be performed at each time point and may include OPA assays using an *S aureus* CP5-expressing strain and CP8-expressing strain, and cLIAs for ClfA and MntC. Additional exploratory assays to measure immune responses may be conducted on all 4 antigens.

Approximately 24 mL of blood will be drawn at each specified visit. This will provide sufficient serum to conduct the immunogenicity assays and any repeat testing or additional immunogenicity assay tests to be performed.

In case of difficulty in obtaining a blood sample, it is possible to reschedule the sampling as long as the date remains in the authorized protocol window for the scheduled study visits.

Immunogenicity assays will be performed at Pfizer's Vaccine Research and Development Laboratory or at a vendor site. Sample collection, storage, and shipping information can be found in the SRM.

7.5. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. Any remaining sera will be stored by the sponsor, and may be used for additional assays and/or analyses to assess immune responses to vaccines or for assay development. The sera will not be used for any unrelated research, and no genetic testing will be performed. The samples will be stored for up to 15 years after the end of the study and then destroyed.

Each bacterial isolate will be labeled with a code so that the laboratory personnel testing the samples will not know the identity of the subject. Bacterial isolates that are received by the sponsor's central laboratory are considered the property of the sponsor. (Note that such isolates do not contain the subject's biological material, eg, deoxyribonucleic acid [DNA].) The isolates may remain stored beyond study completion (up to 15 years).

The subject may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples will remain the property of the sponsor and may be shared with other researchers as long as confidentiality is maintained.

7.6. Healthcare-Utilization Assessment

Upon hospital discharge from the index hospital admission, from each subsequent hospitalization, and from each postoperative follow-up visit, a healthcare-utilization assessment will be conducted (Appendix 4).

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of vaccine group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through Visit 6. SAEs occurring in a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product will be reported to the sponsor.

AEs will be recorded in the CRF from the signing of the ICD to Visit 4.

Newly diagnosed chronic medical disorders will be recorded in the CRF from Visit 4 to Visit 6.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease
- Drug abuse
- Drug dependency

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Extravasation

- Exposure during pregnancy (EDP)
- Exposure via breastfeeding
- Medication error
- Occupational exposure

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage. Such medication errors occurring to a study participant will be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

Other examples include, but are not limited to:

- The administration of expired investigational product
- The administration of an incorrect investigational product
- The administration of an incorrect dosage
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death

- Is life-threatening (immediate risk of death)

- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)

- Results in congenital anomaly/birth defect

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

For this study, deep venous thrombosis events are all considered important medical events and should be reported as an SAE.

Medical device complaints may meet the SAE reporting requirement criteria (see section on Medical Device Complaint Reporting Requirements). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- a life-threatening illness, even if temporary in nature

- a permanent impairment of a body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent the above 2 bulleted items

  Examples: clinically relevant increase in the duration of a surgical procedure, a condition that requires hospitalization or significant prolongation of existing hospitalization
- any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use
- fetal distress, fetal death, or any congenital abnormality or birth defects

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between investigational product and the efficacy endpoints specified below, the events noted below should not be reported by the investigator as SAEs as described in Section 8.14.1.

The following events are anticipated to occur in a study population following spinal surgery:

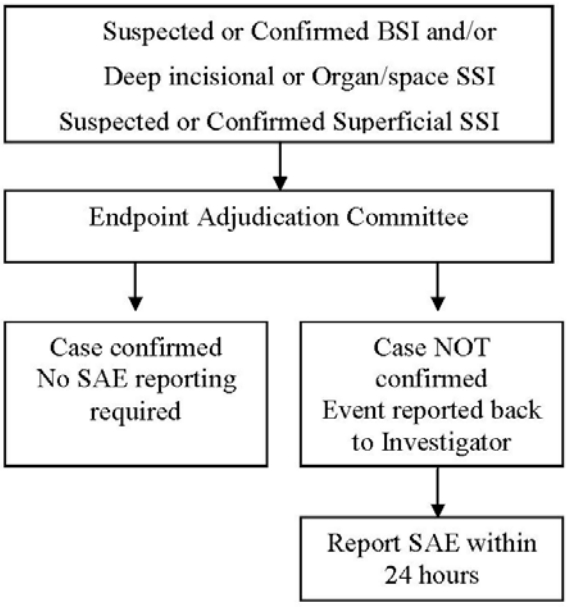
- Suspected or confirmed BSI and/or deep incisional or organ/space SSI
- Suspected or confirmed superficial SSI

Any suspected BSI or SSI event has the potential to meet endpoint criteria and is therefore to be adjudicated by the EAC. Reporting requirements (Figure 2) are summarized below while additional details are provided in the SRM:

- If the EAC confirms that the event meets the primary or secondary endpoint criteria, the event is **not reported as an SAE**.
- If the EAC confirms that the event **does not meet** the primary or secondary endpoint criteria, the event is reported back to the investigator as a nonendpoint SAE. The investigator will evaluate and **report the event as an SAE** (and AE), in accordance with the time frames described in the Serious Adverse Event Reporting Requirements section of this protocol (Section 8.14.1)
  Under these circumstances, the investigator's SAE awareness date is the date that the investigator receives the nonendpoint SAE back from the EAC.

All other events that meet SAE criteria will be reported by the investigator as described in previous sections.

Figure 2. Protocol-Specified SAE Reporting



8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

- For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline value and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with

- For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious, with the exception of the index hospital admission.

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities

- Hospice facilities
- Respite care (eg, caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Same-day surgeries (as outpatient/same-day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality)
- Social admission (eg, subject has no place to sleep)
- Administrative admission (eg, for yearly physical examination)
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. As noted previously, the indication for the index surgical procedure is not an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.
3	SEVERE	Interferes significantly with subject's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

The severity grading scale shown above should be used when assessing the severity of any AE/SAE, and Grade 4 postvaccination local reactions and systemic events as described in Section 7.2.1.3 and Section 7.2.1.4. Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (Section 8.14). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female subject becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female subject becomes, or is found to be, pregnant after discontinuing and/or being exposed to the investigational product;

  An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) comes into unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure will be reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator will report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE will be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer will be notified within 24 hours of investigator awareness of the event.

If an SAE occurs requiring EAC adjudication, Pfizer will be notified within 24 hours of notification that an SAE has been deemed a nonendpoint and has been sent back to the site. The investigator's SAE awareness date in this instance is identified as the date that the investigator receives the nonendpoint SAE back from the EAC.

As noted in the Protocol-Specified Serious Adverse Events section (Section 8.6.1), should an investigator judge one of the identified protocol-specified SAEs to have a causal relationship with the investigational product, the investigator must report the event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator will report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be collected on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might have led to death or serious deterioration in health.

Pfizer will be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

The section outlines statistical considerations and methodologies. Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

The primary comparison is between subjects receiving SA4Ag and subjects receiving placebo.

9.1. Hypotheses and Acceptance Criteria

Vaccine efficacy (VE) is defined as VE = 1 - RR, where RR is the relative risk in SA4Ag compared to placebo, ie, the proportion of SA4Ag recipients meeting the primary endpoint relative to the proportion of placebo recipients meeting the primary endpoint. SA4Ag will be compared to placebo testing the hypotheses H_0: VE ≤20% vs H_a: VE >20%.

A conditional power–based[59] futility procedure will be implemented during case accrual. Periodically the current estimate of VE will be assessed, and there will be a calculation of the power of the study at its planned completion at 48 cases conditional upon that value. The DMC will review the calculation and if the conditional power of the study is low, corresponding to the critical case splits shown in Table 15, futility may be declared and the study may cease enrollment. It is anticipated that this procedure will be implemented after approximately 10 and 15 cases have been accrued, and also at the time of the interim analysis at 24 cases. The assessments after 10 and 15 cases can only result in a possible declaration of futility, not efficacy; as such, there is no impact on the overall alpha level of the study. Full details of the conditional power–based futility procedure will be provided in the SAP.

An interim analysis will be performed after accumulating 24 per-protocol cases for review by the DMC. Only the primary endpoint, defined in Section 9.3.2, will be examined. The probability of the number of vaccine cases will be calculated using the binomial distribution with 24 trials and p = 0.444 because, under the null hypothesis and 1:1 randomization, the probability that a selected case is from SA4Ag is 0.444. If the number of vaccine cases is 3 or fewer, then the null hypothesis will be rejected in favor of the vaccine. If significant efficacy is observed at the interim analysis, the study may continue to enroll subjects to ensure that the study will provide sufficient safety data for vaccine licensure.

A 99.7% confidence interval (CI) will be obtained for VE. The confidence level is obtained from the O'Brien-Fleming[60] alpha levels, explained below. If the study does end for efficacy at interim analysis, events collected subsequent to the interim analysis will be reported in a supplement in a similar manner to that described in Whitehead[61] for overrunning data, described below. Otherwise, the study will continue to the accumulation of 48 cases.

Once 48 per-protocol cases have accumulated SA4Ag will be compared to placebo for the primary endpoint, testing the hypotheses H_0: VE ≤20% vs H_a: VE >20%. SA4Ag will be deemed efficacious if it has 14 cases or fewer out of a total of 48 cases (point estimate of VE = 58.8% and 2-sided lower 95.1% confidence limit >20%).

Although the final analysis is expected to have 48 cases, it is possible that additional potential cases will be present in the adjudication system (entered into the adjudication electronic case report form [eCRF]) on the same day that the 48th per-protocol case is reported to the EAC. These additional cases will be included in the final analysis, if confirmed as cases by the EAC. Therefore, the time order of case entry into the adjudication system will determine which cases will be included in the analysis. O'Brien-Fleming boundaries will be maintained for decisions regarding VE. In other words, in the event that more than 48 cases are available for the final analysis, the null hypothesis will be rejected if the lower bound of the 95.1% confidence interval is greater than 20%.

Similarly, although the interim analysis is expected to have 24 cases, it is possible that additional potential cases will be present in the adjudication system (entered into the adjudication eCRF) on the same day that the 24th per-protocol case is reported to the EAC. These additional cases will be included in the interim analysis, if confirmed as cases by the EAC. The time order of case entry into the adjudication system will determine which cases will be included in the interim analysis. O'Brien-Fleming boundaries will be maintained for decisions regarding VE. In other words, in the event that more than 24 cases are available for the interim analysis, the null hypothesis will be rejected if the lower bound of the 99.7% confidence interval is greater than 20%. Even if more than 24 cases are included in the interim analysis, the final analysis will be performed on 48 cases, unless additional cases are available as described in this section. Similar rules for case inclusion will apply to the futility analyses planned at 10 and 15 per-protocol cases.

No multiplicity adjustments will be applied to the secondary endpoints. All other secondary endpoints will be evaluated at a 2-sided alpha level of 0.05.

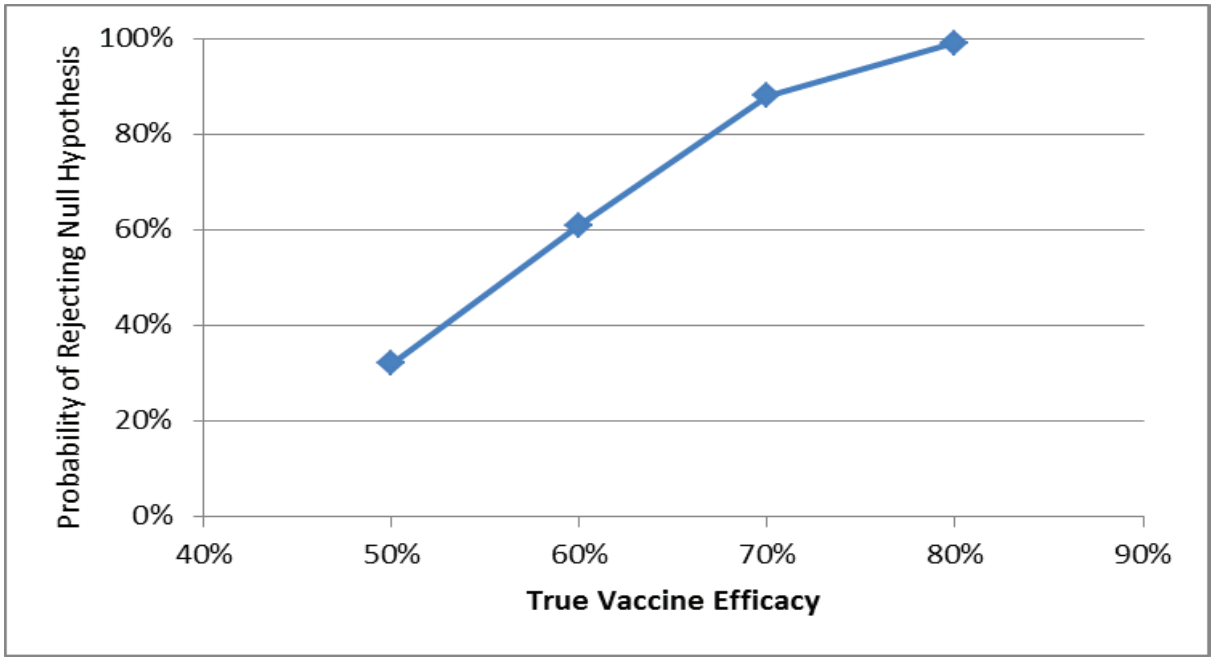
9.2. Sample Size Determination

This sequential analysis uses O'Brien-Fleming limits. Comparing 2 treatments in the number of cases may be restated as a 1-sample test of proportions.[62] The specifications in the software package EAST (Version 6.4, Cytel Inc, 2016) were 1-sample test on a binomial proportion, 1-sided alpha = 0.025, and an interim analysis, null hypothesis proportion = 0.444 (corresponding to VE = 20%), and alternate hypothesis proportion = 0.230 (corresponding to VE = 70%). The first-stage probability for rejecting the null hypothesis = 0.0015, the first-stage probability for rejecting the alternate hypothesis = 0.2595, and 1-sided probability of rejecting the null hypothesis at the final stage = 0.0245.

One-sided probability = 0.0015 corresponds to a 2-sided confidence level = 99.7%. One-sided probability = 0.0245 corresponds to a 2-sided confidence level = 95.1%. If power is set to 0.88, then the total would be 48. The interim analysis would be performed after 24 cases have accumulated.

Power is plotted against a range of true efficacy values in Figure 3. These power values are based on the final analysis with 48 cases.

Figure 3. Probability of Rejecting the Null Hypothesis of No Efficacy for a Range of True Efficacy Values at the Final Analysis (48 Cases)



It is anticipated that approximately 6000 subjects may be needed to accumulate 48 per-protocol cases, depending upon the incidence in the placebo group, VE, and dropout rate. For example, if the incidence of cases among placebo recipients is ~1.4% and the VE is 70%, then approximately 6000 individuals would need to be enrolled to detect 48 cases, assuming a dropout rate of 10%. Fewer subjects would need to be enrolled if the incidence of cases is higher among the control group or the VE is less than 80%. For example, if the VE is 60%, under the same assumptions, then approximately 5440 subjects would need to be enrolled to detect 48 cases.

In the event that futility is declared at any point, the study may cease subject enrollment. Vaccinated subjects will continue to be monitored for safety for 6 months after vaccination.

Procedural details for adjusting the sample size will be described in the SAP and/or DMC charter.

9.3. Efficacy Analysis

The per-protocol population will be the primary population for analysis of all efficacy objectives. Efficacy objectives will also be assessed using the modified intent-to-treat (mITT) populations. Subgroup analyses will be performed on both the per-protocol and the mITT populations.

All analyses for the SSI endpoints assume 100% correct classification of suspected *S aureus* cases, ie, no cases are missed and no noncases are included in the statistical analysis. All primary and secondary efficacy analyses will be repeated for sex, race, ethnicity, and age subgroups.

9.3.1. Efficacy Analysis Populations

Two analysis populations are defined: per-protocol and mITT. To be included in the per-protocol efficacy population, a subject must meet all eligibility criteria, be vaccinated as randomized, undergo the index surgery 10 to 60 days after vaccination, undergo surgery consistent with study-defined criteria for the index surgery, have no major protocol violations prior to reporting of the suspected *S aureus* infection, and have no infection or malignancy identified at the index surgical procedure. To be included in the mITT population, a subject must be vaccinated and undergo spinal surgery. For both populations, subjects will be assigned to the investigational product to which they were randomized (SA4Ag or placebo).

9.3.2. Analysis of the Primary Endpoint

For the primary objective, the efficacy of SA4Ag will be based on the number of per-protocol 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. In case of multiple occurrences meeting the primary endpoint from the same subject, only the first episode will be used to calculate the VE.

Examples of the estimated efficacy and associated CIs for a selected number of SA4Ag cases are presented in Table 15.

Table 15. Estimated Efficacy and Associated Confidence Intervals for a Select Number of SA4Ag Cases

Analysis Stage	Total Cases	SA4Ag Cases	Estimated Efficacy and Confidence Interval[a]	Comments
Futility	10	7	-133% (-1298%, 46.7%)	Conditional power <20%; possible futility declaration
	15	9	-50% (-412%, 52.3%)	Conditional power <20%; possible futility declaration
	24	11	15.4% (-105%, 66%)	Conditional power <20%; possible futility declaration
Interim	24	3	85.7% (24.9%, 99.0%)	Max number of SA4Ag cases that permits inference that true VE is >20%

Table 15. Estimated Efficacy and Associated Confidence Intervals for a Select Number of SA4Ag Cases

Analysis Stage	Total Cases	SA4Ag Cases	Estimated Efficacy and Confidence Interval[a]	Comments
Final	48	8	80.0% (56.5%, 91.9%)	Estimated efficacy = 80%
	48	11	70.3% (40.3%, 86.4%)	Estimated efficacy =70%
	48	14	58.8% (21.0%, 79.6%)	Max number of SA4Ag cases that permits inference that true VE is >20%

Abbreviations: N/A = not applicable; VE = vaccine efficacy.

a. 99.7% confidence level for interim analysis; 95.1% confidence level for final analysis; 95% confidence level for futility.

The findings at the time of the final analysis will serve as the primary basis for efficacy conclusions.

9.3.2.1. Supplementary Analysis

After completion of the final protocol analysis, additional cases may be identified and submitted for adjudication. Cases collected after the final analysis (ie, overrunning - Whitehead, 1997)[61] will be included in supplementary descriptive analyses using 95% CIs (as the final number of events is unknown); these analyses are supplementary and provided for completeness.

9.3.3. Analysis of Secondary Endpoints

9.3.3.1. Efficacy

All secondary endpoints will be analyzed using the per-protocol population. The binomial methodology described above will be used to test the null hypothesis of no difference between treatments, with p = 1/2 and number of trials set to total number of cases from SA4Ag and placebo. Two-sided p-values of the probability of the indicated SA4Ag cases or fewer will be calculated.

As sensitivity analyses, the secondary endpoints will be evaluated in the mITT populations with p = 1/2 and number of trials set to total number of cases from SA4Ag and placebo.

Secondary endpoints will be analyzed only after all subjects have completed the study and the database is locked.

9.3.4. Analysis of Exploratory Endpoints

9.3.4.1. Immunogenicity Analysis

The immunogenicity endpoints are the results from antigen-specific functional assays (OPA assay for CP5 and CP8, and cLIA antibody titers for ClfA and MntC). Additional exploratory assays to measure immune responses may be conducted on all 4 antigens. Assay titers will be obtained at each applicable visit.

The immunogenicity baseline will be Visit 1.

Windows for obtaining blood samples are:

- Visit 1: up to 7 days prior to vaccination.
- Visit 2 (index hospital admission): day of surgery blood sample collection any time from admission up to but before the index surgical procedure.
- Visit 2 (index hospital admission): day of discharge blood sample collection: up to 3 days before discharge, but must be after index surgical procedure.
- Visits 4 and 5: ±7 days.
- Visit 6: -2 to +12 days.

There are no windows for unscheduled blood sample collections.

Missing assay results are not to be replaced or imputed.

The number and proportion of subjects achieving threshold values will be determined at each scheduled time point for each vaccine group. Two-sided 95% CIs will be calculated. Threshold values will be specified in the SAP.

Geometric mean titers (GMTs), geometric mean fold rises (GMFRs) relative to baseline (Visit 1), and the proportion of subjects who achieve specific thresholds to the SA4Ag antigens, as well as their corresponding 95% CIs, will be compiled at each visit by vaccine group. Antigen-specific immunoglobulin and OPA titers will be logarithmically transformed prior to analysis. Within each vaccine group and for each antigen separately, GMTs at each visit will be calculated. Two-sided 95% CIs will be constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution.

Two-sided 95% CIs for the GMFR at each postvaccination blood draw visit will be constructed by back transformation of the CIs for the mean of the logarithmically transformed fold rise on the assay data computed using the Student t distribution.

In addition, GMTs and CIs will be estimated from an analysis of covariance (ANCOVA), also computed using the logarithmically transformed assay results. The model terms will be treatment, site, visit, baseline assay value, and treatment-visit interaction. 'Visit' for the index hospital admission will be partitioned into 'day of surgery' and 'day of discharge.' The difference between least squares (LS) means for SA4Ag minus placebo will be exponentiated to obtain a ratio of the geometric means. The corresponding 2-sided 95% CIs will be obtained.

For sensitivity purposes, the ANCOVA will be repeated by adding 1 factor and its interaction at a time, eg, add sex and treatment-sex interaction to the model. This will be performed for

sex, race, age group, baseline colonization status, and other subgroups as specified in the SAP. Significant interactions of subgroups with treatment, defined as $p < 0.10$, will be examined further for synergistic and antagonistic effects.

The proportions of subjects achieving n-fold rises from baseline to each postbaseline visit will be compiled, as well as their 95% CIs. N-fold rises will be 2-, 4-, 8-, 16-, and 32-fold.

Reverse cumulative distribution curves (RCDCs) will be generated to present the immunogenicity data at baseline and the Day 42 postoperative assessment time point. RCDCs may be repeated, but limited to cases.

All immunogenicity analyses will be performed in the per-protocol and mITT populations, but limited to subjects with at least 1 postvaccination assay value. It is anticipated that the immunogenicity analyses will be conducted following database lock; however, an interim immunogenicity analysis may be performed on a subset of subjects, if these results are required to support regulatory agency interactions to expedite the clinical development of SA4Ag.

If an interim immunogenicity analysis is performed, it will be limited to subjects who have at least 1 valid and determinate postvaccination assay value. The interim analysis will be limited to group-level statistics and will be conducted by an unblinded team, independent of the sponsor, in order to maintain blinding. All immunogenicity endpoints are defined as exploratory and the study will not be prematurely terminated or altered in any way (eg, no design or operational changes) from the interim immunogenicity analysis; therefore, no type I error adjustment is proposed.

9.3.4.2. Colonization Analysis

Windows for obtaining colonization swabs will be the same as for immunogenicity. Colonization swabs at Visit 2 (index hospital admission) will be collected both on admission and again, prior to discharge.

Baseline colonization status is defined as:

- Positive for any subject with at least 1 positive *S aureus* colonization swab at either Visit 1 or Visit 2 (admission sample only) or both.
- Negative for any subject with all negative *S aureus* colonization swabs at both Visit 1 and Visit 2 (admission sample only) and no missing colonization swabs.
- Missing for subjects without any colonization swab results from either Visit 1 or Visit 2 (admission sample only) or subjects with any combination of negative colonization swabs and at least 1 missing colonization swab.

At each postsurgery time point, the proportions of colonization swabs testing positive for *S aureus* at each anatomical site and the RR between the 2 vaccine groups along with its exact 2-sided 95% CI will be obtained. Subgroup compilations will be performed based on

age group, sex, baseline colonization status, and primary endpoint status (ie, case or noncase). Statistical significance of treatment-subgroup interactions will be obtained from logistic regression. The logistic regression will include treatment, subgroup, and treatment-subgroup interaction. One subgroup will be examined at a time. Some subgroups may be combined to achieve reasonable sample size. Anatomical sites will be examined separately.

Analyses will be performed for the per-protocol and mITT populations, further limited to subjects having at least 1 nonmissing colonization swab value at any visit.

9.4. Other Analysis

9.4.1. Demographics and Clinical Characteristics

The demographic characteristics to be summarized using descriptive statistics include sex, race, and age at time of vaccination. Other demographic characteristics, such as body mass index (BMI), smoking status, etc, will also be compared. Each vaccine group will be summarized separately. Preoperative and perioperative data will be summarized by vaccine group. Compilations will be performed for the per-protocol, mITT, and safety populations.

The CCI and ASA scores will be summarized by vaccine group.

Age group is defined as 18 to <50 years, 50 to <65 years, and 65 years and older. Age will be calculated from the date of randomization.

9.4.2. Healthcare Utilization

Healthcare utilization will be determined for each vaccine group and will include days in hospital, days in an ICU, discharge disposition, inpatient days in skilled nursing or rehabilitation facilities after discharge, number of readmissions to hospital, number of reoperations, days of antibiotic use, and outpatient visits for rehabilitation/physical therapy. Descriptive statistics will be calculated for each vaccine group. Two-sided 95% CIs for the mean or median difference between vaccine groups will be obtained where applicable (ie, not for categorical responses such as postdischarge disposition). Comparisons of healthcare use will be performed between vaccine groups for the per-protocol, mITT, and safety populations.

9.5. Safety Analysis

All subjects who receive study vaccine will be included in the safety population.

AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by vaccine group. AEs will be summarized for the following intervals:

- From the day of vaccination until the day of surgery
- From the day of 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)

Subjects may be vaccinated 10 to 60 days before the day of surgery, so the recording period for preoperative AEs will vary among subjects. AEs before surgery will be recompiled, but using AEs per 100 or per 1000 days, in order to adjust for varying exposure. Only AEs that start between the day of vaccination and before surgery will be so analyzed. The 3-tier methodology will not be used for preoperative AEs because they will be categorized as rates.

SAEs will be categorized according to MedDRA and will be summarized by vaccine group for all subjects for the following intervals:

- From the day of vaccination until the Day 180 postoperative evaluation

- From the day of vaccination until the day of surgery

- From the day of surgery until the Day 180 postoperative evaluation

Causes of deaths will be categorized according to MedDRA and descriptively summarized for subjects receiving SA4Ag and subjects receiving placebo. Mortality will be further categorized as associated with *S aureus* infection or not associated with *S aureus* infection, as determined by the EAC.

AEs will be summarized using 3-tier methodology:

1. Tier 1 includes all AEs of special interest. These may be determined by vaccine knowledge, experience with similar vaccines, and results from Phase 1 and 2 studies, and will be specified in the SAP. For such AEs, incidence proportions, the difference between treatments in proportions, 95% CI on the difference, 2-sided p-value on the difference, and graphical displays of the differences will be compiled. The defined tier 1 AEs will be specified by the sponsor in a separate safety review plan.

2. Tier 2 includes all AEs with ≥1% incidence in either treatment in either the preoperative period or the postoperative period. For such AEs, incidence proportions, the differences between treatments in proportions, and 95% CIs on the differences will be compiled.

3. Tier 3 includes all remaining AEs. For such AEs, only incidence proportions and the differences between treatments in proportions will be compiled.

The CIs on the difference between treatments will be computed using the Chan and Zhang method.[63]

The reanalysis of AEs before surgery, compiled on the basis of 100 or 1000 days of exposure, will be analyzed in terms of RR.

Postvaccination local reactions and systemic events reported in the e-diary will be summarized by the maximum severity across the 10-day observation period. Descriptive statistics will be compiled by vaccine group.

All AE safety analyses will be repeated for sex, race, ethnicity, and age subgroups.

Immunogenicity blood samples will be collected from subjects developing MOF. Descriptive statistics will be compiled by vaccine group. The population is the safety population.

9.6. Analysis Timing

There will be periodic futility checks after approximately 10 and 15 cases have accrued, and an interim analysis performed after the accrual of 24 cases that meet the primary efficacy endpoint as confirmed by the EAC. The DMC will perform these analyses, in association with the independent statistical team (IST), as required to discharge its responsibilities.

It is anticipated that immunogenicity analyses will be conducted following database lock; however, an interim immunogenicity analysis may be performed on a subset of subjects, if these results are required to support regulatory agency interactions to expedite the clinical development of SA4Ag (Section 9.3.4.1).

All other analyses will be performed after database lock and unblinding, with the exception of the primary endpoint analysis (Section 9.3.2).

9.7. Data Monitoring Committee

This study will use an independent, external data monitoring committee (DMC). Membership and conduct of the DMC is described in a separate DMC charter.

The DMC is responsible for ongoing monitoring of the safety of subjects in the study, and for the assessment of VE/futility, in accordance with the charter. The DMC is also responsible for providing recommendations on the need for adjusting the sample size required to achieve 48 per-protocol cases. The DMC is not specifically responsible for evaluating immunogenicity or *S aureus* carriage data collected as part of the protocol.

The DMC may review unblinded data during closed meeting sessions; however, the sponsor will remain blinded and will not be permitted access to the randomization assignments until the database is locked.

The DMC will review efficacy and safety data at defined intervals as specified in the charter. The DMC may conduct additional meetings to review safety data at other time points during the study, at its discretion, or at the request of the sponsor. In addition, as determined by the sponsor clinician, the DMC may meet on an ad hoc basis to evaluate any SAEs related to vaccination, or related AEs that may jeopardize further subject participation, in order to determine that the study may be continued safely.

The DMC will work in association with the IST in order to conduct both the safety and futility/efficacy evaluations. The IST will include statistician(s) and programmer(s) who are independent of the sponsor and who have unrestricted access to the randomization assignments during the study. The IST will perform statistical analysis and prepare unblinded data and reports to provide to the DMC for assessment in accordance with the DMC charter. The IST will report the outcome of the planned futility checks (only whether the futility rule has been passed or not) to the sponsor and the DMC separately.

After each meeting, the DMC will make recommendations that may include the following: continue the study with or without modification, pause or stop vaccination for safety or other reasons, or pause or stop the study for efficacy or futility (assessed at an efficacy/futility meeting only). The recommendations made by the DMC will be forwarded to Pfizer for consideration and final decision. Information on the current efficacy cases (number occurring in vaccine and placebo groups) will not be disclosed until a decision is made to permanently stop the study. Pfizer will forward the DMC recommendations and Pfizer's response to regulatory authorities, as appropriate. Supporting documents forwarded to regulatory agencies may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed ICDs, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The ICDs must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The ICDs used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by independent ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

The end of the clinical phase of the study will be defined as LSLV. At this time, sites will be closed out, the IRB/IEC will be informed, and no further CIOMS reports will be sent. For other purposes, the end of the study will be defined as the last serology sample assayed or characterization of the last strain isolate.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, or drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of SA4Ag at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) immediately. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication will be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Wertheim HFL, Melles DC, Vos MC, et al. The role of nasal carriage in *Staphylococcus aureus* infections. Lancet Infect Dis 2005;5(12):751-62.

2. Lowy FD. *Staphylococcus aureus* infections. N Engl J Med 1998;339(8):520-32.

3. World Health Organization. Report on the burden of endemic health care-associated infection worldwide. Geneva, Switzerland: World Health Organization; 2011.

4. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. Clin Infect Dis 2001;32(Suppl 2):S114-32.

5. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol 2008;29(11):996-1011.

6. McCaig LF, McDonald LC, Mandal S, et al. *Staphylococcus aureus*–associated skin and soft tissue infections in ambulatory care. Emerg Infect Dis 2006;12(11):1715-23.

7. Moet GJ, Jones RN, Biedenbach DJ, et al. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998-2004). Diagn Microbiol Infect Dis 2007;57:7-13.

8. Noskin GA, Rubin RJ, Schentag JJ, et al. The burden of *Staphylococcus aureus* infections on hospitals in the United States: an analysis of the 2000 and 2001 Nationwide Inpatient Sample database. Arch Intern Med 2005;165(15):1756-61.

9. Noskin GA, Rubin RJ, Schentag JJ, et al. National trends in *Staphylococcus aureus* infection rates: impact on economic burden and mortality over a 6-year period (1998-2003). Clin Infect Dis 2007;45:1132-40.

10. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of *Staphylococcus aureus:* epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev 1997;10(3):505-20.

11. Malinas MF, Mawhorter SD, Jain A, et al. *Staphylococcus aureus* bacteremia in solid organ transplant recipients: evidence for improved survival when compared with nontransplant patients. Transplantation 2012;93(10):1045-50.

12. Streit JM, Jones RN, Sader HS, et al. Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). Int J Antimicrob Agents 2004;24:111-8.

13. Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000--2006. J Infect Dis 2008;198:336-43.

14. Jacobsson G, Dashti S, Wahlberg T, et al. The epidemiology of and risk factors for invasive *Staphylococcus aureus* infections in western Sweden. Scand J Infect Dis 2007;39:6-13.

15. Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). Diagnost Microbiol Infect Dis 2004;50:59-69.

16. Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet 2011;377:228-41.

17. Laupland KB, Lyytikainen O, Sogaard M, et al. The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect 2013;19:465-71.

18. Weber DJ, Rutala WA, Sickbert-Bennett EE, et al. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia. Infect Control Hosp Epidemiol 2007;28(7):825-31.

19. Jones RN. Global epidemiology of antimicrobial resistance among community-acquired and nosocomial pathogens: a five-year summary from the SENTRY Antimicrobial Surveillance Program (1997-2001). Semin Resp Crit Care Med 2003;24(1):121-33.

20. Fedler KA, Biedenbach DJ, Jones RN. Assessment of pathogen frequency and resistance patterns among pediatric patient isolates: report from the 2004 SENTRY Antimicrobial Surveillance Program on 3 continents. Diagn Microbiol Infect Dis 2006;56:427-36.

21. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Infect Control Hosp Epidemiol 1999;20(4):247-78.

22. Zimlichman E, Henderson D, Tamir O, et al. Health care-associated infections. A meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013;173(22):2039-46.

23. Anderson DJ. Surgical site infections. Infect Dis Clin North Am 2011;25:135-53.

24. Weigelt JA, Lipsky BA, Tabak YP, et al. Surgical site infections: causative pathogens and associated outcomes. Am J Infect Control 2010;38:112-20.

25. Jernigan JA. Is the burden of *Staphylococcus aureus* among patients with surgical-site infections growing? Infect Control Hosp Epidemiol 2004;25(6):457-60.

26. Petti CA, Sanders LL, Trivette SL, et al. Postoperative bacteremia secondary to surgical site infection. Clin Infect Dis 2002;34:305-8.

27. Harrington G, Russo P, Spelman D, et al. Surgical-site infection rates and risk factor analysis in coronary artery bypass graft surgery. Infect Control Hosp Epidemiol 2004;25:472-6.

28. Schuster JM, Rechtine G, Norvell DC, et al. The influence of perioperative risk factors and therapeutic interventions on infection rates after spine surgery: a systematic review. Spine 2010;35(9 Suppl):S125-37. doi: 10.1097/BRS.0b013e3181d8342c.

29. Peleg AY, Weerarathna T, McCarthy JS, et al. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev 2007;23:3-13.

30. Pull ter Gunne AF, Cohen DB. Incidence, prevalence, and analysis of risk factors for surgical site infection following adult spinal surgery. Spine 2009;34(13):1422-8.

31. Dowsey MM, Choong PFM. Obese diabetic patients are at substantial risk for deep infection after primary TKA. Clin Orthop Relat Res 2009;467(6):1577-81.

32. Choban PS, Heckler R, Burge JC, et al. Increased incidence of nosocomial infections in obese surgical patients. Am Surg 1995;61:1001-5.

33. Birkmeyer NJO, Charlesworth DC, Hernandez F, et al. Obesity and risk of adverse outcomes associated with coronary artery bypass surgery. Circulation 1998;97:1689-94.

34. Moller AM, Villebro N, Pedersen T, et al. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet 2002;359:114-7.

35. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA 2007;298(15):1763-71.

36. Guvener M, Pasaoglu I, Demircin M, et al. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. Endocrine J 2002;49(5):531-7.

37. Ata A, Lee J, Bestle SL, et al. Postoperative hyperglycemia and surgical site infection in general surgery patients. Arch Surg 2010;145(9):858-64.

38. Marchant MH Jr, Viens NA, Cook C, et al. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am 2009;91:1621-9.

39. Smith RL, Bohl JK, McElearney ST, et al. Wound infection after elective colorectal resection. Ann Surg 2004;239:599-607.

40. Russo PL, Spelman DW. A new surgical-site infection risk index using risk factors identified by multivariate analysis for patients undergoing coronary artery bypass graft surgery. Infect Control Hosp Epidemiol 2002;23:372-6.

41. Moller A, Tonnesen H. Risk reduction: perioperative smoking intervention. Best Pract Res Clin Anaesthesiol 2006;20(2):237-48.

42. Koutsoumbelis S, Hughes AP, Girardi FP, et al. Risk factors for postoperative infection following posterior lumbar instrumented arthrodesis. J Bone Joint Surg Am 2011;93:1627-33.

43. Millbourn D, Cengiz Y, Israelsson LA. Effect of stitch length on wound complications after closure of midline incisions: a randomized controlled trial. Arch Surg 2009;144(11):1056-9.

44. Gaynes RP, Culver DH, Horan TC, et al. Surgical site infection (SSI) rates in the United States, 1992-1998: the National Nosocomial Infections Surveillance System basic SSI risk index. Clin Infect Dis 2001;33(Suppl 2):S69-77.

45. Rao SB, Vasquez G, Harrop J, et al. Risk factors for surgical site infections following spinal fusion procedures: a case-control study. Clin Infect Dis 2011;53(7):686-92.

46. Rosenberger LH, Politano AD, Sawyer RG. The Surgical Care Improvement Project and prevention of post-operative infection, including surgical site infection. Surg Infect 2011;12(3):163-8.

47. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 1996;334:1209-15.

48. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 2010;33(8):1783-8.

49. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. N Engl J Med 2002;346(24):1871-7.

50. Pfizer analysis of Nationwide Inpatient Sample (NIS), 2009 (USA).

51. Veeravagu A, Patil CG, Lad SP, et al. Risk factors for postoperative spinal wound infections after spinal decompression and fusion surgeries. Spine 2009;34:1869-72.

52. Schimmel JJP, Horsting PP, de Kleuver M, et al. Risk factors for deep surgical site infections after spinal fusion. Eur Spine J 2010;19(10):1711- 9.

53. Urquhart DM, Hanna FS, Brennan SL, et al. Incidence and risk factors for deep surgical site infection after primary total hip arthroplasty: a systematic review. J Arthroplasty 2010;25(8):1216-22.

54. US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, Md: US Department of Health and Human Services; September 2007.

55. Charlson ME, Sax FL. The therapeutic efficacy of critical care units from two perspectives: a traditional cohort approach vs a new case-control methodology. J Chron Dis 1987;40(1):31-9.

56. American Society of Anesthesiologists. ASA physical status classification system. Available: http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System. 18 Jun 2014.

57. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286(14):1754-8.

58. Grissom et al. Disaster Med Public Health Prep. 2010;4(4):277-84

59. Halperin M, Lan KKG, Ware JH, et al. An aid to data monitoring in long-term clinical trials. Control Clin Trials 1982;3(4):311-23.

60. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton, Fla: Chapman & Hall/CRC; 2000: p. 29-39.

61. Whitehead J. Underrunning and overrunning. In: The design and analysis of sequential clinical trials. Chichester, England: John Wiley & Sons; 1997: p. 151-7.

62. Chow SC, Shao J, Wang H. Sample size calculations in clinical research. New York: Marcel Dekker; 2003: p. 323-4.

63. Chan ISF, Zhang Z. Test based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55:1202-9.

Appendix 1. Protocol-Defined Infection Events

Adapted from: CDC NHSN Surgical Site Infections (SSI), January 2014 Edition

Reporting Instructions:

Bone and joint infections (joint or bursa infections, osteomyelitis, vertebral disc space infection) meningitis, spinal abscess without meningitis, and intra-abdominal infections (relevant only for procedures involving an anterior intra-abdominal incision) which involve tissue which was opened or manipulated during the index surgical procedure are to be reported as organ/space infection and not according to the PDI term.

BLOODSTREAM INFECTIONS (BSI)

– ***Clinical Criteria***

Confirmed Bloodstream Infection must meet at least *1* of the following criteria:

1. Patient has a recognized pathogen cultured from one or more blood cultures

OR

2. The same common commensal organism is cultured from two or more blood cultures drawn on separate occasions. Criterion elements must occur within a time frame that does not exceed a gap of 1 calendar day between two adjacent elements

AND the Patient has at least one of the following signs or symptoms:

- Fever (>38°C or >100.4°F)
- Chills
- Hypotension

Microbiological Classification:

Confirmed bloodstream infection cases are to be classified as:

- **Microbiologically confirmed *S aureus* bloodstream infection** if the subject has *S aureus* cultured from blood, as part of clinical criterion 1
- **Microbiologically confirmed non–*S aureus* bloodstream infection** if the subject has only non–*S aureus* organism(s) cultured from blood, as part of clinical criterion 1 or 2

BONE AND JOINT INFECTIONS

OSTEOMYELITIS

An osteomyelitis directly attributable to an infection via the index surgery incision site is to be classified as an organ/space SSI. If no such attribution exists, the event is reported as osteomyelitis.

– ***Clinical Criteria***

Confirmed osteomyelitis must meet at least *1* of the following criteria:

1. Patient has organisms cultured from bone.
2. Patient has evidence of osteomyelitis on direct examination of the bone during an invasive procedure or histopathologic examination.
3. Patient has at least *2* of the following signs or symptoms (*with no other recognized cause):
   - Fever (>38°C or >100.4°F)
   - Localized swelling*
   - Tenderness*
   - Heat*
   - Drainage at suspected site of bone infection*

AND At least *1* of the following:

a. Organisms cultured from blood

b. Positive laboratory test on blood (eg, antigen tests for *H. influenzae* or *S pneumoniae*)

c. Imaging test evidence of infection (eg, abnormal findings on x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc])

Microbiological Classification

Confirmed osteomyelitis cases are to be classified as:

- **Microbiologically confirmed *S aureus* osteomyelitis** if the subject has *S aureus* cultured from bone (clinical criterion 1), or from blood as part of clinical criterion 3

- **Microbiologically confirmed non–*S aureus* osteomyelitis** if the subject has only non–*S aureus* organism(s) cultured from bone (clinical criterion 1), or from blood as a component of clinical criterion 3

- **Non–microbiologically confirmed osteomyelitis** if the above criteria for microbiologically confirmed osteomyelitis are not met.

VERTEBRAL DISC SPACE INFECTION

A vertebral disc space infection directly attributable to an infection via the index surgery incision site is to be classified as an organ/space SSI. If no such attribution exists, the event is reported as vertebral disc space infection.

- ***Clinical Criteria***

Confirmed vertebral disc space infection must meet at least *1* of the following criteria:

1. Patient has organisms cultured from vertebral disc space tissue obtained during an invasive procedure

2. Patient has evidence of vertebral disc space infection seen during an invasive procedure or histopathologic examination

3. Patient has fever (>38°C or >100.4°F) or pain at the involved vertebral disc space, with no other recognized cause ***AND***

   Imaging test evidence of infection, (eg, abnormal findings on x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc])

4. Patient has fever (>38°C or >100.4°F) and pain at the involved vertebral disc space, with no other recognized cause ***AND***

   Positive laboratory test on blood or urine (eg, antigen tests for *H. influenzae*, *S. pneumoniae*, *N. meningitidis*, or group B streptococcus).

Microbiological Classification

Confirmed vertebral disc space infection cases are to be classified as

- **Microbiologically confirmed *S aureus* vertebral disc space infection** if the subject has *S aureus* cultured from vertebral disc space (clinical criterion 1)

- **Microbiologically confirmed non–*S aureus* vertebral disc space** infection if the subject has only non–*S aureus* organism(s) cultured from vertebral disc space (clinical criterion 1)

- **Non–microbiologically confirmed vertebral disc space infection** if the above criteria for microbiologically confirmed vertebral disc space infection are not met

JOINT OR BURSA INFECTION

A joint and bursa infection attributable to infection via the index surgery incision site (eg, harvesting bone from the iliac crest) is to be classified as an organ/space SSI. If no such attribution exists, the event is reported as a joint and bursa infection.

– ***Clinical Criteria***

Confirmed joint or bursa infection must meet at least *1* of the following criteria:

1. Patient has organisms cultured from joint fluid or synovial biopsy
2. Patient has evidence of joint or bursa infection seen during an invasive procedure or histopathologic examination
3. Patient has at least *2* of the following signs or symptoms with no other recognized cause:
   - Joint pain
   - Swelling
   - Tenderness
   - Heat
   - Evidence of effusion
   - Limitation of motion

AND at least *1* of the following:

   a. Organisms and white blood cells seen on Gram stain of joint fluid
   b. Positive laboratory test on blood culture or appropriate antigen test on blood, urine, or joint fluid
   c. Cellular profile and chemistries of joint fluid compatible with infection and not explained by an underlying rheumatologic disorder
   d. Imaging test evidence of infection (eg, abnormal findings on x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc])

Microbiological Classification

Confirmed joint or bursa infection cases are to be classified as

- **Microbiologically confirmed *S aureus* joint or bursa infection** if the subject has *S aureus* cultured from joint fluid or synovial biopsy (clinical criterion 1)
- **Microbiologically confirmed non–*S aureus* joint or bursa infection** if the subject has only non–*S aureus* organism(s) cultured from joint fluid or synovial biopsy (clinical criterion 1)
- **Non–microbiologically confirmed joint or bursa infection** if the above criteria for microbiologically confirmed joint or bursa infection are not met

PERIPROSTHETIC JOINT INFECTION

- ***Clinical Criteria***

Confirmed periprosthetic joint infection must meet at least *1* of the following criteria:

1. Two positive periprosthetic (tissue or fluid) cultures with identical organisms
2. A sinus tract communicating with the joint
3. Having *3* of the following minor criteria:
   a. Elevated serum C-reactive protein (CRP; >100 mg/L) *AND* erythrocyte sedimentation rate (ESR; >30 mm/hour)
   b. Elevated synovial fluid white blood cell (WBC; >10,000 cells/µL) count *OR* ++ (*or greater)* change on leukocyte esterase test strip of synovial fluid
   c. Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN% >90%)
   d. Positive histological analysis of periprosthetic tissue (>5 neutrophils [PMNs] per high power field)
   e. A single positive periprosthetic (tissue or fluid) culture

Microbiological Classification

Confirmed periprosthetic joint infection cases are to be classified as

- **Microbiologically confirmed *S aureus* periprosthetic joint infection** if the subject has 2 *S aureus*-positive periprosthetic (tissue or fluid) cultures (clinical criterion 1), or a single *S aureus*-positive periprosthetic (tissue or fluid) culture as part of clinical criterion 3

- **Microbiologically confirmed non–*S aureus* confirmed periprosthetic joint infection** if the subject has 2 non–*S aureus*-positive periprosthetic (tissue or fluid) cultures with identical organisms (clinical criterion 1), or a single non–*S aureus*-positive periprosthetic (tissue or fluid) culture as part of clinical criterion 3

- **Non–microbiologically confirmed periprosthetic joint infection** if the above criteria for microbiologically confirmed periprosthetic joint infection are not met

CARDIOVASCULAR SYSTEM INFECTIONS

ENDOCARDITIS

– ***Clinical Criteria***

Confirmed endocarditis of a natural or prosthetic heart valve must meet at least *1* of the following criteria:

1. Patient has organisms cultured from valve or vegetation
2. Patient has *2* or more of the following signs or symptoms (*with no other recognized cause)
   - Fever (>38°C or >100.4°F)
   - New or changing murmur*
   - Embolic phenomena*
   - Skin manifestations* (ie, petechiae, splinter hemorrhages, painful subcutaneous nodules)
   - Congestive heart failure*
   - Cardiac conduction abnormality*

AND at least *1* of the following:

   a. Organisms cultured from 2 or more blood cultures
   b. Organisms seen on Gram's stain of valve when culture is negative or not done
   c. Valvular vegetation seen during an invasive procedure or autopsy
   d. Positive laboratory test on blood or urine (eg, antigen tests for *H. influenzae, S. pneumoniae, N. meningitidis*, or group B streptococcus)
   e. Evidence of new vegetation seen on echocardiogram

AND if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

Microbiological Classification

Confirmed endocarditis cases are to be classified as

- **Microbiologically confirmed *S aureus* endocarditis** if the subject has *S aureus* cultured from a valve or vegetation (clinical criterion 1), and/or from 2 or more blood cultures as part of clinical criterion 2

- **Microbiologically confirmed non–*S aureus* endocarditis** if the subject has only non–*S aureus* cultured from a valve or vegetation (clinical criterion 1), and/or from 2 or more blood cultures as part of clinical criterion 2

- **Non–microbiologically confirmed endocarditis** if the above criteria for microbiologically confirmed endocarditis are not met

CENTRAL NERVOUS SYSTEM INFECTIONS

MENINGITIS

When meningitis is directly attributable to an infection via the index surgery surgical incision, the meningitis is to be classified as an organ/space SSI. Where no such attribution exists, the infection is reported as meningitis.

- ***Clinical Criteria***

Confirmed meningitis must meet at least *1* of the following criteria:

1. Patient has organisms cultured from cerebrospinal fluid (CSF)
2. Patient has at least *1* of the following signs or symptoms (*with no other recognized cause):
   - Fever (>38°C or >100.4°F)
   - Headache*
   - Stiff neck*
   - Meningeal signs*
   - Cranial nerve signs*
   - Irritability*

AND at least *1* of the following:

   a. Increased white cells, elevated protein, and decreased glucose in CSF
   b. Organisms seen on Gram stain of CSF
   c. Organisms cultured from blood
   d. Positive laboratory test of CSF, blood, or urine
   e. Diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen

AND if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy

Microbiological Classification

Confirmed meningitis cases are to be classified as

- **Microbiologically confirmed *S aureus* meningitis** if the subject has *S aureus* cultured from cerebrospinal fluid (clinical criterion 1), and/or blood as part of clinical criterion 2
- **Microbiologically confirmed non–*S aureus* meningitis** if the subject has only non–*S aureus* cultured from cerebrospinal fluid (clinical criterion 1), and/or from blood as part of clinical criterion 2
- **Non–microbiologically confirmed meningitis** if the above criteria for microbiologically confirmed meningitis are not met

SPINAL ABSCESS WITHOUT MENINGITIS

When a spinal abscess without meningitis is attributable to the index surgery surgical incision, the spinal abscess without meningitis is to be classified as an organ/space SSI. Where no such attribution exists, the infection is reported as spinal abscess without meningitis.

– ***Clinical Criteria***

Confirmed spinal abscess without meningitis (abscess of the spinal epidural or subdural space, without involvement of the cerebrospinal fluid or adjacent bone structures), must meet at least 1 of the following criteria:

1. Patient has organisms cultured from abscess in the spinal epidural or subdural space.
2. Patient has an abscess in the spinal epidural or subdural space seen during an invasive procedure or at autopsy or evidence of an abscess seen during a histopathologic examination.
3. Patient has at least *1* of the following signs or symptoms (*with no other recognized cause):
   - Fever (>38°C or >100.4°F)
   - Back pain*
   - Focal tenderness*
   - Radiculitis*
   - Paraparesis*
   - Paraplegia*

AND at least 1 of the following:

   a. Organisms cultured from blood

   b. Imaging test evidence of a spinal abscess (eg, abnormal findings on myelography, ultrasound, CT scan, MRI, or other scans [gallium, technetium, etc]).

AND if the diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy. **Microbiological Classification**

Confirmed spinal abscess without meningitis cases are to be classified as

- **Microbiologically confirmed *S aureus* spinal abscess without meningitis** if the subject has *S aureus* cultured from abscess in the spinal epidural or subdural space (clinical criterion 1) or from blood (as part of clinical criterion 3)
- **Microbiologically confirmed non–*S aureus* spinal abscess without meningitis** if the subject has only non–*S aureus* organisms cultured from abscess in the spinal epidural or subdural space (clinical criterion 1) or from blood (as part of clinical criterion 3)
- **Non–microbiologically confirmed spinal abscess without meningitis** if the above criteria for microbiologically confirmed spinal abscess are not met

INTRA-ABDOMINAL INFECTIONS

When an intra-abdominal infection is attributable to an infection via the index surgery incision site, eg, an intraperitoneal incision, the intra-abdominal infection is to be classified as an organ/space SSI. Where no such attribution exists, the infection is reported as an intra-abdominal infection using the verbatim term. Includes infections of the gallbladder, bile ducts, liver (excluding viral hepatitis), spleen, pancreas, peritoneum, subphrenic or subdiaphragmatic space, or other intra-abdominal tissue.

– ***Clinical Criteria***

Confirmed intra-abdominal infection must meet at least *1* of the following criteria

1. Patient has organisms cultured from abscess and/or purulent material from intra-abdominal space obtained during an invasive procedure.
2. Patient has abscess or other evidence of intra-abdominal infection seen during an invasive procedure or histopathologic examination.
3. Patient has at least *2* of the following signs or symptoms (*with no other recognized cause):
   - Fever (>38°C or >100.4°F)
   - Nausea*
   - Vomiting*
   - Abdominal pain*
   - Jaundice*

AND at least *1* of the following:

a. Organisms cultured from drainage from an aseptically placed drain (eg, closed suction drainage system, open drain, T-tube drain, CT-guided drainage)

b. Organisms seen on Gram's stain of drainage or tissue obtained during invasive procedure or from an aseptically placed drain

c. Organisms cultured from blood and imaging test evidence of infection (eg, abnormal findings on ultrasound, CT scan, MRI, or radiolabel scans [gallium, technetium, etc] or on abdominal x-ray)

Microbiological Classification

- **Microbiologically confirmed *S aureus* intra-abdominal infection** if the subject has *S aureus* organisms isolated from an aseptically obtained culture of an abscess and/or purulent material from the intra-abdominal space obtained during an invasive procedure
- **Microbiologically confirmed non–*S aureus* intra-abdominal infection** if the subject has only non–*S aureus* organisms isolated from a culture of an abscess and/or purulent material from the intra-abdominal space obtained during an invasive procedure
- **Non–microbiologically confirmed intra-abdominal infection** if the above criteria for microbiologically confirmed intra-abdominal infection are not met

PNEUMONIA

– ***Clinical Criteria***

Confirmed pneumonia must meet the following criteria

1. Two or more serial chest radiographs with at least *1* of the following *(in patients without underlying pulmonary or cardiac disease [eg, respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease], 1 definitive chest radiograph is acceptable)*:
   - New or progressive and persistent infiltrate
   - Consolidation
   - Cavitation
2. At least 1 of the following:
   - Fever (>38°C or >100.4°F)
   - Leukopenia (<4000 WBC/mm^3) or leukocytosis (≥12,000 WBC/mm^3)
   - For adults ≥70 years old, altered mental status with no other recognized cause

     AND at least 2 of the following:
     - New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
     - New-onset or worsening cough, or dyspnea or tachypnea
     - Rales or bronchial breath sounds
     - Worsening gas exchange (eg, O_2 desaturations [eg, PaO_2/FiO_2 ≤240], increased oxygen requirements, or increased ventilator demand)

Microbiologically confirmed pneumonia must demonstrate at least 1 of the following criteria:

- Positive growth in blood culture not related to another source of infection
- Positive growth in culture of pleural fluid
- Positive quantitative culture from minimally contaminated lower respiratory tract (LRT) specimen (eg, bronchial alveolar lavage or protected specimen brushing)

Microbiological Classification

Confirmed pneumonia cases are to be classified as

- **Microbiologically confirmed *S aureus* pneumonia** if the subject has *S aureus* cultured from blood, pleural fluid, and/or minimally contaminated LRT specimen, as per microbiologically confirmed pneumonia criteria
- **Microbiologically confirmed non–*S aureus* pneumonia** if the subject has only non–*S aureus* organism(s) cultured from blood, pleural fluid, and/or minimally contaminated LRT specimen, as per microbiologically confirmed pneumonia criteria
- **Non–microbiologically confirmed pneumonia** if the above criteria for microbiologically confirmed pneumonia are not met

SURGICAL-SITE INFECTIONS

SUPERFICIAL SSI

Clinical Criteria

Confirmed superficial SSI must meet the following criteria:

1. Involves only skin and subcutaneous tissue of the incision

AND

2. Patient has at least *1* of the following:
   a. Purulent drainage from the superficial incision
   b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
   c. Superficial incision that is deliberately opened by a surgeon or attending physician or designee and is culture-positive or not cultured (a culture-negative finding does not meet this criterion)

      AND At least 1 of the following signs or symptoms of infection:
      - pain or tenderness
      - localized swelling
      - redness
      - heat

   d. Diagnosis of a superficial incisional SSI by the surgeon or attending physician or designee

Microbiological Classification

Confirmed superficial SSI cases are to be classified as

- **Microbiologically confirmed *S aureus* superficial SSI** if the subject has *S aureus* cultured from an aseptically obtained culture of fluid or tissue from the superficial incision, or from a superficial incision that is deliberately opened, as part of clinical criterion 2
- **Microbiologically confirmed non–*S aureus* superficial SSI** if the subject has only non–*S aureus* organism(s) cultured from an aseptically obtained culture of fluid or tissue from the superficial incision, or from a superficial incision that is deliberately opened, as part of clinical criterion 2
- **Non–microbiologically confirmed superficial SSI** if the above criteria for microbiologically confirmed superficial SSI are not met

DEEP INCISIONAL SSI

– ***Clinical Criteria***

Confirmed deep incisional SSI must meet the following criteria:

1. Involves deep soft tissues of the incision (eg, fascial and muscle layers)

AND

2. Patient has at least *1* of the following:

   a. Purulent drainage from the deep incision

   b. A deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician or designee and is culture-positive or not cultured (culture-negative finding does not meet this criterion)

      AND the patient has at least *1* of the following signs or symptoms:

      - fever (>38°C or >100.4°F)
      - localized pain or tenderness

   c. An abscess or other evidence of infection involving the deep incision that is found on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

Microbiological Classification

Confirmed deep incisional SSI cases are to be classified as:

- **Microbiologically confirmed *S aureus* deep incisional SSI** if the subject has a deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician or designee and is culture-positive for *S aureus* as part of clinical criterion 2
- **Microbiologically confirmed non–*S aureus* deep incisional SSI** if the subject has a deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician or designee and is culture-positive for only non–*S aureus* organism(s), as part of clinical criterion 2
- **Non–microbiologically confirmed deep incisional SSI** if the above criteria for microbiologically confirmed deep incisional SSI are not met

ORGAN SPACE SURGICAL SITE INFECTION

– ***Clinical Criteria***

Confirmed organ space SSI must meet the following criteria:

1. Infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure

AND

2. Patient has at least *1* of the following:
   a. Purulent drainage from a drain that is placed into the organ/space
   b. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
   c. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during invasive procedure, or by histopathologic examination or imaging test

AND

3. Meets at least *1* criterion for an organ/space infection site listed below:
   - Osteomyelitis
   - Vertebral disc space infection
   - Meningitis
   - Spinal abscess without meningitis
   - Intra-abdominal infection
   - Joint or bursa infection

Microbiological Classification

Confirmed organ/space SSI cases are to be classified as

- **Microbiologically confirmed *S aureus* organ/space SSI** if the subject has *S aureus* organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space, as part of clinical criterion 2
- **Microbiologically confirmed non–*S aureus* organ/space SSI** if the subject has only non–*S aureus* organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space, as part of clinical criterion 2
- **Non–microbiologically confirmed organ/space SSI** if the above criteria for microbiologically confirmed organ space SSI are not met

Appendix 2. Preoperative Assessment

- American Society of Anesthesiologists (***ASA***) Physical Status Classification Score
- Source of admission (other healthcare facility)
- Wound site preparation method (clippers, shaving, etc)
- *S aureus* /MRSA carriage evaluation
- Decolonization therapy
  - Intranasal mupirocin
  - Chlorhexidine
  - Other

Appendix 3. Perioperative Assessment

- Skin preparation (eg, betadine, chlorhexidine)
- Surgical procedure performed (eg, posterior lumbar interbody fusion)
- Wound classification (eg, clean, clean contaminated, contaminated)
- Skin closure type (eg, staples, sutures, other)
- Primary incision site (eg, midline posterior, posterolateral)
- Secondary incision(s)
  - Spinal site(s) (anterior, endoscopic, etc.)
  - Graft donor site(s)
- Intervertebral level(s) fused (eg, lumbar 4 through thoracic 5)
- Implanted material (type and composition eg, rod, titanium)

Device Type	Composition
• Rods	• Titanium
• Plates	• Stainless steel
• Screws	• Other
• Cages	
• Other	

- Graft type (eg, autograft, allograft, bone morphogenic protein, other)
- Duration of surgery (knife to skin closure)
- Surgical site drains, indwelling catheters

- Vancomycin powder application to wound
- Prophylactic antibiotic (name, start and stop time, date, and dose)
- Estimated blood loss (mL)
- Blood product transfusion (eg, whole blood, red blood cells, platelets, clotting factors, cryoprecipitate, white blood cells, immunoglobulins, albumin, and plasma) and origin (heterologous or autologous donation/ transfusion of whole blood or red blood cells)
- Postoperative patient temperature (°C or °F) (first recorded postoperative value on return to ward)

Appendix 4. Healthcare-Utilization Assessment

- Number of days in hospital
- Number of days in an intensive care unit
- Number of readmissions to hospital
- Number of reoperations
- Number of inpatient days in a rehabilitation facility after discharge
- Number of inpatient days in a skilled nursing care facility/nursing home after discharge
- Discharge disposition
  - Home
  - Rehabilitation
  - Skilled nursing care facility
  - Death
  - Other
- Number of rehabilitation/physical therapy visits as an outpatient
- Days of antibiotic use

Appendix 5. Country-Specific Appendix – Applicable to France Only

The following supplementary text should be read in conjunction with the B3451002 protocol:

- Prior to enrollment of any subjects, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice (GCP) training course ("Pfizer GCP Training"). Any investigators who later join the study will complete Pfizer GCP Training before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training every 3 years during the term of the study, or more often if there are significant changes to the International Conference on Harmonisation (ICH) GCP guidelines or course materials.

- No subjects or third-party payers will be charged for investigational product.

- The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

- Information relating to the investigator, subinvestigators, and research staff will be held in 1 or more databases for the purpose of determining their involvement in future research and in order to comply with any regulatory requirements. All affected personnel will be furnished with a form of notice setting out the intended use of the personal data and be asked to sign a consent form.

Appendix 6. Country-Specific Appendix – Applicable to Japan Only

The following supplementary text should be read in conjunction with the B3451002 protocol:

- When the subject is a minor under local law, the investigator, or a person designated by the investigator, will obtain written informed consent from the subject's legally acceptable representative, or parent(s) or legal guardian, and the subject's assent (affirmative agreement) before any study-specific activity is performed. The investigator will retain the original of each signed consent and assent document.
    - The assent form for a minor must be in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), local regulatory requirements, and legal requirements, including applicable privacy laws.
    - The assent form for a minor used during the informed consent process must be reviewed by the sponsor, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.
    - The investigator must ensure that the subject's legally acceptable representative, or parent(s) or legal guardian, is fully informed about the nature and objectives of the study and possible risks associated with participation.
    - The source documents must record that the subject was a minor at the time of signing the informed consent document (ICD), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent), and that the subject's assent was obtained.
- When the minor subjects reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study.
- Axillary temperature will be measured at Visit 1, as required at an unscheduled visit, and will be measured by the subject for 10 days following vaccination.
- An axillary temperature of ≥37.5°C meets the definition of a current febrile illness in the criteria for temporarily delaying vaccine administration described in Section 4.3 for subjects enrolled in Japan.
- For the purpose of recording the temperature in the electronic diary (e-diary), fever is defined as an axillary temperature of ≥38.0°C (100.4°F) for subjects enrolled in Japan.
- To facilitate ease of understanding in the e-diary for the subject, the same terms of local reactions and systemic events in Table 9 and Table 10 will be described with simple wording and pronunciation upon translating them into Japanese.