003-02

A Randomized, Multicenter, Double-Blind, Group-Sequential Study to Evaluate the Efficacy, Immunogenicity, and Safety of a Single Dose of Merck 0657nI Staphylococcus aureus Vaccine (V710) in Adult Patients Scheduled for Cardiothoracic Surgery

Product: V710
Protocol/Amendment No.: 003-02

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TITLE:

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INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

Product: V710 1
Protocol/Amendment No.: 003-02

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The aim of this protocol amendment is to remove the success criterion at the 2nd interim analysis to maximize the robustness of the V710 Protocol 003 dataset supporting efficacy evaluation in the event the study is stopped early for success. Before the 2nd interim analysis, blinded assessment of data reported in the trial has indicated differences in the primary and secondary endpoint rates across sites, countries and regions. Removing success criterion at the 2nd interim analysis will allow accrual of additional endpoints across geographic regions through the 3rd interim or final analyses. This revision will provide a more robust dataset to support the evaluation of vaccine efficacy. The futility criterion at the 2nd interim analysis will remain unchanged, still allowing to stop the study in the event of low efficacy.

Changes were made in the following sections:

- Section 1.5 (Sample Size Estimation) was updated to reflect the following:
    - The last sentence at the 1st Interim Analysis (*Stage 1*) stating that it is anticipated that ~1,800 patients will be required in order to accrue the 24 *S. aureus* cases necessary for this analysis was removed.
    - The success criterion at the 2nd Interim Analysis (*Stage 2*) was removed.
    - The last sentence at the 2nd Interim Analysis (*Stage 2*) stating that it is anticipated that ~3,600 patients will be required in order to accrue the 48 *S. aureus* cases necessary for this analysis was removed.
    - The last sentence at the 3rd Interim Analysis (*Stage 3*) stating that it is anticipated that ~5,790 patients will be required in order to accrue the 77 *S. aureus* cases necessary for this analysis was removed.
    - For the *Final Stage*, the new anticipated final enrollment (15,000 versus 8,044) is based on the blinded rate of primary endpoints observed prior to when Amendment 003-02 was updated.
- Section 2.4.1 (Summary of Study Design/Study Duration) was updated to reflect the revised text for the overall study duration.
- Section 2.4.2 (Treatment Plan) was updated to reflect the new anticipated final enrollment of 15,000. Sample Size estimates for Stages 1 through 3 were removed from Table 2-1 as well.
- Section 2.5.1 (Primary Efficacy Measurements) was updated to reflect that the success criterion at the 2nd Interim Analysis (*Stage 2*) was removed.
- Section 2.8.1 (Overall Analysis Strategy) was updated to reflect that the success criterion at the 2nd Interim Analysis (*Stage 2*) was removed.

- Section 2.8.5 (Power and Sample Size) was updated to remove the power statements related to success at the 2nd Interim Analysis (*Stage 2*) and to update the success probabilities at the later interim analysis time points. The new anticipated final enrollment (15,000) was updated, along with the assumptions used for the primary endpoint rate.

- Section 3.5.5.1 (Overall Analysis Strategy) was updated to reflect that the success criterion at the 2nd Interim Analysis (*Stage 2*) was removed.

- Section 3.5.7 (Sample Size and Power) was updated to reflect the new anticipated final enrollment (15,000), along with the assumptions used for the primary endpoint rate.

- Section 3.5.8 (Interim Efficacy Analyses) was updated to remove the power statements, confidence intervals, and other references related to success at the 2nd Interim Analysis (*Stage 2*), and to explain that the amount of alpha-spend associated with the originally planned efficacy look (0.0564%) at *Stage 2* was retained in order to maintain the overall alpha-adjustment as defined in Protocol Amendment 003-01. Table 3-2 was updated to reflect the removal of the success criterion at *Stage 2*, and to note that the alpha-spend was still retained at *Stage 2*.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

1) Enrollment number was changed from ~8,044 patients to ~15,000 patients.

   The above change was made in the following sections:

   - Section 1.4 (Summary of Study Design)
   - Section 1.5 (Sample Size Estimation)
   - Section 1.7 (Study Flow Chart)
   - Section 2.4.1 (Summary of Study Design)
   - Section 2.4.2 (Treatment Plan)
   - Section 3.6.1 (Patient and Replacement Supply Information)

2) It is clarified that adjudication by an independent efficacy endpoint adjudication committee (EEAC) will be performed on all suspected *S. aureus* infections identified in this study occurring at any time from vaccination through postoperative Day 360, or throughout the duration of the study.

   The above clarification was made in the following sections:

   - Section 2.4.1 (Summary of Study Design/Efficacy)
   - Section 2.5.1 (Primary Efficacy Measurements)
   - Section 2.5.2 (Secondary Efficacy Measurements)
   - Section 2.5.3 (Exploratory Efficacy Endpoints)

- Section 3.2.4.13 (Evaluation for Presence of Postoperative *S. aureus* Infections)
- Section 3.3.3 (Efficacy Endpoint Adjudication Committee [EEAC])
- Section 3.3.3.1 (EEAC Adjudication Procedure)
- Section 3.3.3.2 (Adjudication Package Documentation for EEAC)
- Section 3.3.4.2 (Summary of DSMB Responsibilities)
- Section 3.3.4.4 (Overall Process Flow of Efficacy Data Between SPONSOR, EEAC, and DSMB)

3) Text was updated regarding in-house blinding procedures following CSR cutoff. The official clinical database will not be unblinded until medical/scientific review has been completed, data have been declared complete, and all protocol violators have been identified by the Clinical Safety Report cutoff date. Due to high enrollment and a large database, the CSR cutoff date may be based on data available for the interim or final analyses. Remaining data reported subsequent to the CSR cut-off date and through postoperative Day 360 visit will be summarized in a separate report.

   The above change was made in the following sections:

   - Section 3.2.6.1 (In-House Blinding Procedures Following Clinical Study Report (CSR) Cutoff Date
   - Section 3.5.1 (Responsibility of Analyses)
   - Section 3.5.3.2 (Safety)

4) The clinical supplies section was updated to remove text that stated that the study site is not required to actively monitor the temperature of the diluent and placebo and that the diluent and placebo should not be stored refrigerated.

   The above change was made in the following sections:

   - Section 3.6.6 (Storage and Handling Requirements)

5) The Clinical Research Specialist(s) (CRS) and Clinical Operations Specialist(s) (COS) job role titles were updated to Clinical Research Personnel and Clinical Operations Personnel, respectively.

   The above change was made in the following sections:

   - Section 3.2.6 (Blinding/Unblinding)
   - Section 3.2.6.1 (In-House Blinding Procedures Following Clinical Study Report [CSR] Cutoff Date)
   - Section 3.3.3.1 (EEAC Adjudication)
   - Section 3.3.4.4 (Overall Process Flow of Efficacy Data Between SPONSOR, EEAC, and DSMB)
   - Section 3.3.5 (Scientific Advisory Committee [SAC])
   - Section 3.6.7 (Standard Policies and Return of Clinical Supplies)

6) List of References Numbers 21 to 23 were updated.

The above change was made in the following sections:

- Section 2.8.4 (Safety)
- Section 3.5.5.4 (Analysis of Vaccine Safety)
- Section 5 (List of References)
- Section 6.2 (Guidelines for Antimicrobial Prophylaxis in the Preoperative Period)

PROTOCOL

A Randomized, Multicenter, Double-Blind, Group-Sequential Study to Evaluate the Efficacy, Immunogenicity, and Safety of a Single Dose of Merck 0657nI Staphylococcus aureus Vaccine (V710) in Adult Patients Scheduled for Cardiothoracic Surgery

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1. SUMMARY

1.1 TITLE

A Randomized, Multicenter, Double-Blind, Group-Sequential Study to Evaluate the Efficacy, Immunogenicity, and Safety of a Single Dose of Merck 0657nI *Staphylococcus aureus* Vaccine (V710) in Adult Patients Scheduled for Cardiothoracic Surgery

1.2 INDICATION

This study will evaluate the ability of the Merck 0657nI *Staphylococcus aureus* vaccine (hereafter referred to as V710) to prevent serious *S. aureus* infections (i.e., bacteremia and/or deep sternal wound infections, including mediastinitis) for a defined period of time following cardiothoracic surgery.

1.3 SUMMARY OF RATIONALE

This study is being performed to assess the efficacy of a single-dose regimen (60 μg) of V710 to prevent *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections (including mediastinitis) through postoperative Day 90 in adult patients (18 years of age or greater) who are prescheduled for cardiothoracic surgery. In addition to several secondary efficacy endpoints, this study will also evaluate the immunogenicity and general safety and tolerability of the vaccine.

1.3.1 Incidence of *S. aureus* Infections Including Post-Cardiothoracic Surgery

A dramatic increase in the number of *S. aureus* infections occurring both in the community and in the hospital [1, 2, 3, 4, 5], coupled with the rise of antimicrobial-resistant *S. aureus* pathogens (specifically, methicillin-resistant *S. aureus* [MRSA]), has resulted in limited therapeutic options for patients with multiresistant isolates of *S. aureus* [1, 6, 7, 8]. Therefore, a vaccine that results in the active protection against a majority or all *S. aureus* strains could have a major impact in the reduction of *S. aureus* infections.

S. aureus infections are a frequent cause of infection in the postoperative patient. This organism is frequently identified in the bloodstream in the postoperative setting, arising from surgical wound infections or intravascular catheters. The risk of *S. aureus* infections is particularly concerning following cardiovascular surgeries involving a median sternotomy, as such patients are at acute risk of developing postoperative mediastinitis. Postoperative mediastinitis can occur in as high as 3% of patients who undergo a full median sternotomy, with approximately two-thirds of the microbiologically-confirmed cases attributed to *S. aureus* [9]. This infection carries a grave prognosis, with an associated mortality of up to 40% [10, 11]. An association between *S. aureus* bacteremia and *S. aureus* mediastinitis has been supported by several studies. In fact, two studies conducted at Duke University Medical Center found that *S. aureus* bacteremia following a median sternotomy had 77 to 91% positive predictive value for *S. aureus* mediastinitis [9, 12].

A *S. aureus* vaccine capable of providing a rapid immune response could be administered to patients prior to cardiothoracic surgery, thereby potentially reducing the incidence of postoperative *S. aureus* bacteremia or *S. aureus* deep sternal wound infections.

1.3.2 Background on Merck 0657nI *S. aureus* Vaccine (V710)

A polypeptide encoded by *S. aureus*, 0657n, was identified in an immunological screen of random recombinantly-expressed polypeptides as having reactivity with acute human serum [13]. Preclinical data have demonstrated the efficacy of a 0657n-containing vaccine (V710) in three murine models, including a sepsis model, a disseminated infection model, and an intravascular catheter model. The results from these murine studies and subsequent studies in rats and nonhuman primates suggest that V710 is immunogenic. In fact, immunogenicity in rats and rhesus monkeys is rapidly achieved following vaccination.

1.3.2.1 Phase I First-In-Man Immunogenicity and Safety Study (Protocol 001)

The first-in-man Phase I clinical trial of V710 (Protocol 001) demonstrated that the vaccine was immunogenic following a single vaccination with any of the 3 V710 dosages (5 μg, 30 μg, or 90 μg). A greater proportion of subjects manifested a positive immune response (defined as a ≥2-fold increase in 0657n-specific IgG titers relative to baseline in a total IgG assay conducted on a LUMINEX™ platform) and achieved higher geometric mean titers (GMT) with the 30- and 90-μg dosages, relative to the 5-μg dosage, at the primary time point (Day 14 postvaccination). Immune responses were noted as early as Day 10 postvaccination (in a limited subset in whom Day 10 data was collected), and these immune responses persisted out to Day 84 postvaccination (the last study visit) in most subjects. Of note, the response achieved in the older cohort of subjects (≥ 40 years of age) was at least comparable to that noted in the younger cohort of subjects (< 40 years of age). All dosage regimens (5 μg, 30 μg, and 90 μg) were well tolerated.

No significant immunogenicity differences were noted between the 30- and 90-μg dosage regimens at the primary immunogenicity time point (Day 14 postvaccination). The 5-μg dosage of V710 did not appear to provide immunogenicity commensurate with the two higher dosing regimens, and it is unknown whether a change in immunogenicity would be detected on the dose-response curve across the ranges of 5 μg and 30 μg. Recognizing that the safety at the highest dosage (90 μg) was similar to the safety at the 30-μg dosage, the SPONSOR has chosen a dosage that would be adequately bracketed between the 30- and 90-μg dosages. Based on these findings, a 60-μg dosage has been chosen for subsequent evaluation in Phase II/Phase III trials, including this study.

1.3.2.2 Phase I MAA Versus Non-MAA Immunogenicity and Safety Study (Protocol 002)

The second-in-man Phase I study of V710 was conducted to determine whether the vaccine evaluated in the current study should contain Merck Aluminum Adjuvant (MAA), as it did in Protocol 001. The preliminary results from Protocol 002 demonstrate that V710 was immunogenic following a single vaccination with both the adjuvanted (MAA-containing) and non-adjuvanted formulations. Notably, the immune responses

were more pronounced in the older age cohort (subjects 50 to 70 years of age). Finally, it is noteworthy that both vaccine regimens (V710 with MAA and V710 without MAA) were well tolerated in all subjects included in Protocol 002. Based on the study data, the decision was made to evaluate a non-adjuvanted V710 formulation in Phase II/Phase III trials, including this study.

The previous Phase I studies (Protocols 001 and 002) were conducted using a liquid formulation of V710. An additional clinical trial (Protocol 004) was conducted to ensure that the reconstituted lyophilized formulation also leads to a sufficient immune response following a single-dose administration. The preliminary results of Protocol 004 indicate that the immunogenicity and safety of the lyophilized V710 formulation is similar to that of the liquid V710 formulation evaluated in Protocols 001 and 002.

Additional details regarding Protocols 001, 002, and 004 can be found in the V710 CIB.

1.4 SUMMARY OF STUDY DESIGN

This is a sequential-design, international, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy, immunogenicity, and safety of a single-dose regimen of V710 (60 μg) in ~15,000 adult patients (18 years of age or greater) who are scheduled to undergo cardiothoracic surgery involving a full median sternotomy 14 to 60 days postvaccination. The study will attempt to rule out a vaccine efficacy of 20% or less based on a combined endpoint of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections out to postoperative Day 90 in patients receiving V710 relative to patients receiving placebo.

All patients will be identified, enrolled, and vaccinated at the time that cardiothoracic surgery is scheduled. Patients will be randomized in a 1:1 ratio at the time of enrollment to receive either a single-dose regimen of V710 (60 μg) or placebo.

Further details regarding the study design, including efficacy, immunogenicity, and safety endpoints, are outlined in Section 2.4.1.

1.5 SAMPLE SIZE ESTIMATION

This is an event-driven study, with total enrollment estimates based on the number of accumulated patient cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections. The study has a group-sequential study design with four separate analyses (*Stages*) of vaccine efficacy:

- ***Stage 1:*** The initial interim analysis will serve as a futility analysis and will take place when 24 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have been identified. This early analysis of the efficacy data will provide an opportunity to terminate the study early in the event that the chance for achieving efficacy success proves remote (i.e., ≥13 *S. aureus* cases [of the 24 cases] occur in the V710 group). If futility is not met, the study will continue until the next interim analysis.

- ***Stage 2:*** The second interim analysis, which will occur once 48 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have been identified, will also serve as a futility analysis. Futility will be declared if ≥22 *S. aureus* cases (of the 48 cases) are observed in the V710 group at this interim analysis. If the criterion for futility is not met, the study will continue enrollment until the next interim analysis.
- ***Stage 3:*** The third interim analysis, which will occur once 77 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have been identified, will assess both futility and efficacy. Futility will be declared if ≥32 *S. aureus* cases (of the 77 cases) are observed in the V710 group at this interim analysis. Likewise, the statistical criterion of success for efficacy (lower bound of the vaccine efficacy 95% confidence interval >20%) would be met at this interim analysis if 22 or fewer cases are observed in the V710 group. If these criteria for futility or success are not met, the study will continue enrollment until the final analysis.
- ***Final Stage:*** The fourth and final analysis (assuming the study is not stopped early following the third interim analysis) will be performed when 107 cases of *S. aureus* bacteremia and/or *S. aureus* sternal wound infections have been identified. It is anticipated that ~15,000 patients will be required in order to accrue the 107 *S. aureus* cases necessary for the final analysis, assuming the 1:1 randomization ratio of V710 to placebo.

The study will continue enrollment until the mandated statistical criterion is achieved (e.g., the lower bound of the 95% confidence interval for the vaccine efficacy estimate is >20%) or the total number of cases (107) have been accrued. Further discussion of the study termination rules are provided in Section 2.8.5 and Section 3.5.8.

1.6 VACCINATION FORMULATION, DOSAGE, REGIMEN, AND ROUTE OF ADMINISTRATION

Patients will be randomized in a 1:1 ratio to receive either a single 0.5-mL injection (60 μg) of V710 or a single 0.5-mL injection of placebo (normal saline solution [0.9%]). Injections of both V710 and placebo will be administered intramuscularly (IM) by needle/syringe in the deltoid muscle.

V710

V710 will be provided in a lyophilized formulation, to be stored at 2 to 8º C. The diluent (saline [0.45%] solution) for reconstitution of the lyophilized V710 will be stored at room temperature conditions (~15 to 30º C). V710 must be reconstituted with the saline (0.45%) diluent immediately prior to use. The reconstituted V710 will be a clear, colorless to slightly yellow liquid. If the appearance of the reconstituted V710 is not as described, it should be disposed of as biohazard waste, and this should be documented on the appropriate vaccine accountability log in the Administrative Binder. In such a case, the site staff will use the Interactive Voice Response System (IVRS) to assign a replacement vial of V710/placebo to be reconstituted and administered (see Section 3.6.8).

Placebo (Normal Saline [0.9%])

The placebo will be provided as a normal saline (0.9%) solution and will be stored at room temperature conditions (~15 to 30º C). The placebo will be a clear, colorless liquid. If the appearance of the placebo is not as described, it should be disposed of as biohazard waste, and this should be documented on the appropriate vaccine accountability log in the Administrative Binder.

1.7 STUDY FLOW CHART

Procedures	Study Visit Date								
	Relative to Vaccination		Relative to Cardiothoracic Surgery[1]						
							Long-Term Safety Contacts and Long-Term Immunogenicity Visits		
	Date of Vaccination	Day 14 to 60 postvaccination (i.e., Hospital Admission)	Postop Day 1[2]	Hospital Discharge	Postop Day 45	Postop Day 90	Postop Day 180	Postop Day 270	Postop Day 360
Obtain written consent	X								
Assign baseline number	X								
Obtain medical history	X								
Physical examination (including vital signs)	X	X	X	X	X	X			
Evaluate inclusion and exclusion criteria	X								
Urine or serum sample collection for pregnancy test[3]	X								
Collection of STS risk score[4]	X								
Assign allocation number and randomize to treatment group	X								
Collect 20 mL blood for antibody testing[5]	X	X			X	X	X[6]	X[6]	X[6]
Nasopharyngeal swab collection for evidence of *S. aureus* colonization of the nares	X					X			X[7]
Vaccinate	X								
Distribute Vaccination Report Card (VRC) and review instructions for completing VRC and for measuring oral temperatures[8]	X								
Update medical history		X	X	X	X	X			
Collect and review VRC for completeness[9]		X							
Safety Follow-up[10]	X[11]	X	X	X	X	X	X[12]		X[12]
Phone calls for efficacy follow-up every 2 weeks (following hospital discharge)[13]					X	X			
Evaluation for presence of *S. aureus* infection[14]			X	X	X	X			

[1] Cardiothoracic surgery will be scheduled 14 to 60 days postvaccination.

[2] Postoperative Day 1 visit (relative to cardiothoracic surgery) represents the first day following cardiothoracic surgery.

[3] Urine or serum pregnancy test for all females of reproductive potential prior to vaccination.

[4] The Society of Thoracic Surgeons (STS) risk score will be collected from all patients at the time of randomization [18]. Factors that will be collected to determine STS scores are outlined in Section 3.2.4.9. The complete STS score calculation table is provided in Appendix 6.1.

[5] Sera collected from all patients will be analyzed for IgG antibodies against *S. aureus* using a LUMINEX™ assay. Sera collected from a subset of the patients in this study will also be used for functional assays (e.g., opsonophagocytic [OP] activity). Sera collected in this study may also be used for other assays in development.

[6] Long-term immunogenicity blood draws (postoperative Day 180, Day 270, and Day 360) will be collected only in a subset of patients (N=400).

[7] An additional nasopharyngeal swab for evidence of *S. aureus* colonization of the nares will be collected for a subset of patients (N=400) at postoperative Day 360. All cultures positive for *S. aureus* will undergo antibiotic susceptibility at the investigative site (or at the investigative site's local microbiology laboratory).

[8] VRC will be completed for Day 1 to 14 postvaccination, with daily monitoring of oral temperatures and local injection site reactions for Days 1 to 5 postvaccination only.

[9] Study staff will review VRC with patient at the time of hospital admission to ensure proper completion.

[10] Systemic and other adverse experiences will be monitored during Days 1 to 14 postvaccination and recorded on the VRC. Similarly, all serious adverse experiences will be reported during Days 1 to 14 postvaccination. However, vaccine-related serious adverse experiences, serious adverse experiences resulting in death, and serious adverse experiences involving the diagnosis of a *S. aureus* infection will be reported throughout the entire follow-up period (i.e., through postoperative Day 360).

[11] Patients will be monitored for 30 minutes postvaccination for any evidence of a hypersensitivity reaction.

[12] All patients enrolled in the study (N=~15,000) will be contacted for long-term safety assessments at postoperative Day 180 and Day 360. These contacts may be conducted through either study site visit or telephone call. Safety information to be collected during these contacts will include the following events since the previous study visit: (1) Any vaccine-related serious adverse experience(s); (2) serious adverse experience(s) resulting in death (and, if so, cause(s) of death); and (3) any serious adverse experience(s) involving the diagnosis of a *S. aureus* infection.

[13] Study staff will contact the patient every two weeks following hospital discharge through postoperative Day 90 in order to confirm that the patient did not have a *S. aureus* infection in the time period since the previous study visit.

[14] At any time through postoperative Day 90, patients will undergo a complete physical examination to evaluate for the presence of postoperative *S. aureus* infection in the event of fever, hypotension, elevated WBC (i.e., WBC count above the limit of the normal range), severe sternal pain or instability, surgical wound drainage, or other concerning symptoms/signs of infection. At that time, 2 sets of blood cultures will be obtained, as well as cultures from other sites of infection, as indicated by the signs and symptoms presented. All cultures positive for *S. aureus* from blood, mediastinum, or other sites of infection will undergo antibiotic susceptibility testing at the investigator site (or site's local microbiology laboratory). Isolates from positive *S. aureus* cultures will also be forwarded to a central laboratory for more detailed evaluation (i.e., clonal and genotype analysis). In addition, radiographic studies (e.g., chest X-ray or CT, MRI, ultrasound) and other histopathological studies should be performed as clinically indicated by the signs, symptoms, and physical examination. All relevant microbiology, histopathologic and radiographic reports should be translated to English and saved for potential submission to the independent efficacy endpoint adjudication committee (EEAC).

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary Efficacy Objective and Hypothesis

Objective: To demonstrate that a single dose of V710 administered prior to cardiothoracic surgery will reduce the proportion of adult patients who acquire *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections through postoperative Day 90. For this study, a *S. aureus* deep sternal wound infection includes *S. aureus* mediastinitis or a *S. aureus* deep incisional surgical-site infection involving the sternal wound.

Hypothesis: Adult patients who receive a single dose of V710 prior to cardiothoracic surgery will have a lower incidence of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections through postoperative Day 90 as compared with those patients who receive placebo. *The statistical criterion for success requires that the lower bound of the 95% confidence interval for the vaccine efficacy excludes 20% or less.*

2.1.2 Primary Safety Objective and Hypothesis

Objective: To evaluate the safety profile of a single dose of V710 administered to adult patients prior to cardiothoracic surgery.

Hypothesis: Vaccination with a single dose of V710 will be generally well tolerated in adult patients planning to undergo cardiothoracic surgery.

2.1.3 Secondary Efficacy Objectives and Hypotheses

1. Objective: To demonstrate that a single dose of V710 administered prior to cardiothoracic surgery will reduce the proportion of adult patients who acquire any invasive *S. aureus* infection through postoperative Day 90. For this study, an invasive *S. aureus* infection includes *S. aureus* bacteremia, *S. aureus* deep sternal wound infections, a deep-tissue organ/space *S. aureus* infection at another surgical site, or any other deep-tissue *S. aureus* infection (e.g., *S. aureus* osteomyelitis/septic arthritis, peritonitis, pneumonia, empyema, etc.).

   Hypothesis: Adult patients who receive a single dose of V710 prior to cardiothoracic surgery will have a lower incidence of invasive *S. aureus* infections through postoperative Day 90 as compared with those patients who receive placebo. *The statistical criterion for success requires that the lower bound of the 95% confidence interval for the vaccine efficacy excludes 0%.*

2. Objective: To demonstrate that a single dose of V710 administered prior to cardiothoracic surgery will reduce the proportion of adult patients who acquire any *S. aureus* surgical-site infection through postoperative Day 90. For this study, a surgical-site infection includes any superficial incisional, deep incisional, or organ/space *S. aureus* infections at the sternotomy site, the vascular harvest (donor)

site(s), or any other site at which a surgical intervention/procedure was performed (e.g., chest tube placement site).

Hypothesis: Adult patients who receive a single dose of V710 administered prior to cardiothoracic surgery will have a lower incidence of any *S. aureus* surgical-site infections through postoperative Day 90 as compared with those patients who receive placebo. *The statistical criterion for success requires that the lower bound of the 95% confidence interval for the vaccine efficacy excludes 0%.*

2.1.4 Exploratory Objectives

2.1.4.1 Exploratory Efficacy Objectives

1. To demonstrate that a single dose of V710 administered prior to cardiothoracic surgery will reduce the proportion of adult patients who acquire *S. aureus* bacteremia and/or a *S. aureus* deep sternal wound infection through postoperative Day 45.

2. To demonstrate that a single dose of V710 administered prior to cardiothoracic surgery will reduce the proportion of adult patients who acquire any *S. aureus* infection through postoperative Day 90. For this study, a *S. aureus* infection is defined as any invasive *S. aureus* infection, any surgical-site *S. aureus* infection, or any other *S. aureus* infection (e.g., *S. aureus* catheter-site infection, *S. aureus* cellulitis, *S. aureus* impetigo, etc.).

3. To evaluate the proportion of patients with nasopharyngeal *S. aureus* colonization through postoperative Day 90.

2.1.4.2 Exploratory Immunogenicity Objectives

1. To evaluate the immune response in patients receiving a single dose regimen of V710 at the time of hospitalization for surgery (Day 14 to Day 60 postvaccination), postoperative Day 45, and postoperative Day 90.

2. To evaluate the long-term immune response in a subset of patients (N=400) receiving a single dose of V710 through postoperative Day 360.

2.1.4.3 Exploratory Health Care Resource Utilization and Outcomes Research Objectives

1. To evaluate the overall mortality and the mortality due to *S. aureus* infection in patients receiving a single dose of V710 as compared to placebo.

2. To evaluate the duration of hospitalization, the type of hospitalization care (i.e., in intensive-care unit or non-intensive care unit), and the rate of rehospitalization for *S. aureus* infections in patients receiving a single dose of V710 as compared to placebo.

3. To evaluate the need for follow-up surgical debridement or other surgery as a result of *S. aureus* infection in patients receiving a single dose of V710 as compared to placebo.

   These exploratory health care resource utilization/outcomes research measures will be evaluated for the S. aureus infections comprising the primary efficacy endpoint (i.e., S. aureus bacteremia and/or S. aureus deep sternal wound infections) and those infections comprising the secondary efficacy endpoint (i.e., any invasive or surgical-site S. aureus infections). The exploratory health care resource utilization/outcomes research measures will also be assessed for the subset of MRSA infections that meet the preceding criteria.

2.2 PATIENT INCLUSION CRITERIA

1. Patient is 18 years of age or greater.

2. Patient is scheduled to undergo cardiothoracic surgery involving a full median sternotomy (not including cardiac transplantation surgery) within 14 to 60 days postvaccination.

3. Patient is able to understand all study procedures and agrees to participate in the study by providing written informed consent.

4. Patient intends to participate for the entire study duration (i.e., through postoperative Day 90 for the purposes of active efficacy surveillance for all patients; through postoperative Day 360 for long-term safety surveillance for all patients; and through postoperative Day 360 for long-term immunogenicity and nasal colonization surveillance for a subset of patients [N=400]).

5. Female patients of reproductive potential are required to have a negative urine or serum pregnancy test immediately prior to study vaccination. Female patients of reproductive potential must have been using an acceptable form of birth control for two weeks prior to enrollment, and agree to use an acceptable method of birth control for one month postvaccination. Acceptable methods of birth control include use of hormonal contraceptives, intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, tubal ligation, condoms, or abstinence.

   NOTE: A female patient who is <u>not</u> of reproductive potential is defined as: (1) One who has reached menopause (no menses for one year); (2) undergone hysterectomy, bilateral oophorectomy, or tubal ligation; (3) is in an exclusively homosexual relationship; or (4) is in an exclusive relationship with a partner who has had a successful vasectomy. A successful vasectomy is defined as microscopic documentation of azoospermia or a vasectomy more that two years ago with no resultant pregnancy despite sexual activity postvasectomy.

2.3 PATIENT EXCLUSION CRITERIA

1. Patient developed an invasive *S. aureus* infection (e.g., bacteremia, endocarditis, pneumonia, mediastinitis, osteomyelitis, etc.) in the three months prior to study entry.

2. Patient's underlying condition is sufficiently unstable so that there is a realistic (>50%) possibility that cardiothoracic surgery will be necessary within the 10 days following study entry/vaccination.

3. Patient is planning to undergo cardiothoracic surgery which does not involve a full median sternotomy (i.e., minimally invasive cardiothoracic surgery).

4. Patient is planning to undergo cardiac transplantation surgery or sternal debridement to remedy an infection resulting from a prior cardiothoracic surgery.

5. Patient has any type of ventricular-assist device in place at the time of study entry.

6. Patient has a history of anaphylaxis to any of the vaccine components.

7. Patient has previously received V710 (in either this study or a previous V710 study).

8. Patient has received any other investigational *S. aureus* vaccine or any investigational *S. aureus* antibodies within the 12 months prior to study entry.

9. Patient has a temperature of ≥100.4ºF (≥38.0ºC), oral equivalent, within 48 hours prior to study vaccination.

10. Patient has received a live virus vaccine within 30 days prior to receipt of the study vaccine or is scheduled to receive any live virus vaccine within 30 days postvaccination.

11. Patient has received any other licensed vaccine (including inactivated or recombinant vaccines) within 14 days prior to receipt of the study vaccine or is scheduled to receive any other licensed vaccine (including non-live virus vaccines) within 30 days postvaccination. *(NOTE: Influenza and pneumococcal vaccines may be administered during the study, but must be given at least 7 days prior to or at least 15 days after study vaccination).*

12. Patient was administered any immunoglobulin within 90 days prior to study vaccination or is scheduled to receive such products at any time through postoperative Day 90.

13. Patient has received treatment with systemic (intramuscular, oral, or intravenous) corticosteroids (at a prednisone-equivalent dose of ≥20 mg daily), another immunosuppressive medication (e.g., calcineurin inhibitors, mycophenolate, azathioprine), or biological agents (e.g., rituximab) in the 14 days prior to study

vaccination, or is anticipated to receive such medications for a chronic medical condition at any time through postoperative Day 90.

14. Patient has a known or suspected impairment of immunologic function including, but not limited to, the following conditions: autoimmune disease, moderate/severe hepatic insufficiency or cirrhosis, renal failure or insufficiency (on hemodialysis or peritoneal dialysis), immunoglobulin deficiency, or other congenital or acquired immunodeficiency, including HIV/AIDS.

15. Patient has a condition such as hemophilia, other severe coagulation disorders, or significantly impaired venous access, in which repeated venipuncture or injections pose more than minimal risk.

16. Patient is currently pregnant or breastfeeding, or planning to conceive at any time through postoperative Day 90.

17. Patient has a medical condition in which the expected survival is less than 90 days.

18. Patient has current evidence or a recent history (within the five years prior to study entry) of intravenous drug abuse.

19. Patient has participated in another clinical trial in the 4 weeks prior to study entry, or plans to participate in a treatment-based trial or another trial in which an invasive procedure is to be performed, at any time through postoperative Day 90. *(NOTE: Participation in a non-interventional surveillance study is acceptable at anytime during the course of this trial).*

20. Patient has a history of any condition that, in the opinion of the investigator, may pose an additional risk to the patient or confound the results of this study.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is a sequential-design, international, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy, immunogenicity, and safety of a single-dose regimen of V710 (60 μg) in ~15,000 adult patients (18 years of age or greater) scheduled to undergo cardiothoracic surgery involving a full median sternotomy in the immediate future. The study will attempt to rule out a vaccine efficacy of 20% or less based on a combined endpoint of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections out to postoperative Day 90 in patients receiving V710 relative to patients receiving placebo.

All patients will be identified, enrolled, and vaccinated at the time that cardiothoracic surgery is scheduled, provided that the surgery is anticipated to occur within 14 to 60 days following enrollment/vaccination. Patients will be randomized in a 1:1 ratio at the time of enrollment to receive either a single-dose regimen of V710 (60 μg) or placebo.

All patients enrolled in this pivotal study will be mandated to receive preoperative antibiotic prophylaxis. The guidelines for preoperative antibiotic prophylaxis for this study are provided in Appendix 6.2. All patients will receive all preoperative and perioperative standard-of-care measures provided at their specific investigative sites/institutions (i.e., all non-antimicrobial measures to reduce postoperative infections), regardless of the treatment group they have been assigned. The only variable between the treatment groups will be the administration of V710 or placebo.

Efficacy: At any time through postoperative Day 90, patients with evidence of a suspected postoperative infection (e.g., fever, elevated WBC [WBC count above the upper limit of the normal range], severe sternal pain or instability, wound drainage, or other concerning symptom/signs) will undergo a complete evaluation of symptoms, vital signs, and physical examination. The specific procedures involved in this evaluation are outlined in detail in Section 3.2.4.13.

Each case of *S. aureus* infection will be defined and categorized based on standardized definitions of nosocomial infections set forth by the United States Center for Disease Control and Prevention (CDC) [14] provided in Appendix 6.3. The primary efficacy endpoint in this study is *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections occurring through postoperative Day 90. The criteria for the primary efficacy endpoint, as well as those for the study's secondary and exploratory efficacy endpoints, are outlined in Section 2.5.1, Section 2.5.2, and Section 2.5.3, respectively.

An independent efficacy endpoint adjudication committee (EEAC) will review the validity of all potential cases of *S. aureus* infection occurring throughout the duration of the study on an ongoing basis based on the standardized definitions (see Section 3.3.3). An independent Data and Safety Monitoring Board (DSMB) will then review the efficacy from this study (based on the EEAC assessments) at periodic interim analyses (see Section 3.3.4).

Immunogenicity: All patients will provide blood samples (20 mL) for immunogenicity evaluation at prevaccination, at the time of hospitalization for surgery (Day 14 to Day 60 following vaccination), and at postoperative Day 45 and Day 90. A subset of patients enrolled in this study (N=400) will provide additional blood samples (20 mL) at postoperative Day 180, Day 270, and Day 360 to allow for a long-term evaluation of the immune response kinetics over time.

Sera will be analyzed using assays described in Section 2.6.

Safety: All patients will be monitored for the following safety parameters:

- Evidence of immediate hypersensitivity reactions for 30 minutes postvaccination.
- Local adverse experiences at the injection site from Days 1 to 5 postvaccination.
- Body temperatures (measured orally) from Days 1 to 5 postvaccination.
- All systemic/clinical adverse experiences from Days 1 to 14 postvaccination.
- All serious adverse experiences from Days 1 to 14 postvaccination.

- All vaccine-related serious adverse experiences, deaths (and cause(s) of death), and serious adverse experiences involving the diagnosis of a *S. aureus* infection throughout the duration of the study (i.e., through postoperative D360).

Safety measurements for this study are described in further detail in Section 2.7 and Section 3.4. An independent DSMB will review the safety data from this study on an ongoing basis, and in conjunction with the predefined interim efficacy analyses, as described in Section 3.3.4.

Study Duration: The total duration of follow-up for each patient will be 14 to 60 days from vaccination to cardiothoracic surgery, plus 90 days following surgery for the evaluation of vaccine efficacy. Postoperative Day 90 reflects the primary efficacy time point for all patients. In addition, all patients will be followed through postoperative Day 360 for long-term safety assessment.

A subset of patients enrolled in this study (N=400) will also be followed for long-term evaluation of immune response and nasopharyngeal *S. aureus* colonization through postoperative Day 360.

The overall study duration will be ~3 to 6 years, depending on enrollment, primary endpoint case accrual, and outcomes of the interim analyses.

2.4.2 Treatment Plan

Patients will be randomized in a 1:1 ratio to receive a single 0.5-mL injection (60 μg) of V710 or a single 0.5-mL injection of placebo (normal saline solution [0.9%]). Injections of both V710 and placebo will be administered intramuscularly (IM) by needle/syringe in the deltoid muscle.

Note: Because V710 and placebo will be provided in different formulations, certain member(s) of the site staff (study coordinator and/or pharmacist) will be unblinded to treatment groups. The unblinded person(s) will be responsible for receiving all clinical supply shipments, monitoring the ongoing clinical supply accountability (temperature), and preparing and administering the clinical supplies to all patients. In order to avoid bias, the unblinded person(s) will have limited contact with the study patients following administration of V710/placebo (i.e., the unblinded person(s) will not be involved in any postvaccination efficacy or safety assessment procedures). The unblinded person(s) must also not disclose any information regarding the allocation of the clinical supplies (V710 or placebo) to any blinded member of the site staff. Conversely, no blinded member of the site staff should have contact with the clinical supplies at any point during the course of the study.

This study is event-driven, with total enrollment estimates based on the number of accumulated cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections. The study has a group-sequential design with four separate analyses of vaccine efficacy, as outlined in Section 1.5. To achieve the required 107 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections, ~15,000 patients

will be randomized in a 1:1 ratio to receive either V710 or placebo. The sequential analysis plan in this study is summarized in Table 2-1.

Table 2-1

Sequential Analysis Plan

	Stage 1	***Stage 2***	***Stage 3***	***Final Stage***
	1st Interim Analysis (Futility)	**2nd Interim Analysis (Futility & Proof-of Concept)**	**3rd Interim Analysis**	**Final Analysis‡**
Required number of S. *aureus* cases† **(Expected Enrollment)**	24	48	77	107 **(~15,000)**

† *S. aureus* cases in this table refer to *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections.

‡ *S. aureus* cases and total enrollment numbers in the final analysis are those required to have ~90% power to achieve a lower bound of the vaccine efficacy 95% confidence interval of >20% with an assumed vaccine efficacy of 60%.

2.5 EFFICACY MEASUREMENTS

All patients will be actively evaluated for evidence of any *S. aureus* infection through postoperative Day 90 (including prior to cardiothoracic surgery). However, the primary analysis will be focused only on *S. aureus* infections occurring after the time of cardiothoracic surgery through postoperative Day 90.

At any time through postoperative Day 90, patients with evidence of a suspected postoperative infection (e.g., fever, elevated WBC [WBC count above the upper limit of the normal range], severe sternal pain or instability, wound drainage, or other concerning symptom/signs) will undergo a complete evaluation of symptoms, vital signs, and physical examination. The procedures involved in this evaluation are outlined in detail in Section 3.2.4.13.

The study site will also contact all patients (either through site visit or telephone call) on postoperative Day 180 and Day 360 to ask them whether they have had any serious adverse experiences involving the diagnosis of a *S. aureus* infection since their previous study visit.

The following subsections outline those types of *S. aureus* infections that comprise this study's primary, secondary, and exploratory efficacy endpoints.

2.5.1 Primary Efficacy Measurements

S. aureus infections that comprise the primary efficacy endpoint are defined based on standardized definitions of nosocomial infections set forth by the CDC [14]. A detailed summary of these criteria is provided in Appendix 6.3. The primary efficacy endpoint for this study is the proportion of patients with evidence of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections at any time through postoperative Day 90. These primary endpoints will be defined as follows:

***S. aureus* Bacteremia:** A case of *S. aureus* bacteremia will be defined as ≥1 positive blood culture for *S. aureus* (regardless of the presence of clinical symptoms).

***S. aureus* Deep Sternal Wound Infection:** For this study, a *S. aureus* deep sternal wound infection includes *S. aureus* mediastinitis or a *S. aureus* deep incisional surgical-site infection involving the sternal wound. Each is defined separately below:

A case of *S. aureus* mediastinitis will be defined as any infection that meets one of the following two criteria:

- A positive *S. aureus* culture from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration; **OR**
- Patient meets the following 2 criteria:
  1. Purulent discharge from the mediastinal area (i.e., from mediastinal fluid or tissue and not only from more anterior sites [including skin, subcutaneous tissue, fascial layer, or muscle layer]) positive on culture for *S. aureus*, **AND**
  2. At least one of the following signs or symptoms with no other recognized cause:
     - Fever (>38ºC [or >100.4ºF]),
     - Chest pain,
     - Sternal instability, OR
     - Radiographic evidence on either chest X-ray/CT of mediastinal widening.

A case of *S. aureus* deep incisional surgical-site infection of the sternal wound will be defined as any infection that meets the following 2 criteria:

- *S. aureus* organisms isolated from an aseptically obtained culture of deep soft tissue (involving the fascial or muscle layers) but not from mediastinal tissue or fluid, **AND**
- The patient has at least one of the following:
  1. Purulent drainage from the deep incision (from fascial or muscle layers, but not from mediastinal space);
  2. The sternal wound spontaneously dehisces or is deliberately opened by the surgeon;
  3. The patient has at least one of the following signs or symptoms: fever (>38˚ C or >100.4ºF), chest pain, or chest tenderness; OR
  4. An abscess or other evidence of infection involving the fascial or muscle layers is found on direct examination, during reoperation, or by histopathologic or radiologic examination (a stitch abscess, which is defined as minimal inflammation and discharge confined to the point of suture penetration, or other abscesses anterior to the fascial layers do not qualify).

All potential cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections occurring at anytime throughout duration of the study will be adjudicated in a blinded fashion by an independent EEAC. The roles and responsibilities of the EEAC are further outlined in Section 3.3.3; full details will be included a separate Standard Operating Procedure (SOP). With the assistance of a SPONSOR Unblinded Statistician (who is otherwise unaffiliated with the conduct of the study), the DSMB will then be responsible for reviewing the overall distribution of adjudicated cases of *S. aureus* bacteremia and *S. aureus* deep sternal wound infections (based on the EEAC assessments) in the two treatment groups (in an unblinded fashion) at the planned interim analyses. Following each interim analysis, the DSMB will make recommendations to a Merck Senior Management Committee (MSMC) regarding the continuation/termination of the study. The DSMB may recommend to the MSMC to: (1) Terminate the study early based on futility, (2) terminate the study early based on overwhelming success (only at 3rd Interim Analysis), or (3) continue enrollment. The roles and responsibilities of the DSMB are further outlined in Section 3.3.4; full details will be included in a separate SOP.

Antibiotic susceptibility testing will be performed at the investigative site (or the investigative site's local microbiology laboratory) on all positive cultures for *S. aureus* from all cases of bacteremia and/or deep sternal wound infections as described in Section 3.3.2. Isolates from all positive cultures for *S. aureus* meeting the primary endpoints will also be forwarded to the Central Laboratory designated by the SPONSOR for more detailed testing.

2.5.2 Secondary Efficacy Measurements

S. aureus infections that comprise the secondary efficacy endpoints will also be defined based on standardized definitions of nosocomial infections set forth by the CDC [14]. A detailed summary of these criteria is provided in Appendix 6.3. Secondary efficacy endpoints for this study include the following:

- The incidence of **invasive** *S. aureus* infection through postoperative Day 90. For this study, an invasive *S. aureus* infection includes *S. aureus* bacteremia; *S. aureus* deep sternal wound infections (including mediastinitis); any other deep-tissue, organ/space *S. aureus* infection at another surgical site; or any other deep-tissue *S. aureus* infection (e.g., *S. aureus* osteomyelitis/septic arthritis, peritonitis, pneumonia, empyema, etc.).
- The incidence of any *S. aureus* **surgical-site** infection through postoperative Day 90. For this study, a *S. aureus* surgical-site infection will include superficial incisional, deep incisional, or organ/space *S. aureus* infections at the sternotomy site, the vascular harvest (donor) site(s), or any other site at which a surgical intervention/procedure was performed (e.g., the chest tube placement site).

All potential cases of *S. aureus* infection occurring throughout the duration of the study that meet the secondary efficacy endpoint will also be adjudicated by an independent EEAC, as described for the primary efficacy endpoint (see Section 2.5.1).

Antibiotic susceptibility testing will be performed at the investigative site (or the investigative site's local microbiology laboratory) on all positive cultures for *S. aureus* from all infections that comprise the secondary efficacy endpoint as described in Section 3.3.2. Isolates from all positive cultures for *S. aureus* meeting the secondary endpoints will also be forwarded to the Central Laboratory designated by the SPONSOR for more detailed testing.

2.5.3 Exploratory Efficacy Endpoints

S. aureus infections that comprise the exploratory efficacy endpoints will also be defined based on standardized definitions of nosocomial infections set forth by the CDC [14]. A detailed summary of these criteria is provided in Appendix 6.3.

Exploratory efficacy endpoints for this study include:

- The proportion of patients with *S. aureus* bacteremia and/or a *S. aureus* deep sternal wound infection through postoperative **Day 45**.
- The proportion of patients with **any *S. aureus* infection** through postoperative Day 90. For this study, a *S. aureus* infection is defined as any invasive *S. aureus* infection, any surgical-site *S. aureus* infection, or any other *S. aureus* infection (e.g., *S. aureus* catheter-site infection, *S. aureus* cellulitis, *S. aureus* impetigo, etc.).
- The proportion of patients with nasopharyngeal *S. aureus* colonization at postoperative Day 90.

All potential cases of *S. aureus* infection occurring throughout the duration of the study that meet the exploratory efficacy endpoint will be adjudicated by the independent EEAC.

Antibiotic susceptibility testing will be performed at the investigative site (or the investigative site's local microbiology laboratory) on all positive cultures for *S. aureus* as described in Section 3.3.2. Similarly, all *S. aureus* specimens obtained from nasopharyngeal swab isolates (at screening and at postoperative Day 90 in all patients, and at postoperative Day 360 for a subset of patients [N=400]) will also undergo antibiotic susceptibility testing at the investigative site (or the investigative site's local microbiology laboratory) as described in Section 3.2.4.8.

Isolates from all positive cultures for *S. aureus* meeting the exploratory endpoints and isolates from nasopharyngeal swabs that are positive for *S. aureus* will not be forwarded to the Central Laboratory.

2.5.4 Exploratory Health Care Resource Utilization/Outcomes Research Measures

Exploratory health care resource utilization/outcomes research measures will be evaluated for the subset of *S. aureus* infections that comprise the primary and secondary efficacy endpoints. These measures will also be evaluated for the subset of MRSA infections that meet the primary or secondary efficacy endpoint criteria.

- An evaluation of the overall mortality and the mortality due to the *S. aureus* infection during the course of the study.
- An estimation of the duration of hospitalization, the type of hospitalization care (i.e., intensive-care unit vs. non-intensive care unit), and the rate of rehospitalization for the *S. aureus* infection.
- An evaluation for the need for follow-up surgical debridement or other surgery as a result of the *S. aureus* infection.

2.6 IMMUNOGENICITY MEASUREMENTS

All patients will provide blood samples (20 mL) for immunogenicity evaluation prevaccination, at the time of hospitalization for surgery (Day 14 to Day 60 postvaccination), at postoperative Day 45, and at postoperative Day 90.

A subset of patients to be enrolled in this study (N=400) will be followed for long-term evaluation of immune response kinetics over time. These patients will provide additional blood samples (20 mL) at postoperative Day 180, Day 270, and Day 360. The method for assigning patients (and study sites) to the long-term immunogenicity subset is outlined in Section 3.1.1.

Sera will be analyzed for 0657n-specific *S. aureus* antibodies using a total IgG assay on the LUMINEX™ platform. Sera collected from a subset of the patients in this study will also be used for functional assays (e.g., opsonophagocytic [OP] activity). Sera collected in this study may also be used for other assays in development.

2.7 SAFETY MEASUREMENTS

All patients will be monitored for 30 minutes postvaccination for any immediate hypersensitivity reactions. Patients will be asked to record local adverse experiences at the injection site and oral temperatures daily for five consecutive days postvaccination on a standardized Vaccination Report Card (VRC) (Days 1 to 5 postvaccination). Patients will also be asked to record all systemic adverse experiences for 14 days postvaccination on the VRC (Days 1 to 14 postvaccination). The VRC will be collected by study personnel and reviewed for completeness at the hospital admission visit (i.e., Day 14 to 60 postvaccination). Due to the timing of the surgery in relation to vaccination, the 14-day safety evaluation period is expected be completed prior to surgery for the majority of patients.

NOTE: Patients must actively monitor and record all local injection-site reactions and oral temperatures from Day 1 through 5 postvaccination. During the remainder of the postvaccination period (Day 1 through 14), local injection-site reactions and elevated temperatures will be passively recorded if/when they occur.

All serious adverse experiences will be reported during Days 1 to 14 postvaccination. After Day 14 postvaccination and through completion of the study (postoperative Day 360), only the following serious adverse experiences will be reported:

- Vaccine-related serious adverse experiences;
- Serious adverse experiences resulting in death (and cause(s) of death); and
- Serious adverse experiences involving the diagnosis of a *S. aureus* infection.

The safety reporting distinction between postvaccination Day 1 to 14 and throughout the remainder of the study was specifically intended to limit the excessive reporting of serious adverse experiences expected to occur frequently following major surgery (thus making the assessment of differences between the two treatment groups very difficult).

All clinical adverse experiences will be graded for intensity. Serious adverse experiences will be graded by the investigator. Nonserious clinical adverse experiences will be graded by the patient on the VRC, reviewed by the investigator, and recorded via Electronic Data Capture (EDC).

An independent DSMB will also review the safety data from this study on an ongoing basis. A full safety review will also occur at each of the interim analyses (see Section 1.5). Following each interim analysis, the DSMB may recommend to the MSMC to terminate the study early based on safety concerns. The roles and responsibilities of the DSMB pertaining to their review of the safety data from this study are outlined in Section 3.3.4. Full details will be included in a separate SOP.

2.8 DATA ANALYSIS SUMMARY

2.8.1 Overall Analysis Strategy

This is a group-sequential study design, based on a fixed number of events (i.e., cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections). As noted in Section 1.5, four separate analyses of vaccine efficacy are planned. The first and second analyses will assess futility, whereas the final two analyses will assess both futility and effectiveness. The stopping boundaries for futility or effectiveness at each analysis are based on the number of cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections observed in vaccine recipients. Based on the assumptions given in Section 2.8.2, exact binomial calculations were used to determine the stopping boundaries. Futility boundaries were chosen to guard against moving forward with study enrollment with a non-efficacious vaccine. Likewise, the effectiveness boundaries were chosen to meet the desired statistical criterion for success. At each analysis, Type I and II error probabilities are appropriately adjusted for the preceding analyses. It is noted, however, that the overall Type I error for the study would still be maintained at the one-sided α=0.025 level even if the futility boundaries were ignored at each stage.

2.8.2 Efficacy

Assuming that the number of cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections in the vaccine and placebo groups are independent Poisson random variables, an exact conditional one-sided test will be used to compare the number of study cases (patients with confirmed *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections) in the group receiving V710 versus the placebo group. The null hypothesis that the vaccine efficacy (VE)=20% versus the alternative that the VE>20%

will be tested at the one-sided 2.5% significance level (where VE=1–RR with RR being the relative risk of the vaccine compared with placebo). The statistical success criterion corresponds to the lower bound of the two-sided 95% confidence interval for vaccine efficacy being >20%. Appropriate multiplicity adjustments will be made for the planned interim analyses.

The secondary efficacy hypotheses will be tested in a similar fashion, but using a one-sided test for efficacy >0%.

The primary efficacy population will be the full analysis set (FAS) which include those patients who were vaccinated and subsequently underwent cardiothoracic surgery involving a full median sternotomy on or after Day 14 postvaccination, and on or prior to Day 60 postvaccination. Any patient developing a serious *S. aureus* infection (e.g., bacteremia, deep sternal wound infection, osteomyelitis, etc.) prior to cardiothoracic surgery will be excluded from this efficacy population.

A secondary efficacy population based on a modified intention-to-treat (MITT) population will include all patients who were vaccinated and subsequently underwent cardiothoracic surgery (irrespective of the type of sternotomy or timing relative to vaccination). Any patient developing a serious *S. aureus* infection (e.g., bacteremia, deep sternal wound infection, osteomyelitis, etc.) prior to cardiothoracic surgery will be included in this efficacy population.

An additional secondary analysis based on a per-protocol population (a subset of the FAS population with additional restrictions pertaining to adherence to protocol guidelines) will also be performed.

2.8.3 Immunogenicity

All immunogenicity analyses in this study are exploratory. The response rates (percentage of patients with ≥2-fold rise in titer from baseline), geometric mean titers (GMT), and geometric mean fold-rises (GMFR) for the 0657n-specific *S. aureus* antibodies will be provided by vaccination group at the scheduled postvaccination and postoperative time points (see Section 2.6). Other exploratory analyses may be performed to determine whether 0657n-specific *S. aureus* immune responses are associated with protection against *S. aureus* infection.

2.8.4 Safety

Safety and tolerability of V710 will be assessed by statistical and clinical evaluation of all relevant safety parameters. All subjects who are vaccinated and have any safety follow-up data will be included in the safety analyses and summaries. The primary safety endpoint of the study will be based on the incidence rate of vaccine-related serious adverse experiences observed through postoperative Day 180 in each vaccination group. Due to the potential for differing follow-up times among patients for this safety endpoint, the risk of the vaccine-related serious adverse experiences will be characterized by the incidence rate based on person-time data (i.e., number of patients with vaccine-related

serious adverse experiences per 1000 person-years). A point estimate of the risk difference (V710-Placebo) of having a vaccine-related serious adverse experience accounting for the potential differential follow-up among patients will be calculated, and a corresponding 2-tailed 95% confidence interval will be obtained using the method for analysis of Poisson rates given by Miettinen and Nurminen [21].

To provide an overall safety assessment during the 14-day follow-up period, safety measures such as the proportion of patients with: (1) Any adverse experience, (2) any injection-site adverse experience, (3) any systemic adverse experience, (4) any serious adverse experience, and (5) any discontinuation due to an adverse experience will be summarized for both vaccination groups. The risk differences on these overall safety parameters between the two groups and the corresponding 2-sided 95% CI on the risk difference will be provided using the asymptotic methods proposed by Miettinen and Nurminen [21].

For adverse experiences specifically prompted for on the VRC, such as elevated temperatures, injection-site swelling, redness, and tenderness (through Day 5 postvaccination), the risk differences between the 2 groups, the 95% CIs, and the corresponding p-values will be provided. For other adverse experiences that are reported by ≥1% of subjects in either group, the risk difference and 95% CI will be provided. Additionally, the number and percentages will be provided for all reported adverse experiences.

2.8.5 Power and Sample Size

This is an event-driven, sequential study, with a 1:1 randomization ratio between patients receiving V710 and placebo. Three interim analyses and one final analysis are planned: The first interim analysis (*Stage 1*) at 24 *S. aureus* cases of bacteremia and/or deep sternal wound infections, the second (*Stage 2*) at 48 cases, the third (*Stage 3*) at 77 cases, and the final (*Final Stage*) at 107 cases.

With a total of 107 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections, an assumed vaccine efficacy of 60%, a 1:1 randomization ratio, and a one-sided α of 0.025, the study will have an overall power of ~92.3% to conclude that the true VE>20%. If 37 cases (47.1% efficacy) were observed in the vaccine group at the final analysis, the 95% multiplicity-adjusted confidence interval for vaccine efficacy would be (20.2%, 65.8%).

At the time of the first futility analysis (24 cases) at *Stage 1*, the probability of stopping the trial for futility (i.e., observe ≥13 cases in the vaccine group) is 41.9% if the true efficacy is 0%, and 0.7% if the true efficacy is 60%.

At the time of the second interim analysis (48 cases) at *Stage 2*, the cumulative probability of stopping the trial for futility (i.e., observe ≥13 cases in the vaccine group at *Stage 1* or ≥22 cases in the vaccine group at *Stage 2*) is 78.1% if the true efficacy is 0%, and 1.3% if the true efficacy is 60%.

At the time of the third interim analysis (77 cases) at *Stage 3*, the cumulative probability of stopping the trial for futility is 95.2% if the true efficacy is 0%, and 2.0% if the true

efficacy is 60%. The cumulative probability of stopping the trial for success (i.e., observe ≤22 cases in the vaccine group at *Stage 3*) is 55.7% if the true efficacy is 60%, and 89.7% if the true efficacy is 70%. If 22 cases (60.0% efficacy) were observed in the vaccine group at this stage, the 95% multiplicity-adjusted confidence interval for vaccine efficacy would be (33.0%, 76.7%).

To accrue the required 107 cases of S. aureus bacteremia and/or S. aureus deep sternal wound infections occurring at any time during the 90-day postoperative period, an enrollment of ~15,000 patients will be required. This is based on the assumption that the incidence of this composite endpoint in the placebo group during the 90-day postoperative period is ~1.14% for the remainder of the study, the VE is 60%, the randomization ratio is 1:1, and that ~5% of the patients will be non-evaluable. The incidence rate estimate is based on the blinded rate of primary endpoints observed in all subjects prior to Protocol Amendment 003-02. As this is an event-driven and group-sequential study, the enrollment number may vary depending on the primary endpoint rate and potential early stop for futility or success.

3. PROTOCOL DETAILS

3.1 RATIONALE

3.1.1 Rationale for Study Design

A dramatic increase in the number of *S. aureus* infections occurring both in the community and in the hospital [1, 2, 3, 4, 5], coupled with the rise of antimicrobial-resistant *S. aureus* pathogens (specifically MRSA), has resulted in limited therapeutic options for patients with multiresistant isolates of *S. aureus* [1, 6, 7, 8]. Therefore, a vaccine that results in the active protection against a majority or all *S. aureus* strains could have a major impact in the reduction of *S. aureus* infections.

Rationale for Study Population (Patients Undergoing Cardiothoracic Surgery)

This study is being performed to assess the efficacy of a single-dose regimen (60 μg) of V710 to prevent *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections through postoperative Day 90 in adult patients (18 years of age or greater) who are prescheduled for cardiothoracic surgery. In addition to several secondary efficacy endpoints, this study will also evaluate the immunogenicity and general safety and tolerability of the vaccine. The decision to initiate this current study for V710 in patients undergoing cardiothoracic surgery patients is based upon of the following considerations:

- *Timing of Infection:* Patients undergoing cardiothoracic surgery are at high risk for serious *S. aureus* infections for a short period of time postoperatively. Risk of *S. aureus* infection is greatest in the first 4 to 6 weeks following surgery, and most remaining infections occur within the first 90 days [9, 12]. The immunogenicity data from the previous Phase I studies of V710 (Protocols 001 and 002) support the evaluation over this timeframe (see Section 1.3.2.1 and Section 1.3.2.2).

- *High Morbidity of S. aureus Infections:* The risk of *S. aureus* infection is particularly concerning following cardiovascular surgeries involving a full median sternotomy, as such patients are at acute risk of developing postoperative *S. aureus* deep sternal wound infections. The most concerning deep sternal wound infection is mediastinitis, which has an associated mortality of ≥40% [10, 11]. *S. aureus* bacteremia is also frequently seen in this patient population; these bloodstream infections have an attributable mortality of approximately 15% and are associated with significant morbidity and frequent metastatic complications (~10%), including endocarditis, osteomyelitis, and septic arthritis [1]. The association between *S. aureus* bacteremia and mediastinitis has been supported by several studies. In fact, two studies conducted at Duke University Medical Center found that among patients with *S. aureus* bacteremia following a median sternotomy, the positive predictive value for *S. aureus* mediastinitis ranged between 77% and 91% [9, 12]. Additionally, *S. aureus* infections following cardiothoracic surgery are associated with a 4-fold increase in hospital length of stay, a 2.5-fold increase in total medical costs, and a 4.7-fold increase in hospital-based mortality [15].

- *Acquisition of Patients for Clinical Trial*: A *S. aureus* vaccine is particularly attractive for this population because patients can be easily identified in advance of the period of high risk for *S. aureus* infection and the consequences of *S. aureus* infection in these patients are significant [10, 11]. Infections following cardiothoracic surgery alone account for 28% of all postoperative *S. aureus* infections. The number of serious *S. aureus* infections seen in postoperative patients are the highest for a given hospital stay following cardiothoracic surgery than following any other major surgery (including orthopedic, neurological, or major gastrointestinal surgery) [15].

- *Generalization of this Study Population to Other Surgical Populations*: The demonstration of vaccine efficacy in preventing *S. aureus* infections in patients undergoing cardiothoracic surgery should also be applicable to those patients undergoing other surgical procedures. For one thing, the host factors in patients undergoing cardiothoracic surgery are relatively similar to those of patients undergoing other surgeries. Specifically, underlying comorbidities (e.g., diabetes, chronic lung disease) are expected to be relatively similar to other populations undergoing major surgery, with the exception of those patients undergoing surgery related to malignancy or with severe immunosuppression. Furthermore, the age range for this surgical population is relatively similar to that in other types of major surgery (i.e., orthopedic surgery, neurosurgery) [1, 15]. Secondly, the pathophysiology for the development of a *S. aureus* infection in patients undergoing cardiothoracic surgery is not unique to this surgical population. In fact, the development of *S. aureus* bacteremia with the surgical site as a likely portal of entry is a very common pathogenesis seen in other major surgeries. Additionally, a deep sternal wound infection, as represented by *S. aureus* mediastinitis or other deep incisional infections at this site, involves direct inoculation or seeding by a hematogenous route. These mechanisms are also common to other surgeries [1].

Rationale for Efficacy Endpoint for the Study

The primary efficacy measure for this study is the proportion of patients who develop *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections [9, 16, 17] in the 90-day period following cardiothoracic surgery. The choice of this combined endpoint is based on the following considerations:

- *Clinically Relevant Endpoint: As described above, there is significantly high morbidity and mortality associated with S. aureus bacteremia and S. aureus deep sternal wound infections (and, specifically, S. aureus mediastinitis) following cardiothoracic surgery. Furthermore, the known association between S. aureus bacteremia and these S. aureus sternal wound infections [9, 12] suggests that these two events are often interrelated. Hence, the choice of a combined endpoint of S. aureus bacteremia and/or S. aureus deep sternal wound infections represents a clinically relevant endpoint for evaluation.*

- *Well-defined Endpoint: The definitions used for this study are based on criteria that have been established by the United States Centers for Disease Control and*

Prevention (CDC) [14]. Specifically, the definition of a S. aureus deep sternal wound infection will include both S. aureus mediastinitis and S. aureus deep incisional surgical-site infections involving the sternal wound; both of these types of infections are defined by the CDC [14]. These definitions are well-defined and relatively unambiguous, therefore this endpoint can be clearly interpreted in the context of a clinical trial.

- *Anticipated Efficacy of V710: V710 induces IgG antibodies against the 0657n S. aureus protein, therefore circulating antibodies against this pathogen would be expected to afford protection against S. aureus bacteremia and other S. aureus deep sternal wound infections (including mediastinitis). Notably, preclinical data for V710 has demonstrated improved survival for vaccinated mice (relative to sham-control) in the murine sepsis (S. aureus bacteremia) model and a deep-tissue S. aureus wound model. This information is described in more detail in the V710 Clinical Investigator's Confidential Information Brochure (CIB).*

The incidence of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections in patients undergoing cardiothoracic surgery with a full sternotomy is sufficiently high to permit its evaluation in a clinical trial setting. Results of a literature review have identified an incidence of up to 3% (range 1 to 3%) for a combined endpoint of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections in patients undergoing elective cardiothoracic surgery with a full sternotomy [9, 16, 17]. In fact, the highest incidence rate (~3%) occurred in those patients followed prospectively in a clinical trial setting [16]. Merck also sponsored an epidemiology risk factor study in patients undergoing cardiothoracic surgery in an effort to better estimate the incidence of serious *S. aureus* infections in this population. This study, which involved eight major U.S. tertiary-care medical centers, linked two independent data sources: (1) The clinical data collected for a national database for the Society for Thoracic Surgeons (STS); and (2) the microbiology data collected during the patients' care (at the hospital where the surgery was performed). Over 16,000 patients undergoing elective cardiothoracic surgery were included in the analyses. The estimated incidence for serious *S. aureus* infections (bacteremia and/or chest wound infections]) occurring during the 90-day postoperative period was 1.3% (ranging from 0.5 to 2.2% at specific centers) in all cardiothoracic patients and 1.6% (ranging from 0.9 to 2.5%) in the subset of patients with a confirmed full median sternotomy. This estimated incidence is most likely an underestimate of the true incidence since: (1) The analyses did not capture the infection status of patients who developed an infection but sought care at another institution after hospital discharge; and (2) the analyses did not capture all patients with confirmed sternal wound infections (as culture data regarding the site of wound infections were not available or may not have been reliably coded from all eight sites). Based on the results of the epidemiology study and the literature reviews, the SPONSOR has predicted that the true incidence of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections, if assessed in a prospective setting, should be approximately 2%.

Finally, it should also be noted that the ability of V710 to prevent other variations of *S. aureus* infections would further enhance its value to patients and physicians. Hence,

the prevention of other types of *S. aureus* infections will be added as secondary or exploratory objectives. These will include the following endpoints: (1) the incidence of any invasive *S. aureus* infection through postoperative Day 90, (2) the incidence of any *S. aureus* surgical-site infection through postoperative Day 90, (3) the incidence of any *S. aureus* infection (irrespective of site of infection) through postoperative Day 90, and (4) the incidence of nasopharyngeal *S. aureus* colonization at postoperative Day 90.

Rationale for Efficacy Time Point for the Study

The timing of the primary efficacy endpoint (i.e., through postoperative Day 90) corresponds with the expected timing for most *S. aureus* infections [9, 12]. In fact, data from the literature and the SPONSOR's retrospective epidemiology study in cardiothoracic patients confirmed that most infections (>70%) will occur within the first 45 days following surgery; in fact, the mean time from surgery to infection was 23.1 days for *S. aureus* bacteremia and 24.4 days for *S. aureus* mediastinitis (and other sternal wound infections). Thus, a 90-day postoperative endpoint represents a conservative estimate to identify most (if not all) postoperative *S. aureus* infections in this patient population.

Rationale for Long-Term Immunogenicity Subset

A subset of patients (N=400) will be identified in order to collect immunogenicity data through one year postoperatively, in order to gain information regarding the long-term kinetics of the immune response following vaccination. These patients will provide additional serum specimens at postoperative Day 180, Day 270, and Day 360. Immunogenicity data was collected through Day 360 postvaccination in one of the Phase I studies (Protocol 002), however this data was limited to a healthier (and relatively younger) group of subjects. The data from Protocol 002 was also collected following administration of a different vaccine dosage (30 μg) and formulation (liquid). The data generated from this poststudy extension phase will assist in planning for future V710 trials in other patient populations (i.e., patients with end-stage renal disease on hemodialysis and patients undergoing orthopedic surgery) in whom the risk of infection due to *S. aureus* is either longer than 3 months, or chronic in nature.

The goal of the long-term immunogenicity subset is to gain data on at least 100 patients in the V710 group through postoperative Day 360. There is concern that there may be significant dropout over the course of the 1-year follow-up period for this relatively frail patient population (either due to patient death, loss to follow-up, etc.). For this reason the cohort has been increased to 400 patients (~200 patients per treatment group).

In addition, a third nasopharyngeal swab will be collected from all patients enrolled in the long-term immunogenicity subset (N=400) for the evaluation of *S. aureus* nasal colonization at Postoperative Day 360.

A Site Validation Questionnaire distributed to all potential study sites will determine each individual site's interest in participation in the long-term immunogenicity subset, as well

as the site's ability to sufficiently follow the patients through postoperative Day 360. Sites that are selected to participate in the long-term immunogenicity subset will enroll their entire patient cohort in this subset (until the target of 400 patients is achieved). Efforts will be made to include sites from all participating countries that express interest, in order to prevent potential ethnic bias. However, consideration will be given to the number of sites per country that participate in the long-term immunogenicity subset, in order to reduce the number of sites that remain open after last patient enrolled (LPE). Additional efforts will be made to enroll patients into the long-term immunogenicity subset early in the study, in order to help ensure completion of the subset's follow-up period prior to the Clinical Study Report (CSR) cutoff date.

Rationale for Institution of International Study Enrollment

The SPONSOR proposes to conduct this study internationally, involving sites from many countries, including the United States and Europe (among others). This decision is supported by the fact that many primary measures to reduce the incidence of postoperative infections (specifically, antibiotic prophylaxis prior to cardiothoracic surgery) are universally recognized. *All sites used in this pivotal study will be mandated to implement preoperative antibiotic prophylaxis as outlined in Appendix 6.2*. Randomization within this study will be appropriately addressed at the investigator-site level (i.e., block randomization by investigator site) to ensure any other site-specific measures (i.e., non-antimicrobial measures to reduce postoperative infections) are distributed among a similar number of patients across the two treatment groups at a given site.

3.1.2 Rationale for Decisions Surrounding Vaccine Regimen, Timing, Dosage, and Formulation

Preclinical data have demonstrated the efficacy of V710 in both a murine sepsis model and a mouse disseminated infection model. The immunogenicity and tolerability of V710 was demonstrated in several Phase I clinical trials. The results of these clinical trials are discussed in Section 1.3. Additional details regarding these study results are provided in the CIB for V710.

The dosing regimen chosen for this study is a single 0.5-mL injection (60 µg) of V710 or a single 0.5-mL injection of placebo (normal saline solution [0.9%]). V710 will be provided in a refrigerated lyophilized formulation. The diluent (saline [0.45%] solution) to be used for reconstitution of the lyophilized V710 will be provided in a separate vial. V710 will be reconstituted with the saline diluent [0.45%] immediately prior to administration. The placebo to be administered in this study will be provided as normal saline solution (0.9%).

The rationales for selection of this dosing regimen are provided in the subsequent paragraphs.

Rationale for Single-Dose Vaccination Regimen and Its Timing Relative to Surgery

The results from Protocol 001 demonstrated that V710 was immunogenic following a single vaccination with any of the three dosages evaluated (5 μg, 30 μg, or 90 μg). As a result, a single-dose vaccination regimen is being employed in this study.

Although immune responses following a single dose of V710 were noted as early as Day 10 postvaccination, higher GMTs were noted on Day 14 postvaccination (as compared to Day 10 postvaccination). Additionally, a larger proportion of patients had a positive immune response (defined as a ≥2-fold increase in 0657n-specific IgG titers relative to baseline in a total IgG assay conducted on a LUMINEX™ platform) at Day 14 postvaccination relative to Day 10 postvaccination. These findings were supported by preliminary immunogenicity data from Protocol 002. As a result, the minimum time period between vaccination and the anticipated cardiothoracic surgery should be 14 days.

Patients undergoing cardiothoracic surgery are at high risk for serious *S. aureus* infections for a short period of time postoperatively. The mean time from surgery to infection is <30 days for *S. aureus* bacteremia and *S. aureus* mediastinitis [9, 12]. In Protocol 001 (and in preliminary data from Protocol 002), immune responses with V710 persisted out to Day 84 postvaccination (the last study visit). As the mean time from surgery to infection is <30 days for *S. aureus* bacteremia and *S. aureus* mediastinitis, the maximum time between vaccination and the anticipated cardiothoracic surgery should be 60 days. This will allow for sufficient immune responses to be present for at least 30 days following surgery.

Rationale for the Selected Dosage of V710 (60 μg)

Based on a consideration of a number of key factors, a 60-μg dosage of V710 has been chosen for this study. The decision was borne out of a careful review of the following factors:

- In V710 Protocol 001, the safety profiles for the two highest dosages (30 μg and 90 μg) were similar, so the dosage selection was not limited by the safety results. In fact, the safety data afforded a range of potential dosages for use in subsequent studies, and it was ideal to select a dosage that would be well-bracketed based on the available clinical experience.

- In Protocol 001, a greater proportion of subjects manifested a positive immune response and achieved higher GMTs with the 30- and 90-μg dosages, relative to the 5-μg dosage or placebo. The 5-μg dosage does not appear to provide immunogenicity commensurate with the two higher dosages. However, the point along the dose-response curve between the 5- and 30-μg dosages (where there may be a drop-off in immunogenicity), remains unknown. As a conservative measure it was important to ensure that the dosage chosen is ≥30 μg.

- In Protocol 001, the data from the functional assay (i.e., opsonophagocytic [OP] uptake assay) support the choice of a dosage ≥30 μg.

- In choosing the dosage, the SPONSOR also considered an allowance for the minor variations inherent in release assays (e.g. in-vitro potency assay [~10%]) and in the V710 manufacturing process with time, with the goal of maintaining the antigen content of the vaccine well above any potential drop-off in response.

Recognizing that the safety at the highest dosage (90 μg) was similar to the safety at the 30-μg dosage, and that there were no significant manufacturing implications in the selection, a dosage adequately bracketed between 30 μg and 90 μg was considered optimal. Based on these findings, a 60-μg dosage has been chosen for evaluation in this trial. The 60-μg dosage regimen was also studied in a clinical trial of healthy subjects (Protocol 004). The preliminary results of this trial indicate that the safety profile and immune responses associated with the lyophilized 60-μg formulation of V710 are similar to those seen with the liquid formulation of V710 evaluated in Protocols 001 and 002.

Rationale for Lyophilized Formulation of V710

Significant changes in the chemical composition of the 0657nI antigen, both in terms of oxidation and isoaspartate formation, were projected based on accelerated stability data of the refrigerated liquid formulation used in the Phase I program (Protocols 001 and 002). The deamidation and oxidation of susceptible amino acid residues are common degradation pathways for proteins. These chemical changes are particularly relevant as they may lead to charge variants, conformational changes, and protein aggregation. Hence, a decision was made to identify a new formulation to remedy the problem.

Lyophilization of V710 was considered as a measure to improve the stability of the vaccine. A lyophilized formulation candidate containing sucrose and D-mannitol as lyoprotectants was identified, and this candidate has shown encouraging stability data (>2 years based on accelerated data). As a result, this formulation will be used in the current study.

An analytical comparison of the liquid formulation (used in the Phase I studies) and the proposed reconstituted lyophilized formulation has been completed. The physical properties and potency of the reconstituted lyophilized formulation and the refrigerated liquid formulation are comparable. No significant difference in the antigenicity, as measured using the IC50 assay, was detected. Furthermore, no significant difference in immunogenicity, as measured using a traditional mouse potency assay, was detected between these 2 formulations.

The prior 2 Phase I studies (Protocols 001 and 002) were conducted using a liquid formulation of V710. An additional clinical trial (Protocol 004) was conducted to ensure the reconstituted lyophilized formulation also leads to a sufficient immune response following a single-dose administration. The preliminary results of this study trial indicate that the safety profile and immune responses associated with the lyophilized 60-μg

formulation of V710 are similar to those seen with the liquid formulation of V710 evaluated in Protocols 001 and 002.

The placebo to be administered in this study will be provided as normal saline solution (0.9%).

3.1.3 Rationale for Assay Method

The immune responses to the study vaccine in this study will be measured using a unique binding assay performed on the LUMINEX™ multianalyte profiling platform. The LUMINEX™ assay monitors the circulating levels of the 0657n-specific total immunoglobulin G (IgG) antibodies in patients. This assay was selected for two reasons: (1) It has been shown to be a successful assay with other Merck investigational vaccines; and (2) the readout is quantitative and continuous, which is an important attribute when assessing the magnitude of the response to the *S. aureus* study vaccine due to the potential for preexisting titers in many patients.

Functional antibody testing (i.e., an opsonophagocytic [OP] uptake assay) will also be performed in a subset of patients. Sera collected in this study may also be used for other assays in development.

3.2 STUDY PROCEDURES

3.2.1 Concomitant Medications/Treatments and Concomitant Vaccinations

Concomitant medications/treatments will be captured during the 30-day period preceding vaccination and during Days 1 to 14 postvaccination period (coinciding with the safety follow-up period). Patients will report the date, dose, and reason for therapy for all medications taken within the 30 days prior to receipt of V710/placebo to the study personnel at the time of enrollment. Patients will also be responsible for recording all medications taken during the Days 1 to 14 postvaccination on a standardized Vaccination Report Card (VRC). This information will be recorded by the site staff using electronic data capture (EDC).

Concomitant vaccinations will be captured during the 30-day period preceding vaccination and through postoperative Day 90 (see Section 3.2.2 for the list of prior and concomitant vaccinations prohibited in this study). Patients will be responsible for recording all vaccinations during Days 1 to 14 postvaccination on the VRC. This information will be recorded by the site staff using EDC. Investigators/site staff will then prompt the patient for any vaccinations at each of the subsequent study visits (through postoperative Day 90) and record this information via EDC.

3.2.2 Prohibited Medications/Treatments and Vaccinations

Patients enrolled in this study should not receive the following medications/treatments or vaccines during the course of the prestudy/study period:

- Any live virus vaccine within 30 days prior to or 30 days following receipt of V710/placebo.
- Any other licensed vaccines (including non-live virus vaccines) within 14 days prior to or 30 days following receipt of V710/placebo. *(NOTE: Influenza and pneumococcal vaccines may be administered during the study, but must be given at least 7 days prior to or at least 15 days following receipt of V710/placebo).*
- Any immunoglobulins within 90 days prior to receipt of V710/placebo, or at any time through postoperative Day 90.
- Systemic (intramuscular, oral, or intravenous) corticosteroids at a prednisone-equivalent dose of ≥20 mg daily within 14 days prior to receipt of V710/placebo or anticipated use of systemic corticosteroids for a chronic medical condition at any time through postoperative Day 90.
- Immunosuppressive medications (e.g., calcineurin inhibitors, mycophenolate, azathioprine) within 14 days prior to receipt of V710/placebo or anticipated use of such medications for a chronic medical condition at any time through postoperative Day 90.
- Biological agents (e.g., rituximab) within 14 days prior to receipt of V710/placebo or anticipated use of such agents for a chronic medical condition at any time through postoperative Day 90.
- V710 (in this or a previous V710 study), any other investigational *S. aureus* vaccine, or any investigational *S. aureus* antibodies within the 12 months prior to study entry or at any time through postoperative Day 360.

In the event that any of the above mentioned "prohibited" treatments becomes necessary (e.g., treatment of an emergent adverse experience), the date, dose, and reason(s) for treatment should be documented and recorded by the site staff via EDC, and a member of the SPONSOR staff should be notified.

3.2.3 Diet/Activity/Other

No special restrictions apply except those noted in the inclusion/exclusion criteria in Section 2.2 and Section 2.3. Special diet and activity precautions should be followed as per the patient's necessary postoperative care.

3.2.4 Study Procedures

Study procedures should be conducted as summarized in the Study Flow Chart in Section 1.7. The following subsections provide additional details regarding each of the study procedures.

3.2.4.1 Informed Consent

General Informed Consent

Study personnel must obtain written informed consent from each patient prior to the initiation of any study-related procedure. The patient's identity and age must be verified

prior to obtaining informed consent. Consent must be documented with a dated signature on the consent form from both the patient and the study personnel conducting the consent discussion. A copy of the signed informed consent form will be given to the patient. If the patient does not speak English, the SPONSOR may provide a certified, accurate translated informed consent form. Detailed guidelines for obtaining informed consent are provided in the Administrative Binder.

Consent and Collection of Specimens for Genetic Analysis

Specimens collected in this study will not be retained for genetic analysis.

3.2.4.2 Assignment of Baseline Number

After the patient has read and signed the informed consent, he/she will be assigned a unique baseline number. The baseline number identifies the patient for all study-related procedures that occur prior to randomization to a treatment group (at which time an allocation number will be assigned). Each investigator site will be provided with a block of unique baseline numbers to assign to patients. Baseline numbers will be 9-digit numbers, with the first 4 digits indicating the SPONSOR-assigned investigator site number and the last 5 digits a sequential list of baseline number suffixes provided by the SPONSOR (e.g., 0001-00001).

It is critical that the EDC system is used to automatically generate baseline numbers. Baseline numbers should not be assigned without the use of the EDC system. Assigning baseline numbers on paper (outside of the EDC system) may result in an incorrect baseline number being assigned to a patient. In this event, all data for the patient(s) affected would need to be deleted from EDC, and re-entered under the proper baseline number(s). This situation can be avoided by using EDC to automatically generate the baseline number.

Each baseline number will be assigned only once and baseline numbers will not be reassigned for any reason. A single patient will not be assigned more than one baseline number.

3.2.4.3 Medical History and Physical Examination

Once the patient has been assigned a baseline number, he/she will participate in screening procedures to determine study eligibility. These screening procedures will be performed on the date of study vaccination. The patient will provide a complete medical history to the study staff, including past and active conditions, procedures, and surgeries. Specifically, any prior history of *S. aureus* infections will be carefully documented during the collection of the medical history. The patient's medical history will be updated at the time of hospital admission for surgery, on the date of cardiothoracic surgery, upon hospital discharge following surgery, and at postoperative Day 45 and Day 90.

The physical examination is to be performed by a physician or nurse practitioner (or physician's assistant as applicable per individual State or Country Law) on the date of study vaccination, and must include a general review and evaluation of body systems, as

well as measurements of vital signs (including oral temperature, height, weight, sitting blood pressure, sitting pulse rate, and respiration rate). A repeat physical examination (including all vital signs excluding height) will be performed at the time of hospital admission for surgery, on postoperative Day 1, at the time of hospital discharge following surgery, and at postoperative Day 45 and Day 90. A physical examination (including all vital signs excluding height) will also be performed at any time during the 90-day postoperative period when it is deemed necessary to evaluate for the potential presence of a *S. aureus* infection (see Section 3.2.4.13).

3.2.4.4 Prevaccination Pregnancy Test

A urine or serum pregnancy test will be administered to all female patients of reproductive potential prior to vaccination or collection of immunogenicity specimens. Any patient with a positive pregnancy test must not be enrolled in the study or vaccinated.

Female patients not considered to be of reproductive potential are defined as the following:

- Reached menopause, with no menses for one year;
- Undergone hysterectomy, bilateral oophorectomy, or tubal ligation;
- Are in an exclusive homosexual relationship; or
- Are in an exclusive relationship with a partner who has had a successful vasectomy. (A successful vasectomy is defined as microscopic documentation of azoospermia or a vasectomy more than two years ago with no resultant pregnancy despite postvasectomy sexual activity).

3.2.4.5 Inclusion/Exclusion Criteria

Upon completion of the physical examination on the date of study vaccination, the patient's study eligibility will be determined based on the inclusion/exclusion criteria provided in Section 2.2 and Section 2.3.

If for any reason the patient fails to meet the eligibility criteria, then complete rescreening will be necessary for study participation at a later date (i.e., all screening procedures must be repeated during rescreening). Patients who do not meet the study inclusion/exclusion criteria and are excluded from the study must provide minimum demographic and status information as described in Section 3.2.5.

3.2.4.6 Randomization/Allocation

After written consent has been obtained, all screening procedures have been completed, and the inclusion/exclusion criteria have been satisfactorily met, the patient will be assigned an allocation number based upon allocation schedules provided by the SPONSOR. These allocation schedules will be generated by a SPONSOR staff member who is otherwise not involved with the conduct of the study. Allocation numbers are 5-digit numbers (e.g., 00001).

Randomization within this study will be appropriately addressed at the study site level (i.e., unique blocks of allocation numbers will be assigned to each study site by an Interactive Voice Response System [IVRS]). This will ensure that any site-specific variables are distributed among a similar number of patients across the two treatment groups at a given site. IVRS will then assign these allocation numbers to individual patients, thereby randomizing them into one of the two treatment groups. There will be no repetition of allocation numbers throughout the study or across investigative sites. The allocation number assigned to a given patient will never change and once assigned, an allocation number cannot be reassigned to another patient for any reason.

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.4.7 Collection, Handling and Storage of Serum Immunogenicity Specimens

Blood (20 mL) for immunogenicity evaluation will be drawn from all patients via venipuncture at four time points: (1) The date of vaccination; (2) the date of hospital admission for surgery (14 to 60 days postvaccination); (3) postoperative Day 45; and (4) postoperative Day 90.

A subset of patients (N=400) to be enrolled in a long-term immunogenicity subset will provide blood (20 mL) at three additional time points for evaluation of long-term immune response kinetics. These additional specimens will be provided on postoperative Day 180, Day 270, and Day 360.

All blood specimens should be drawn trauma-free, and be allowed to clot in the collection tube (with no additives) for 30 to 60 minutes at room temperature. Venipuncture supplies for drawing all blood will be provided by the investigative site. ***Newly collected blood specimens must not be refrigerated as this will cause hemolysis.*** Once clotted, the specimen should be centrifuged, with the serum separated from the clot within two hours of collection of the specimen. The separated serum should be collected into two equal aliquots (~5 mL each) in the 8-mL Cryovials provided by the SPONSOR. Every effort should be made to collect a minimum of 10 mL of ***serum*** per each time point. However, all serum specimens collected should be retained and shipped to the SPONSOR, regardless of volume collected. At the end of the study, no serum specimens should be retained at the site.

Once aliquotted into the provided 8-mL Cryovials, the serum specimens should be labeled with the preprinted, barcoded labels provided by the SPONSOR and frozen immediately. Serum must be maintained in a -20ºC to -70ºC freezer until shipped to the SPONSOR.

All sera collected in this study will be analyzed as outlined in Section 3.3.6.

3.2.4.8 Collection of Nasopharyngeal Swab for Evidence of *S. aureus* Colonization

Nasopharyngeal swabs will be collected prior to vaccination and at postoperative Day 90 for all patients in order to detect evidence of *S. aureus* colonization.

The subset of patients (N=400) to be followed in a long-term immunogenicity subset will submit an additional nasopharyngeal swab on postoperative Day 360 to detect the long-term effect of vaccination on S. aureus nasopharyngeal colonization. The method for assigning patients (and study sites) to the long-term immunogenicity subset is outlined in Section 3.1.1.

Nasopharyngeal swabs will be supplied by the study site. To test for *S. aureus* nasopharyngeal colonization, specimens will be collected per the study site's (or local microbiology laboratory's) collection methods.

All nasopharyngeal swab cultures will be tested at the investigator site (or site's local microbiology laboratory). Only cultures positive for *S. aureus* will undergo antibiotic susceptibility testing at the investigator site (or site's local microbiology laboratory) using standard Clinical Standard Laboratory Institute (CSLI) methods (or regional equivalent). Once the results of the nasopharyngeal swab culture have been confirmed (including antibiotic susceptibility for those swab cultures that test positive for *S. aureus*), then the nasopharyngeal swabs and culture materials may be discarded.

3.2.4.9 Collection of Society of Thoracic Surgeons (STS) Risk Scores

As part of the screening process for each patient, specific preoperative variables will be collected in order to calculate a Society of Thoracic Surgeons (STS) risk score [18]. The specific variables that will be collected (not including those collected via standard study demographics) for each patient are as follows:

- Patient age
- Patient gender
- Patient body mass index (BMI)
- History of diabetes mellitus
- History of renal failure
- Recent history of congestive heart failure
- History of peripheral vascular disease
- History of chronic lung disease
- Recent history of cardiogenic shock
- History of myocardial infarction
- Need for concomitant surgery

These variables will be recorded by the study staff via electronic data capture (EDC). A total STS risk score will be calculated based on the individual risk factors collected by the study staff during patient screening. The complete scoring system for calculation of the STS risk score is provided in Appendix 6.1.

3.2.4.10 Study Vaccination

Because V710 and placebo will be provided in different formulations, certain member(s) of the site staff (study coordinator and/or pharmacist) will be unblinded to treatment groups. The unblinded person(s) will be responsible for receiving all clinical supply

shipments, monitoring the ongoing clinical supply accountability (temperature), and preparing and administering the clinical supplies to all patients. In order to avoid bias, the unblinded person(s) will have limited contact with the study patients following administration of V710/placebo (i.e., the unblinded person(s) will not be involved in any postvaccination efficacy or safety assessment procedures). The unblinded person(s) must also not disclose any information regarding the allocation of the clinical supplies (V710 or placebo) to any blinded member of the site staff. Conversely, no blinded member of the site staff should have contact with the clinical supplies at any point during the course of the study.

Preparation of V710

V710 will be provided as a lyophilized formulation in a vial, and will be provided with a diluent (saline [0.45%] solution) in a separate vial for reconstitution. To reconstitute V710, only the diluent (saline [0.45%] solution) specifically provided by the SPONSOR for this study should be used.

Using a needle and syringe, transfer the entire contents from the vial of the diluent (~0.75-0.85 mL) to the vial that contains the lyophilized V710 and gently swirl to mix thoroughly for at least 30 seconds until the lyophilized V710 is completely dissolved. Do not use if the lyophilized V710 cannot be dissolved. Using a new needle, carefully withdraw the entire contents of reconstituted V710 into the syringe to administer to the patient. A 1- to 1½ -inch, 22- to 23-gauge needle is recommended. The volumes of both the diluent and lyophilized V710 vials have been precalibrated to administer the ~0.5 mL volume of reconstituted V710 to the patient (thereby accounting for a loss of some of the volume during the reconstitution and administration process).

Preparation of Placebo

The placebo to be administered in this study will be provided as normal saline solution (0.9%).

Using a new needle, carefully withdraw 0.5 mL of the normal saline solution into the syringe to administer to the patient. A 1- to 1½ -inch, 22- to 23-gauge needle is recommended.

Administration of V710/Placebo

The unblinded person(s) should administer the V710 to the patient as soon as possible following reconstitution. If the V710 is not reconstituted and administered within 30 minutes after removal of the lyophilized V710 from the refrigerator, it should be disposed of as biohazard waste, and this should be documented on the appropriate vaccine accountability log in the Administrative Binder. In such a case, the unblinded person(s) will use an Interactive Voice Response System (IVRS) to assign replacement vials of V710/diluent to be reconstituted and administered (see Section 3.6.8).

Both the V710 and placebo are to be administered intramuscularly (IM) at a 90º angle into the deltoid muscle of the nondominant arm. However, if this is not feasible, the dominant arm may be used. If a patient has received an injection or implant contraceptive such as DEPO-PROVERA™ in both arms in the previous 9 months, or if it the patient's preference, the injection may be given in the thigh. If the injection is given in the thigh, a 1½-inch, 22- to 23-gauge needle is recommended. If NORPLANT™ is used by the patient, the arm with the implant is to be avoided. Injections should not be given within 2 cm of a tattoo, scar, or skin deformity. Data with other vaccines suggest that injections given in the gluteal muscles are frequently administered into fatty tissue rather than muscle. Such injections have resulted in a lower seroconversion rate than desired. Therefore, V710/placebo is not to be administered into the gluteal muscle.

After administration of the V710/placebo, the empty V710/diluent and placebo vials, as well as the used syringe and needles, are to be disposed of as biohazard waste.

NOTE: The V710/diluent and placebo vials are designated for specific patient allocation numbers by component ID numbers, as detailed in Section 3.6.3 and Section 3.6.8.

3.2.4.11 Postvaccination Safety Monitoring

NOTE: In order to avoid potential bias, the unblinded study person(s) responsible for vaccinating patients must not be involved in any postvaccination safety assessment procedures.

3.2.4.11.1 Immediate Postvaccination Hypersensitivity Monitoring

Immediately following study vaccination, the patient will be monitored for 30 minutes for any signs of a hypersensitivity reaction to the V710/placebo, such as swelling (of the lips, tongue, face or throat), difficulty breathing, urticaria, fatigue, dizziness, or tachycardia. If a serious hypersensitivity reaction does occur, the study staff should contact a member of the SPONSOR staff. During this 30-minute postvaccination period, a VRC will be provided to the patient (see Section 3.2.4.11.3).

3.2.4.11.2 Serious Adverse Experiences

All serious adverse experiences will be reported during the Days 1 to 14 postvaccination. As a result of the timing of cardiothoracic surgery relative to study vaccination (Day 14 to 60 postvaccination), the adverse experience reporting window will be completed for the majority of patients prior to hospital admission for surgery. Throughout the remainder of the study, only the following serious adverse experiences will be reported:

- Vaccine-related serious adverse experiences;
- Serious adverse experiences resulting in death (and cause(s) of death); and
- Serious adverse experiences involving the diagnosis of a *S. aureus* infection.

The definition of a serious adverse experience is provided in Table 3-1.

3.2.4.11.3 The Vaccination Report Card (VRC)

A VRC will be distributed to each patient during the 30-minute postvaccination safety monitoring period (see Section 3.2.4.11.1). The VRC is to be **completed by the patient**, and reviewed for completeness and accuracy by the site staff and patient at the time of hospital admission for cardiothoracic surgery. At this time, the complete VRC will be initialed and dated by the patient.

NOTE: In order to avoid potential bias, the unblinded study person(s) responsible for vaccinating patients must not be involved in any postvaccination safety assessment procedures.

Injection-Site Reactions and Temperatures

Patients will actively record on the VRC any local adverse experiences associated with the injection site that occur on Days 1 through 5 postvaccination. Patients will also actively record oral temperatures on the VRC for Days 1 through 5 postvaccination. For this study, any oral temperature ≥100.4ºF (≥38.0ºC) will be considered an "elevated temperature" and must be recorded as an adverse experience on the VRC. Digital oral thermometers will be provided by the SPONSOR.

All Adverse Experiences

Patients will record on the VRC all systemic/clinical adverse experiences and any other adverse experiences that occur on Days 1 to 14 postvaccination.

Concomitant Therapies

For any treatments, medications, or vaccinations taken during Days 1 to 14 postvaccination (as permitted per the study criteria outlined in Section 2.3), the patient will document the date, dose, and reason(s) for treatment or medication on the VRC.

Any medications taken prior to the study (in the 30 days prior to vaccination) will be documented by the site staff via EDC.

Concomitant vaccinations will be also captured during the 30-day period preceding vaccination and throughout the course of the study (through postoperative Day 90). Patients will be responsible for recording all vaccinations during Days 1 to 14 postvaccination on the VRC. Investigators/site staff will then prompt the patient for any vaccinations at each of the subsequent study visits (through postoperative Day 90) and record this information via EDC.

Completion of the VRC by the Patient

All data fields on the VRC must be completed by the patient. To validate the authenticity of the entries, the patient will initial and date the last page of the VRC after it has been reviewed by the study staff at the hospital admission visit. If discrepancies or omissions

are observed upon collection, the patient (not the site staff) must make the correction(s). Corrections are to be made with a single strikethrough of the incorrect entry, with the correct entry provided and initialed/dated by the patient. All entries in the VRC should be made by the patient in ink (preferably black). Correction fluids and pencils should never be used.

Review of the VRC by Site Staff

The site staff will review the instructions for completion of the VRC with the patient during the 30-minute postvaccination safety monitoring period. At the time of hospital admission, a final review of the VRC will be performed by the site staff (with the patient) in order to ensure that the VRC contains no discrepancies or omissions. The VRC will be collected at this visit and retained as a source document. All information provided by the patient on the VRC will be entered by the site staff via EDC.

NOTE: In the unexpected event that the patient's hospital admission visit occurs prior to Day 14 postvaccination, the VRC will still be reviewed/collected by the site staff on Day 14 postvaccination. The site staff may need to work with the patient during that hospitalization (up through Day 14 postvaccination) to ensure all relevant information through Day 14 postvaccination is collected on the VRC. The VRC must be completed for the full 14-day postvaccination period.

3.2.4.11.4 Long-Term Safety Contacts

All patients in this study will be contacted on postoperative Day 180 and Day 360 in order to evaluate the long-term safety profile of the study vaccine. These contacts may be conducted by either site visit or telephone contact. At these safety contacts, the site staff will collect the following events:

- Vaccine-related serious adverse experiences;
- Serious adverse experiences resulting in death (and cause(s) of death); and
- Serious adverse experiences involving the diagnosis of a *S. aureus* infection.

3.2.4.12 Preoperative and Perioperative Standard-Of-Care

All patients included in this pivotal study will be mandated to receive preoperative antibiotic prophylaxis.

The guidelines for preoperative antibiotic prophylaxis for this study are provided in Appendix 6.2. All patients will receive all preoperative and perioperative standard-of-care measures provided at their specific investigator sites/institutions (i.e., all non-antimicrobial measures to reduce postoperative infections), regardless of the treatment group they have been assigned. Randomization within this study will be appropriately addressed at the investigator-site level (i.e., block randomization by investigator site) to ensure any other site-specific measures are distributed among a similar number of patients across the two treatment groups at a given site.

3.2.4.13 Evaluation for Presence of Postoperative *S. aureus* Infections

NOTE: In order to avoid potential bias, the unblinded study person(s) responsible for vaccinating patients must not be involved in any postvaccination efficacy assessment procedures.

Patients will be evaluated for evidence of a postoperative *S. aureus* infection for a total of 90 days following the surgery. At any time through postoperative Day 90, patients with evidence of a suspected postoperative infection (e.g., fever, elevated WBC [WBC count above the upper limit of the normal range], severe sternal pain or instability, wound drainage, or other concerning symptoms/signs) will undergo a complete evaluation comprised of the following:

- An evaluation and assessment of all present symptoms and signs of infection will be performed.
- A physical examination including vital signs (including oral temperature, sitting blood pressure, sitting pulse rate, and respiration rate) will be performed.
- Two sets of blood cultures will be obtained. All unique isolates of *S. aureus* from blood will be saved and analyzed for antibiotic susceptibility.
- Cultures from other potential sites of infection (e.g., superficial or deep incisional wounds, or sterile, invasive sites) will also be obtained, as clinically indicated by the signs, symptoms, and physical examination. All unique isolates of *S. aureus* from other potential sites of infection will also be saved and analyzed for antibiotic susceptibility.
- Histopathological or cytological samples from potential sites of infection (e.g., from superficial or deep incisional wounds or from sterile, invasive sites) will be obtained as clinically indicated by the signs, symptoms, and physical examination.
- Radiographic studies (i.e., chest X-ray or CT, MRI, ultrasound) will be obtained from potential sites of infection (e.g., chest CT for suspected *S. aureus* mediastinitis or echocardiography for suspected *S. aureus* endocarditis), as clinically indicated by the signs, symptoms, and physical examination.

It is anticipated that most infections will be identified by the investigator and/or the study staff while the patient is still in the hospital. However, it is also recognized that many patients may be discharged to a rehabilitation center or to home prior to the development of an infection. *Therefore, it is extremely critical that patients are educated to recognize symptoms/signs suggestive of a S. aureus infection. Symptoms/signs of fever, chills/rigors, severe sternal pain or instability, wound drainage, or other symptoms/signs of concern should prompt the patient or the caregiver (at a rehabilitation center or other facility) to contact the investigator/site staff to ensure the evaluation noted above is thoroughly executed and documented.*

Following hospital discharge, study staff will contact the patient every two weeks through postoperative Day 90 in order to confirm that the patient did not have a *S. aureus* infection in the time period since the previous study visit.

All postoperative *S. aureus* infections will be defined and categorized based on standardized definitions of nosocomial infections set forth by the CDC [14]. These definitions are provided in Section 3.3.1.1 (primary efficacy endpoints), Section 3.3.1.2 (secondary efficacy endpoints), and Section 3.3.1.3 (exploratory efficacy endpoints). The complete definitions are specifically detailed in Appendix 6.3. All potential *S. aureus* cases occurring at anytime throughout the duration of the study will be adjudicated by an independent Efficacy Endpoint Adjudication Committee (EEAC) (see Section 3.3.3).

3.2.4.13.1 Collection, Storage, and Shipment of Positive *S. aureus* Cultures for Postoperative Efficacy Assessment

Collection and Testing of S. aureus Culture Isolates at the Investigator Site: The isolation and preliminary identification of *S. aureus* isolates for postoperative efficacy assessment will be conducted at the investigator site (or the site's local microbiology laboratory). The supplies for the collection, processing, and long-term storage (freezing) of the culture isolates will be provided by the site (or the site's local microbiology laboratory). All cultures from postoperative infections that grow positive for *S. aureus* will also undergo antibiotic susceptibility at the investigator site (or site's local microbiology laboratory), using standard Clinical Standard Laboratory Institute (CSLI) methods, or regional equivalent. The culture results and susceptibility (if applicable) will then be recorded by site personnel via EDC.

The investigator site is encouraged to follow the procedures that are routinely used in their local microbiology laboratory to culture all *S. aureus* pathogens. Neither the SPONSOR nor the Central Laboratory have outlined the specific procedures for collection and preparation of the *S. aureus* cultures, in order to allow flexibility in procedures utilized across different study sites and regions.

Shipment of S. aureus Culture Subisolates to the Central Laboratory: In addition to being tested at the investigator site (or site's local microbiology laboratory), all positive *S. aureus* isolates comprising the primary and secondary efficacy endpoints only will also be forwarded to the Central Laboratory designated by the SPONSOR for more detailed evaluation (i.e., clonal and genotype analysis). Specifically, the Central Laboratory will perform genotyping for the presence of pathogens associated with community-acquired *S. aureus* infections (e.g., USA-300, USA-400, etc.).

- Primary Efficacy Endpoint: *S. aureus* bacteremia and *S. aureus* deep sternal wound infections (see Section 3.3.1.1 for complete primary efficacy endpoint criteria).
- Secondary Efficacy Endpoint: Invasive *S. aureus* infections and *S. aureus* surgical-site infections (see Section 3.3.1.2 for complete secondary efficacy endpoint criteria).

Instructions for the collection and shipment of subisolates to be forwarded to the Central Laboratory are provided in a separate laboratory manual provided by the Central Laboratory.

Retention of Back-up Isolates Positive for S. aureus: A back-up isolate of all *S. aureus*-positive cultures is required to be stored (frozen) at each investigator site (or site's local

microbiology laboratory) for the duration of the study. Local microbiology laboratory procedures and materials should be utilized for the storage of back-up isolates positive for *S. aureus*.

3.2.4.14 Evaluation of *S. aureus* Health Care Resource Utilization/Outcomes Research

NOTE: In order to avoid potential bias, the unblinded study person(s) responsible for vaccinating patients must not be involved in any postvaccination health care resource utilization assessment procedures.

In order to evaluate exploratory healthcare resource utilization objectives, detailed information will be collected on all patients who develop the following types of postoperative *S. aureus* infections comprising the primary and secondary efficacy endpoints for this study: (1) bacteremia and/or deep sternal wound infections; (2) invasive infections; and (3) surgical-site infections.

The site staff will collect the following information via EDC:

- *Whether the patient died during the course of the study.*
- *Whether a patient's death during the course of the study was attributed to the S. aureus infection:* For this study, a death will be attributed to the *S. aureus* infection if either of the following 2 criteria are satisfied: (a) the investigator determined that the death was a result of the *S. aureus* infection or its complication, OR (b) the patient had microbiological or histopathological evidence of *S. aureus* infection at the time of death or within 48 hours of death (either in premortem evaluations or at autopsy).
- *The total duration of hospitalization for a S. aureus infection in the patient*: This will include the duration (in days) from the time of surgery onset until hospital discharge and the duration (in days) from time of onset of the *S. aureus* infection until hospital discharge. The average duration (in days) of hospitalization for patients with a *S. aureus* infection may also be compared relative to the average duration (in days) of hospitalization for patients without a *S. aureus* infection.
- *Whether the postoperative S. aureus infection led to rehospitalization:* This analysis will be focused on those patients who were not hospitalized at the time of infection onset.
- *Whether the patient was hospitalized in an intensive care or non-intensive care setting for the postoperative S. aureus infection*: This may also include an assessment as to whether the patient had to be readmitted to an intensive care unit as a result of the *S. aureus* infection (for those patients who were still hospitalized at infection onset but in a non-intensive care setting). The total duration (in days) of intensive-care hospitalization for patients with a *S. aureus* infection may also be compared relative to the duration (in days) of intensive-care hospitalization for patients without a *S. aureus* infection.
- *Whether the postoperative S. aureus infection led to surgical debridement or other surgery.*

These exploratory health economic measures will be assessed for all *S. aureus* infections that comprise the primary and secondary efficacy endpoints, as well as the subset of methicillin-resistant (MRSA) infections that meet the primary and secondary efficacy endpoints.

3.2.5 Nonrandomized Patients

It is possible for a patient to provide written informed consent for study participation and be assigned a baseline number, yet not be randomized to a study treatment group and receive an allocation number. In this event, the site staff must collect the following patient demographic and status information via EDC:

- Visit date;
- Demographics;
- Inclusion/Exclusion criteria;
- Adverse experiences (if the adverse experience(s) caused the patient to be excluded from the study, or if the adverse experience occurred as a result of a protocol-specified intervention); and
- Disposition (primary reason for exclusion from the study).

3.2.6 Blinding/Unblinding

This is a double-blind study in which the patient, the investigator (and site staff), and members of the SPONSOR staff directly involved in the conduct of the study will remain blinded to the treatment administered to all patients.

NOTE: Because V710 and placebo will be provided in different formulations, certain members of the site staff (study coordinator and/or pharmacist) will be unblinded to treatment groups. The unblinded person(s) will be responsible for receiving all clinical supply shipments, monitoring the ongoing clinical supply accountability (temperature), and preparing and administering the clinical supplies to all patients. In order to avoid bias, the unblinded person(s) will have limited contact with the study patients following administration of V710/placebo (i.e., the unblinded person(s) will not be involved in any postvaccination efficacy or safety assessment procedures). The unblinded person(s) must also not disclose any information regarding the allocation of the clinical supplies (V710 or placebo) to any blinded member of the site staff. Conversely, no blinded member of the site staff should have contact with the clinical supplies at any point during the course of the study.

Members of the SPONSOR staff who will remain blinded to treatment groups at the patient level throughout the duration of the study (through the time that all study data has been collected, screened, cleaned, and the study database has been locked) include: (1) SPONSOR Clinical Monitor(s) responsible for monitoring safety and conduct of the study; (2) SPONSOR Clinical Research Personnel responsible for scientific conduct of the study; (3) SPONSOR Clinical Operations Personnel responsible for the operational aspects of the study; (4) SPONSOR Clinical Research Associates (CRA) responsible for the blinded site-monitoring activities; (5) SPONSOR Worldwide Clinical Data Management Organization (WCDMO) personnel responsible for reviewing study data;

(6) all SPONSOR laboratory personnel involved in the conduct of immunogenicity assays for the study; and (7) international SPONSOR subsidiary personnel responsible for the conduct of the study.

For the purposes of emergency unblinding, the Interactive Voice Response System (IVRS) can be used to unmask the treatment group assignments for individual patients (see Section 3.6.5). The IVRS unmasking feature is intended to be used only in situations that require emergency unblinding of the patient (e.g., knowledge of the exact treatment group administered to the patient is necessary for treatment of a serious adverse experience).

In the event that an individual patient becomes unblinded to treatment group (either accidental unblinding or emergency unblinding for a serious adverse experience), the investigator must do the following:

- Immediately notify the SPONSOR Clinical Monitor or Clinical Research Personnel.
- Promptly document the circumstances in the patient's study chart.
- Document the unblinding on the Patient Unblinding Log located in the Administrative Binder.

Every effort should be made to contact the SPONSOR Clinical Monitor or Clinical Research Personnel prior to performing an emergency unblinding of any patient.

3.2.6.1 In-House Blinding Procedures Following Clinical Study Report (CSR) Cutoff Date

This study will be conducted using in-house blinding procedures. In the event of a stop for success, the official clinical database will be unblinded when medical/scientific review has been completed, data have been declared complete, and all protocol violators have been identified by the Clinical Study Report (CSR) cutoff date. At this time, all patient safety data declared complete will be summarized in the CSR; the remaining data reported subsequent to CSR cutoff date will then be summarized in a separate report.

Following the CSR cutoff date, the responsibilities for ongoing monitoring and conduct of the study (i.e., the remaining postoperative Day 360 safety contacts) will be transferred to personnel (Clinical Monitor and Clinical Research Personnel) who will remain blinded to patient treatment assignments and will not have access to any unblinded data.

3.2.6.2 Discontinuation/Withdrawal from Study

Patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a patient has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are

present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.4.

3.2.7 Study Visits and Variance

As noted on the Study Flow Chart (see Section 1.7), study visits are scheduled for the following time points: (1) Screening/randomization/study vaccination; (2) hospital admission for surgery (14 to 60 days postvaccination); (3) postoperative Day 1; (4) hospital discharge; and (5) postoperative Day 45 and Day 90. Additionally, for the subset of patients to be followed for long-term immune response (N=~400), study visits are also scheduled for the postoperative Day 180, Day 270, and Day 360.

All efforts should be made to ensure that the study visits are conducted per the protocol-specified timeframes. However, the following variances are permitted:

- Cardiothoracic surgery is to be performed 14 to 60 days postvaccination. However, patients who undergo cardiothoracic surgery <14 days postvaccination or >60 days postvaccination will remain in the study and complete all study procedures.
- There is a ±1-day variance permitted for the hospital admission visit (i.e., this visit may be performed the day prior to the patient's hospital admission or the day following the patient's hospital admission).
- There is a ±1-day variance permitted for the postoperative Day 1 patient visit (i.e., this visit may be performed on the actual date of cardiothoracic surgery or on postoperative Day 2) *NOTE: The postoperative Day 1 visit must be performed <u>after</u> the patient's cardiothoracic surgery.*
- There is a ±2-day variance permitted for the hospital discharge visit (i.e., the visit may be performed between 2 days prior to hospital discharge and 2 days following the date of the patient's hospital discharge).
- There is a ±10-day variance permitted for the postoperative Day 45 and Day 90 visits (e.g., the postoperative Day 45 visit may be performed between postoperative Day 35 and Day 55). *NOTE: These visits must be performed even in the event these fall outside of this variance.*
- There is a ±15-day variance permitted for the postoperative Day 180 and Day 360 long-term safety contacts (e.g., the postoperative Day 180 safety contact may be performed between postoperative Day 165 and Day 195). *NOTE: These visits must be performed even in the event these fall outside of this variance.*
- For the subset of patients to be followed for long-term immune response (N=400), there is a ±15-day variance permitted for the postoperative Day 180, Day 270, and Day 360 visits (e.g., the postoperative Day 180 visit may be performed between postoperative Day 165 and Day 195). *NOTE: These visits must be performed even in the event these fall outside of this variance.*

3.3 EFFICACY AND IMMUNOGENICITY MEASUREMENTS

3.3.1 Clinical Measurements of Efficacy

NOTE: In order to avoid potential bias, the unblinded study person(s) responsible for vaccinating patients must not be involved in any postvaccination efficacy assessment procedures.

All patients will be evaluated for evidence of any *S. aureus* infection during the course of the study (including the time period prior to cardiothoracic surgery). However, the primary analysis will be focused only on *S. aureus* infections occurring during the 90-day postoperative period.

At any time through postoperative Day 90, patients with evidence of a suspected postoperative infection (e.g., fever, elevated WBC [WBC count above the upper limit of the normal range], severe sternal pain or instability, wound drainage, or other concerning symptoms/signs) will undergo a complete evaluation comprised of the following:

- An evaluation and assessment of all present symptoms and signs of infection will be performed.
- A physical examination, including vital signs (including oral temperature, sitting blood pressure, sitting pulse rate, and respiration rate), will be performed.
- Two sets of blood cultures will be obtained. All unique isolates of *S. aureus* from blood will be saved and analyzed for antibiotic susceptibility.
- Cultures from other potential sites of infection (e.g., superficial or deep incisional wounds, or sterile, invasive sites) will also be obtained, as clinically indicated by the signs, symptoms, and physical examination. All unique isolates of *S. aureus* from other potential sites of infection will also be saved and analyzed for antibiotic susceptibility.
- Histopathological or cytological samples from potential sites of infection (e.g., from superficial or deep incisional wounds or from sterile, invasive sites) will be obtained as clinically indicated by the signs, symptoms, and physical examination.
- Radiographic studies (i.e., chest X-ray or CT, MRI, ultrasound) will be obtained from potential sites of infection (e.g., chest CT for suspected *S. aureus* mediastinitis or echocardiography for suspected *S. aureus* endocarditis), as clinically indicated by the signs, symptoms, and physical examination.

It is anticipated that most infections will be identified by the investigator and/or the study staff while the patient is still in the hospital. However, it is also recognized that many patients may be discharged to a rehabilitation center or to home prior to the development of an infection. *Therefore, it is extremely critical that patients are educated to recognize symptoms/signs suggestive of a S. aureus infection. Symptoms/signs of fever, chills/rigors, severe sternal pain or instability, wound drainage, or other symptoms/signs of concern should prompt the patient or the caregiver (at a rehabilitation center or other facility) to*

contact the investigator/site staff to ensure the evaluation noted above is thoroughly executed and documented.

Following hospital discharge, study staff will contact the patient every two weeks through postoperative Day 90 in order to confirm that the patient did not have a *S. aureus* infection in the time period since the previous study visit.

The following subsections define the types of infections that comprise the primary, secondary, and exploratory efficacy endpoints for this study. These categorizations are based on standardized definitions of nosocomial infections set forth by the United States CDC [14]. These definitions are provided in detail in Appendix 6.3.

3.3.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint for this study is the proportion of patients with evidence of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections at any time following cardiothoracic surgery through postoperative Day 90. These cases are defined as follows:

S. *aureus* Bacteremia: A case of *S. aureus* bacteremia is defined as ≥1 positive blood culture for S. aureus (regardless of the presence of clinical symptoms).

S. *aureus* Deep Sternal Wound Infection: For this study, a *S. aureus* deep sternal wound infection includes *S. aureus* mediastinitis or a *S. aureus* deep incisional surgical-site infection involving the sternal wound. Each is defined separately below:

A case of *S. aureus* mediastinitis will be defined as any infection that meets one of the following two criteria:

- A positive *S. aureus* culture from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration; **OR**
- Patient meets the following 2 criteria:
  1. Purulent discharge from the mediastinal area (i.e., from mediastinal fluid or tissue and not only from more anterior sites [including skin, subcutaneous tissue, fascial layer, or muscle layer]) positive on culture for *S. aureus*, **AND**
  2. At least one of the following signs or symptoms with no other recognized cause:
     - Fever (>38ºC [or >100.4ºF]),
     - Chest pain,
     - Sternal instability, OR
     - Radiographic evidence on either chest X-ray/CT of mediastinal widening.

A case of *S. aureus* deep incisional surgical-site infection of the sternal wound will be defined as any infection that meets the following 2 criteria:

- *S. aureus* organisms isolated from an aseptically obtained culture of deep soft tissue (involving the fascial or muscle layers) but not from mediastinal tissue or fluid, **AND**
- The patient has at least one of the following:
  1. Purulent drainage from the deep incision (from fascial or muscle layers, but not from mediastinal space).

2. The sternal wound spontaneously dehisces or is deliberately opened by the surgeon.
3. The patient has at least one of the following signs or symptoms: fever (>38˚ C or >100.4ºF), chest pain, or chest tenderness.
4. An abscess or other evidence of infection involving the fascial or muscle layers is found on direct examination, during reoperation, or by histopathologic or radiologic examination (a stitch abscess, which is defined as minimal inflammation and discharge confined to the point of suture penetration, or other abscesses anterior to the fascial layers do not qualify).

The complete CDC definitions for *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections) are also provided in Appendix 6.3.

3.3.1.2 Secondary Efficacy Endpoints

There are 2 secondary efficacy endpoints for this study: (1) The proportion of patients with evidence of **invasive** *S. aureus* infections at any time following cardiothoracic surgery through postoperative Day 90; and (2) the proportion of patients with evidence of *S. aureus* **surgical-site** infections at any time following cardiothoracic surgery through postoperative Day 90. These cases are defined as follows:

1. **Invasive *S. aureus* Infections:** Includes *S. aureus* bacteremia, *S. aureus* deep sternal wound infections (including mediastinitis), any other deep-tissue, organ/space *S. aureus* infection at another surgical site, or any other deep-tissue *S. aureus* infection (e.g., *S. aureus* osteomyelitis/septic arthritis, peritonitis, pneumonia, empyema, etc.).
2. **Surgical-Site *S. aureus* Infections:** Includes superficial incisional, deep incisional, or organ/space *S. aureus* infections at the sternotomy site, the vascular harvest (donor) site(s), or any other site at which a surgical intervention/procedure was performed (e.g., the chest tube placement site).

The complete CDC definitions for **invasive** and **surgical-site** *S. aureus* infections are provided in Appendix 6.3.

3.3.1.3 Exploratory Efficacy Endpoints

There are 3 exploratory efficacy endpoints for this study, which are defined as follows:

1. The proportion of patients with *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections at any time following cardiothoracic surgery through postoperative **Day 45** (see Section 3.3.1.1 for definitions of *S. aureus* bacteremia and/or deep sternal wound infections).
2. The proportion of patients with **any** *S. aureus* infection following cardiothoracic surgery through postoperative Day 90. For this study, **any** *S. aureus* infection includes:
   - Any invasive *S. aureus* infection;
   - Any surgical-site *S. aureus* infection;

- Any other *S. aureus* infection (e.g., *S. aureus* catheter-site infection, *S. aureus* cellulitis, *S. aureus* impetigo, etc.)

3. The proportion of patients with nasopharyngeal *S. aureus* colonization at postoperative Day 90. Further details on the collection and testing of nasopharyngeal *S. aureus* swabs are provided in Section 3.2.4.8.

The complete CDC definitions for **any** *S. aureus* infection are provided in Appendix 6.3.

3.3.2 Laboratory Measurements of Efficacy

Collection and Testing of S. aureus Culture Isolates at the Investigator Site: The isolation and preliminary identification of *S. aureus* isolates for postoperative efficacy assessment will be conducted at the investigator site (or the site's local microbiology laboratory). The supplies for the collection, processing, and long-term storage (freezing) of the culture isolates will be provided by the site (or the site's local microbiology laboratory). All cultures from postoperative infections that grow positive for *S. aureus* will also undergo antibiotic susceptibility at the investigator site (or site's local microbiology laboratory), using standard Clinical Standard Laboratory Institute (CSLI) methods, or regional equivalent. The culture results and susceptibility (if applicable) will then be recorded by site personnel via EDC.

The investigator site is encouraged to follow the procedures that are routinely used in their local microbiology laboratory to culture all *S. aureus* pathogens. Neither the SPONSOR nor the Central Laboratory have outlined the specific procedures for collection and preparation of the *S. aureus* cultures, in order to allow flexibility in procedures utilized across different study sites and regions.

Shipment of S. aureus Culture Subisolates to the Central Laboratory: In addition to being tested at the investigator site (or site's local microbiology laboratory), all positive *S. aureus* isolates comprising the primary and secondary efficacy endpoints only will also be forwarded to the Central Laboratory designated by the SPONSOR for more detailed evaluation (i.e., clonal and genotype analysis). Specifically, the Central Laboratory will perform genotyping for the presence of pathogens associated with community-acquired *S. aureus* infections (e.g., USA-300, USA-400, etc.).

- Primary Efficacy Endpoint: *S. aureus* bacteremia and *S. aureus* deep sternal wound infections (see Section 3.3.1.1 for complete primary efficacy endpoint criteria).
- Secondary Efficacy Endpoint: Invasive *S. aureus* infections and *S. aureus* surgical-site infections (see Section 3.3.1.2 for complete secondary efficacy endpoint criteria).

Instructions for the collection and shipment of subisolates to be forwarded to the Central Laboratory are provided in a separate laboratory manual provided by the Central Laboratory.

Retention of Back-up Isolates Positive for S. aureus: A back-up isolate of all *S. aureus*-positive cultures is required to be stored (frozen) at each investigator site (or site's local

microbiology laboratory) for the duration of the study. Local microbiology laboratory procedures and materials should be utilized for the storage of back-up isolates positive for *S. aureus*.

3.3.3 Efficacy Endpoint Adjudication Committee (EEAC)

The primary, secondary, and exploratory efficacy endpoints are defined in Section 3.3.1.1, Section 3.3.1.2, and Section 3.3.1.3, respectively.

The definitive diagnosis of *S. aureus* infections is often challenging. Specifically, the distinction between an invasive versus non-invasive *S. aureus* infection, or between a superficial incisional, deep incisional, and organ/space surgical-site *S. aureus* infection may occasionally pose a challenge to clinicians, as many of these infections require the interpretation of multiple components (i.e., clinical, microbiological, radiographic, and/or histopathological parameters) for diagnostic confirmation. To partially address this concern, this study will employ standardized definitions for *S. aureus* infections, which have been adapted from the CDC Guidelines for Nosocomial Infections [14]. In addition, the types of *S. aureus* infections which fulfill the primary, secondary, and exploratory efficacy endpoints (as well as the diagnostic criteria necessary to confirm these diagnoses) are included in Appendix 6.3.

Despite these efforts, it is recognized that the diagnostic classification of certain infections may be somewhat subjective, due to the careful interpretation of multiple components that is required. As a result, the SPONSOR will appoint an independent efficacy endpoint adjudication committee (EEAC) to assess data blinded to treatment group for all *S. aureus* infections identified by the investigators throughout the duration of the study. The EEAC will be comprised of three independent expert adjudicators with expertise in infectious diseases (specifically postoperative infections) who will review each applicable case and determine whether it meets the predefined endpoint criteria. As the EEAC is an independent committee, no personnel from the SPONSOR can serve as an adjudicator on the EEAC. Additionally, no member of the EEAC may participate as a primary investigator, a member of the Scientific Advisory Committee (SAC) or the data and safety monitoring board (DSMB), or be involved in any other way with the conduct of the study.

3.3.3.1 EEAC Adjudication Procedure

The general adjudication procedure for the study is outlined below. The full details regarding the adjudication process will be summarized in a separate SOP.

- All suspected *S. aureus* infections identified in this study occurring at anytime throughout the duration of the study will be sent to the SPONSOR Clinical Research team (i.e., Clinical Monitor or Clinical Research Personnel), who will remain blinded to treatment groups.
- The SPONSOR Clinical Research team will review the documentation for completeness, request any missing documentation from the investigator site, and resolve any clinical questions concerning the case with the investigator. Each case will

be assembled into a package to be provided to each member of the EEAC. All data provided to the EEAC will be blinded to treatment group. *NOTE: All cases of S. aureus infection* occurring at anytime throughout the duration of the study *must be adjudicated by the EEAC.*

- Upon review of an individual suspected case, each of the three EEAC members will provide the specific diagnosis and confirm which, if any, of the efficacy endpoints have been satisfied. In the event that that all three adjudicators agree with the assessment, it will be documented and no further discussion of the case will occur. However, if there is a discrepancy between the three EEAC members or if additional information is necessary in order to make a final determination, then the adjudicator will indicate this on the adjudication form. The additional information requested (including radiographs) will be obtained by the SPONSOR Clinical Research team, if possible, and the suspected case will be discussed by the entire EEAC during a face-to-face or teleconference meeting. During these meetings, those suspected cases in disagreement will be discussed and voted upon by all three EEAC members for final determination.
- The decision of the EEAC (either unanimous or majority vote) will be considered the final outcome. The final adjudication decision for each suspected case will be entered into the SPONSOR's database and made available to a SPONSOR Unblinded Statistician (who is not involved with development of the Statistical Analysis Plan [SAP] or the conduct of the final study analyses) for subsequent interim efficacy analyses.
- The case assessments of the EEAC will be considered final for the diagnostic clarification of *S. aureus* infections (i.e., further adjudication will not be conducted by the investigator, SAC, the DSMB, the SPONSOR, or any other individual/group).

3.3.3.2 Adjudication Package Documentation for EEAC

NOTE: In order to avoid potential bias, the unblinded study person(s) responsible for vaccinating patients must not be involved in the preparation of any adjudication package documentation.

In order to assist the independent EEAC in its adjudication of suspected *S. aureus* infections, documentation which supports the diagnosis will be submitted to the SPONSOR Clinical Research team. All potential *S. aureus* infections occurring at anytime throughout the duration of the study will be adjudicated. Sites should make every effort to prioritize collecting and submitting this documentation (including translating to English, if applicable). Examples of the supporting documentation, depending on the types and sites of *S. aureus* infection, are as follows:

- **Blood Culture Reports:** Includes reports of all blood cultures performed to confirm the diagnosis of the *S. aureus* infection.
- **Culture Reports:** Includes culture results from all specimens that are not from blood. The reports from gram stains or other specialized stains should also be included, if they help support the *S. aureus* diagnosis.

- **Procedure & Surgical Reports (Including Histopathological Reports):** Contains descriptions of clinical (gross) findings and results of the procedure or surgery, including reports of the findings from the culture or histological, pathological, or cytological exams that were performed on the surgical/biopsy specimens in support of the *S. aureus* diagnosis. Official reports of major non-surgical procedures should also be submitted if they help confirm the diagnosis of the *S. aureus* infection (e.g., echocardiography for *S. aureus* endocarditis).
- **Films and Radiographic Reports:** Includes X-ray, CT, MRI of brain/chest/ abdomen/other site) that were performed to help confirm the diagnosis of the *S. aureus* infection. The films may either be sent in as actual copies or as digitized versions on compact disc. In addition to the films, official radiologist reports need also be included. If the patient had a baseline radiograph (i.e., X-ray, CT, or MRI) of the involved infection site, the baseline films and reports will also be included to provide a basis for comparison.
- **Autopsy Report (if applicable):** Includes gross and microscopic findings with evidence of *S. aureus* infection.

3.3.4 Data and Safety Monitoring Board (DSMB)

An independent, unblinded DSMB will be appointed and be responsible for review of the interim efficacy data for this study. The DSMB will also review the accumulating safety data from the study, in conjunction with the scheduled interim efficacy reviews. The general responsibilities of the DSMB are outlined in the subsections that follow.

The full roles and responsibilities of the DSMB will be summarized in a separate SOP.

3.3.4.1 DSMB Membership

The DSMB will be comprised of 4-7 independent (i.e., non-SPONSOR) experts in operational, medical, and biostatistical aspects of clinical trials, specifically senior national (and possibly international) healthcare leaders, clinicians, and/or statisticians. One member of the DSMB will be selected to serve as Chairman. No member of the DSMB may participate as a primary investigator, a member of the Scientific Advisory Committee (SAC) or EEAC, or be involved in any other way with the conduct of the study. A SPONSOR Unblinded Statistician will act as a liaison between the EEAC and the DSMB and will be responsible for preparing the unblinded interim summaries of efficacy and safety data for this study. The DSMB Chairman will be responsible for reporting post-meeting decisions and/or recommendations to a steering committee comprised of Merck Senior Management members (Merck Senior Management Committee, or MSMC) who will hold the authority to discontinue the study in the event of overwhelmingly favorable or unfavorable efficacy results or safety concerns.

The criteria for determining overwhelmingly favorable or unfavorable efficacy results are summarized in the form of stopping boundaries provided in Table 3-2.

3.3.4.2 Summary of DSMB Responsibilities

Efficacy Data Review

A primary responsibility of the DSMB is to evaluate the efficacy data from this study *on an interim basis only*. The purpose of these interim analyses is to evaluate whether there is overwhelming efficacy or very poor efficacy (i.e., futility) with respect to the end-of-study success criteria. The SPONSOR Unblinded Statistician will perform the interim analyses, which will then be confirmed by the DSMB. Three interim analyses are planned as follows:

- ***Stage 1:*** The *first* interim analysis will be performed when 24 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have accrued.
- ***Stage 2:*** The *second* interim analysis (coinciding with proof-of-concept) will be performed when 48 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have accrued.
- ***Stage 3:*** The *third* interim analysis will be performed when 77 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have accrued.

As "suspected" cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections occur throughout the duration of the study, they will be adjudicated by the EEAC on an ongoing basis. When the predetermined number of positively-adjudicated primary efficacy cases for an interim analysis has been accrued, the DSMB will meet to evaluate the V710-placebo case split. The study stopping boundaries (which are based on the number of *S. aureus* cases observed in the vaccine group), as well as the probability of stopping given varying assumed vaccine efficacies, are summarized in Section 3.5.8 in Table 3-2. The DSMB will not have the authority to repeat (or alter) the individual case adjudications performed by the EEAC. Following each meeting, the Chairman of the DSMB will communicate the committee's decisions and/or recommendations to the MSMC. If required, the MSMC may also have access to the data presented at these interim analyses (at a treatment group level) to assist in its implementation of the DSMB's recommendations.

Safety Data Review

Another primary responsibility of the DSMB is to evaluate the unblinded safety data from this study both on an ongoing basis and at fixed interims (coinciding with the efficacy interim analyses). The timing and the extent of the ongoing safety review will be delineated in the separate SOP for the DSMB. Specifically, at the time of the 3 interim efficacy interim analyses (after 24, 48, and 77 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have accrued, respectively), the SPONSOR Unblinded Statistician will provide the DSMB with the following:

- **Serious Adverse Experiences:** A listing of serious adverse experiences that have occurred during the study, including allocation number, AE term, and date (relative to

vaccination). These will also be grouped based on treatment group, and categorized by whether they were vaccine-related or led to death or study discontinuation.

- **Most Common Adverse Experiences:** Counts of the most common (≥1% rate in any treatment group) adverse experiences by treatment group, sorted by AE term. These will also be grouped based on vaccine relationship and seriousness.

The DSMB may reserve the authority to request summaries of any other safety data that the committee determines to be of interest. The need for additional reports at these interim analyses will be assessed once the DSMB has been appointed and the study is underway.

The data cutoff points for evaluation of safety at these interim analyses will be determined by the total enrollment at the time that the respective number of cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections have accrued for a particular interim analysis.

3.3.4.3 DSMB Meetings at the Interim Analyses

Formal face-to-face or teleconference meetings of the DSMB will be scheduled for the predefined interim efficacy analyses, which are based on the accrual of cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections in the study (see Section 3.5.8.1). The Chairman of the DSMB will also have the authority to call ad hoc meetings as needed.

The DSMB will keep all interim study results (both efficacy and safety) strictly confidential. These may only be shared with the MSMC, which will also be unblinded to treatment group. However, any data shared with the MSMC will be at the treatment-group level (i.e., individual patient data will not be shared with the MSMC).

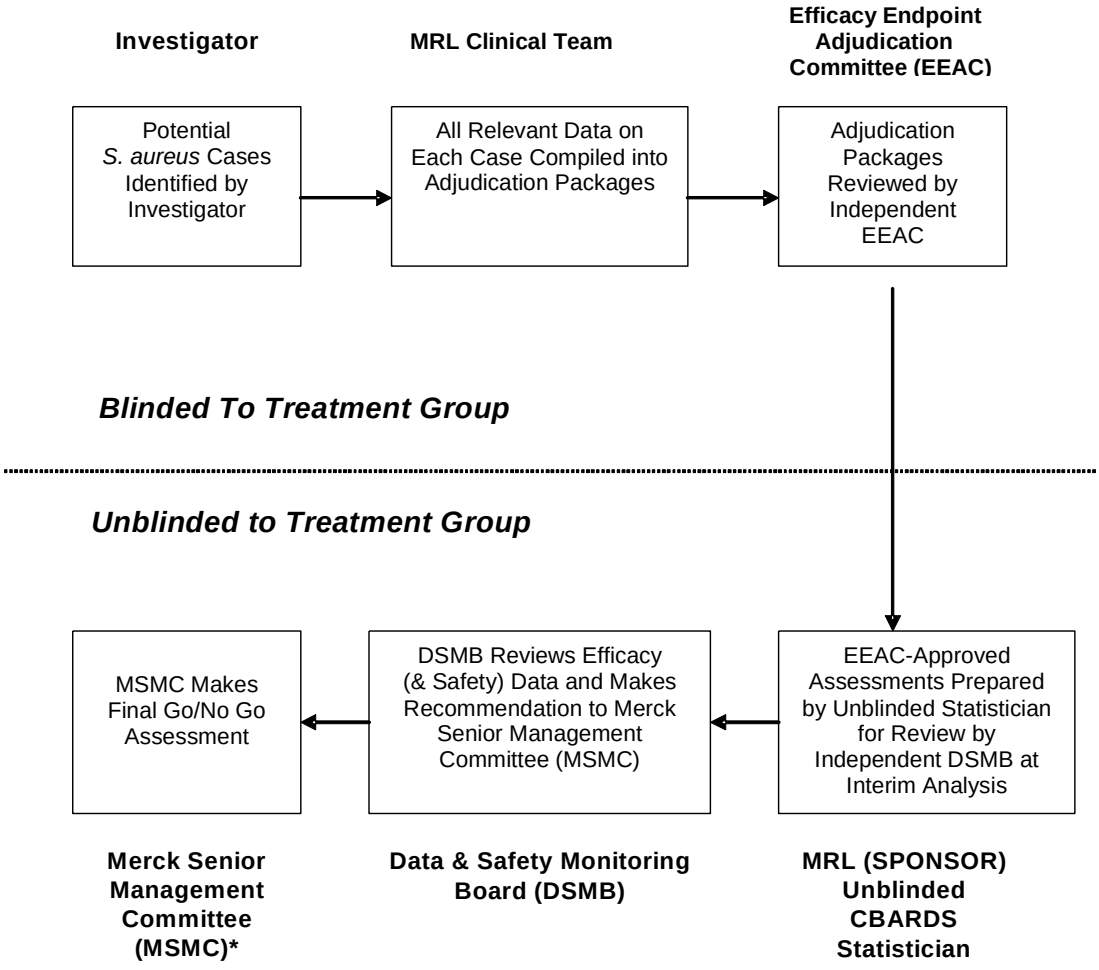
After each interim analysis meeting, it is the role of the DSMB to notify the MSMC regarding its recommendations. If the DSMB recommends that the trial be modified or terminated, the DSMB chairman will immediately contact the chairman of the MSMC. It will be the responsibility of the MSMC to implement the recommendations and to ensure the investigators and the respective Institutional Review Boards (IRBs)/Independent Ethical Committees (IECs) are properly notified. The investigator and study site staff will remain blinded to the treatment groups until the study has ended.

3.3.4.4 Overall Process Flow of Efficacy Data Between SPONSOR, EEAC, and DSMB

Figure 3-1 provides a process flow from the time that a suspected *S. aureus* case is identified by the investigator through advisement of the MSMC by the DSMB, and indicates those activities and personnel that are blinded and unblinded to treatment group.

Figure 3-1

Overall Process Flow for Efficacy Endpoint Adjudication Committee (EEAC) and Data and Safety Monitoring Board (DSMB)



* The MSMC will only be unblinded to the data at a treatment group level. The DSMB and the SPONSOR unblinded statistician will be unblinded to the data at both the treatment group level and at an individual patient level.

In summary, the members of the independent EEAC will remain blinded to the treatment administered to all patients during their adjudication of all potential *S. aureus* infections that occur at anytime throughout the duration of the study. The investigator (and study staff), SPONSOR Clinical Monitor, SPONSOR Statistician, and SPONSOR clinical research team (including Clinical Research Personnel, Clinical Operations Personnel, and Clinical Research Associates [CRA]) will also remain blinded to patient treatment groups at all times throughout the course of the study. The patient, investigator (and site staff), and the members of the SPONSOR identified above will be informed whether individual cases have been positively- or negatively-adjudicated for meeting the criteria of a *S. aureus* infection.

The SPONSOR Unblinded Statistician who will act as a liaison between the DSMB and EEAC members. This Unblinded Statistician will be responsible for tracking the final adjudications for the primary, secondary, and exploratory efficacy endpoints, evaluating the efficacy and safety data, and preparing unblinded interim analyses as described in Section 3.5.8.1 and Section 3.5.8.2. Both the SPONSOR Unblinded Statistician and the DSMB members will be unblinded to the treatment administered to all patients.

3.3.5 Scientific Advisory Committee (SAC)

A Scientific Advisory Committee (SAC) has been established for this study. The primary purpose of the SAC is to provide guidance and advice to the SPONSOR regarding the design of the protocol and the Statistical Analysis Plan (SAP). The SAC, which will convene throughout the entire course of this study, will also assist in the interpretation of the final study results and the publication efforts for this study. The SAC is comprised of both external scientific leaders and SPONSOR members. The external participants will include experts in the areas of infectious diseases (in particular, *S. aureus* infections), cardiothoracic surgery, epidemiology, and statistics. SPONSOR members of the SAC will include the Clinical Monitor, Clinical Research Personnel, Statistician, and Medical Communications Director.

Members of the SAC may also participate as primary investigators in this study; however, they may not also be members of the EEAC or DSMB.

3.3.6 Immunogenicity Measurements

All patients will provide serum specimens for evaluation of immune response to V710 at the following time points: (1) Prior to vaccination; (2) at the time of hospital admission for cardiothoracic surgery (Day 14 to Day 60 postvaccination); and (3) at postoperative Day 45 and Day 90.

A subset of patients (N=400) to be enrolled in a long-term immunogenicity subset will be followed for long-term immune response kinetics. These patients will provide additional serum specimens at postoperative Day 180, Day 270, and Day 360. The method for assigning patients (and study sites) to the long-term immunogenicity subset is outlined in Section 3.1.1.

Sera will be analyzed for 0657n-specific *S. aureus* antibodies using a total IgG assay on the LUMINEX™ platform. Sera collected from a subset of patients in this study will also be used for functional assays (e.g., opsonophagocytic [OP] activity). Sera collected in this study may also be used for other assays in development.

3.4 SAFETY MEASUREMENTS

NOTE: In order to avoid potential bias, the unblinded study person(s) responsible for vaccinating patients must not be involved in any postvaccination safety assessment procedures.

3.4.1 Clinical Measurements for Safety

All patients will be monitored for 30 minutes postvaccination for any immediate reaction to the clinical materials, with particular attention to any evidence of allergic phenomena. Local adverse experiences at the injections site and body temperatures (measured orally) will be actively monitored by the patient on Days 1 through Day 5 postvaccination. Systemic/clinical and any other adverse experiences will also be actively recorded by the patient on the VRC on Day 1 through Day 14 postvaccination.

Serious adverse experiences will be reported on Day 1 through Day 14 postvaccination. As a result of the timing of cardiothoracic surgery relative to study vaccination (Day 14 to Day 60 postvaccination), the 14-day adverse experience reporting period will be completed for the majority of patients prior to hospital admission for surgery. Throughout the remainder of the study (through postoperative Day 360), only the following serious adverse experiences will be reported:

- Vaccine-related serious adverse experiences;
- Serious adverse experiences resulting in death (and cause(s) of death); and
- Serious adverse experiences involving the diagnosis of a *S. aureus* infection.

This distinction was specifically intended to limit the excessive reporting of serious adverse experiences expected to occur frequently following major surgery (thus making the assessment of differences between the two groups very difficult).

All clinical adverse experiences will be graded for intensity. Serious adverse experiences will be graded by the investigator. Nonserious clinical adverse experiences will be graded by the patient on the VRC, reviewed by the investigator, and recorded via EDC.

An independent DSMB will also review the safety data from this study on an ongoing basis. A full safety review will also occur at each of the interim analyses. Following each interim analysis, the DSMB may recommend to the MSMC to terminate the study early based on safety concerns. The roles and responsibilities of the DSMB pertaining to their review of the safety data from this study are outlined in Section 3.3.4. Full details will be included a separate SOP.

The procedures for collecting safety measurements are described in further detail in Section 3.2.4.11.1 (immediate postvaccination hypersensitivity monitoring), Section

3.2.4.11.2 (serious adverse experiences), Section 3.2.4.11.3 (the VRC), and Section 3.2.4.11.4 (long-term safety contacts).

3.4.2 Laboratory Measurements for Safety

There will be no laboratory safety data collected for this study.

3.4.3 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

All adverse experiences will be collected from the time the consent form is signed through 14 days following study vaccination, and such events will be recorded at each examination via EDC.

Serious adverse experiences will be collected as described in Section 3.4.6.1.

3.4.4 Definition of an Overdose

For the purposes of this study, an overdose is defined as the receipt of more than one dose of V710/placebo by any patient.

Any overdose, whether or not associated with an adverse experience, must be reported within 24 hours to one of the individuals on the Contact Information Page (located in the Administrative Binder).

3.4.5 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigator(s) or their designees to report any pregnancy in a subject (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.6 Immediate Reporting of Serious Adverse Experiences to the SPONSOR

Any serious adverse experience, including death due to any cause, which occurs to any subject from the time the consent is signed through 14 days following study vaccination, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the SPONSOR contact information page found in the Administrative Binder.

Additionally, any serious adverse experience brought to the attention of an investigator who is a qualified physician at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the SPONSOR contact information page (found in the administrative binder) if the event is either:

1. A death which resulted in the patient discontinuing the study;

or

2. A serious adverse experience that is considered by an investigator who is a qualified physician to be possibly, probably, or definitely vaccine related;

or

3. A serious adverse experience that involves the diagnosis of a *S. aureus* infection.

All patients with serious adverse experiences must be followed up for outcome.

3.4.7 Evaluating Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

Refer to Table 3-1 for instructions in evaluating adverse experiences.

Table 3-1

Instructions for Evaluation of Adverse Experiences

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to word or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities) **Injection site redness or swelling from the day of vaccination through Day 5 post-vaccination will be evaluated by maximum size.**
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject/patient taking the product regardless of time to diagnosis);or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional. Any overdose whether or not associated with an adverse experience must be reported within 24 hours to one of the individuals on the Contact Information Page found in the Administrative Binder.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse experience? The determination of the likelihood that the test vaccine caused the adverse experience will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet, that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse experience based upon the available information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse experience (AE):	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g. diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject/patient reexposed to the test vaccine in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EXPERIENCE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
	The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements. **Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**	
	Definitely related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test vaccine or test vaccine class.
	Probably related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
	Probably not related	There is evidence of exposure to the test vaccine. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test vaccine. **OR** Temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable. **OR** There is another obvious cause of the AE.

3.5 DATA ANALYSIS

3.5.1 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics Department of Merck Research Laboratories. A comprehensive Statistical Analysis Plan (SAP) will be provided prior to the unblinding of the trial. This study will be conducted using in-house blinding procedures. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, data have been declared complete, and all protocol violators have been identified on all of the required patients by the CSR cutoff date.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the SAP and/or the Clinical Study Report (CSR), as appropriate.

It is important to note that the interim efficacy analyses and safety summaries will be conducted by a SPONSOR Unblinded Statistician who will not be involved with development of the SAP or conduct of the end of study analyses.

3.5.2 Study Hypotheses

3.5.2.1 Primary Hypotheses

3.5.2.1.1 Primary Efficacy Hypothesis

Adult patients who receive a single dose of V710 prior to cardiothoracic surgery will have a lower incidence of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections through postoperative Day 90 as compared with those patients who receive placebo. *(The statistical criterion for success requires that the lower bound of the 95% confidence interval for the vaccine efficacy excludes 20% or less.)*

3.5.2.1.2 Primary Safety Hypothesis

Vaccination with a single dose of V710 will be generally well tolerated in adult patients planning to undergo cardiothoracic surgery following vaccination.

3.5.2.2 Secondary Efficacy Hypotheses

1. Adult patients who receive a single dose of V710 prior to cardiothoracic surgery will have a lower incidence of invasive *S. aureus* infections through postoperative Day 90 as compared with those patients who receive placebo. *(The statistical criterion for success requires that the lower bound of the 95% confidence interval for the vaccine efficacy excludes 0%.)*

2. Adult patients who receive a single dose of V710 prior to cardiothoracic surgery will have a lower incidence of any *S. aureus* surgical-site infections through postoperative Day 90 as compared with those patients who receive placebo. *(The statistical criterion for success requires that the lower bound of the 95% confidence interval for the vaccine efficacy excludes 0%.)*

3.5.3 Variables/Time Points of Interest

3.5.3.1 Efficacy

The primary analysis of efficacy will be based on a comparison of incidences of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections through postoperative Day 90 between the vaccine and placebo arms. Secondary efficacy endpoints of interest are **invasive** *S. aureus* infections through postoperative Day 90 and any *S. aureus* **surgical-site** infections through postoperative Day 90.

3.5.3.2 Safety

Safety and tolerability of V710 will be assessed by evaluation of all relevant safety parameters. The primary safety endpoint of the study will be based on the incidence rate of vaccine-related serious adverse experiences observed through postoperative Day 180. Any adverse experiences considered by the primary investigator to be both: (1) Serious (based on criteria outlined in Table 3-1, and (2) possibly, probably, or definitely related to V710/placebo, will count towards this primary safety analysis. Key safety measures include proportions of patients with (1) any adverse experience, (2) any injection-site adverse experience, (3) any systemic adverse experience, (4) any serious adverse experience, and (5) any discontinuation due to an adverse experience. Other key safety parameters include the proportions of patients reporting elevated (≥100.4ºF [≥38.0ºC]) oral temperatures (Days 1 to 5 postvaccination), vaccine-related local adverse experiences (Days 1 to 5 postvaccination), and vaccine-related systemic adverse experiences (Days 1 to 14 postvaccination). In the event that the study stops for success, the completed safety data by the CSR cutoff date will be unblinded and summarized in the Clinical Study Report (CSR); the remaining data reported subsequent to CSR cutoff date will then be summarized in a separate report.

NOTE: All non-serious adverse experiences and serious adverse experiences will be reported for the Day 1 to 14 postvaccination time period. Throughout the remainder of the study, only the following serious adverse experiences will be reported:

- *Vaccine-related serious adverse experiences;*
- *Serious adverse experiences resulting in death (and cause(s) of death); and*
- *Serious adverse experiences involving the diagnosis of a S. aureus infection.*

This distinction was specifically intended to limit the excessive reporting of serious adverse experiences expected to occur frequently following major surgery (thus making the assessment of differences between the two groups very difficult).

3.5.3.3 Immunogenicity

An exploratory evaluation of immunogenicity will be based on a comparison of the vaccine and placebo arms with respect to 0657n-specific *S. aureus* responses (using a total IgG assay on the LUMINEX™ platform) which will include response rates (percentage of patients with ≥2-fold rise in titer from baseline), geometric mean titers (GMTs), and geometric mean fold rises (GMFR) from baseline. All patients will provide blood samples (20 mL) for immunogenicity evaluation prevaccination, at the time of hospital admission for surgery (14 to 60 days postvaccination), and at postoperative Days 45 and 90.

A subset of patients in this study (N=400) will be followed for long-term immune response. These patients will provide additional blood samples (20 mL) at postoperative Day 180, Day 270, and Day 360.

In the event the study fulfills its primary objectives, the immunogenicity data for this study may also be reviewed in the context of the available efficacy data. This analysis will be conducted in an exploratory fashion in an effort to provide a basis for identification of a correlate of immune protection. Further details will be provided in the SAP.

3.5.4 Approaches to Analyses

3.5.4.1 Efficacy

The primary analyses of efficacy will be based on the full analysis set (FAS) population and will include those patients who were vaccinated and subsequently underwent cardiothoracic surgery involving a full median sternotomy on or after Day 14 postvaccination, but on or prior to Day 60 postvaccination. Any patient developing a serious *S. aureus* infection (e.g., bacteremia, deep sternal wound infection, osteomyelitis, etc.) prior to cardiothoracic surgery will be excluded from this efficacy population.

A secondary analysis based on a modified intention-to-treat (MITT) population will be performed which will include all patients who were vaccinated and subsequently underwent cardiothoracic surgery (irrespective of the type of sternotomy or timing relative to vaccination). Any patient developing a serious *S. aureus* infection (e.g., bacteremia, deep sternal wound infection, osteomyelitis, etc.) prior to cardiothoracic surgery will be included in this efficacy population.

An additional secondary analysis based on a per-protocol population (a subset of the FAS population with additional restrictions pertaining to adherence to protocol guidelines) will also be performed.

3.5.4.2 Immunogenicity

Summaries will be based on time points relative to surgery (e.g., hospital admission at the time of surgery, postoperative Day 45, postoperative Day 90), which will encompass a window of time from vaccination (e.g., time of surgery is 14 to 60 days postvaccination).

The primary immunogenicity summaries and analyses will be based on the FAS population, as defined in Section 3.5.4.1. For observed summaries, the only additional exclusions would be patients who have a missing baseline and/or postvaccination serology result at the time point of interest.

Secondary analyses will be performed which will include all patients, regardless of type of sternotomy, timing relative to vaccination, or occurrence of serious *S. aureus* infection prior to surgery.

As the timing for surgery may vary in patients (from 14 to 60 days following vaccination), immunogenicity results may also be presented relative to the time of vaccination.

3.5.4.3 Safety

Any patient who was vaccinated will be included in the safety analyses.

3.5.5 Statistical Methods

3.5.5.1 Overall Analysis Strategy

This is a group-sequential study design, based on a fixed number of events (i.e., cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections). Four separate analyses of vaccine efficacy are planned. The first and second analyses will assess futility, whereas the final two analyses will assess both futility and effectiveness. The stopping boundaries for futility or effectiveness at each analysis are based on the number of cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections observed among vaccine recipients. Futility boundaries were chosen to guard against moving forward with enrollment with a non-efficacious vaccine. Likewise, the effectiveness boundaries were chosen to meet the desired statistical criterion for success. At each analysis, Type I and Type II error probabilities will be appropriately adjusted for the preceding analyses. It is noted, however, that the overall Type I error for the study would still be maintained at the one-sided α=0.025 level even if the futility boundaries were ignored at each stage. See Section 3.5.8 for complete details regarding the interim analyses.

3.5.5.2 Analysis of Vaccine Efficacy

The primary efficacy hypothesis will be tested using a one-sided test for efficacy >20% against *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections occurring from the time of surgery through postoperative Day 90. Assuming that the number of *S. aureus* cases of bacteremia and/or *S. aureus* deep sternal wound infections in the vaccine and placebo groups are independent Poisson random variables, an exact conditional one-sided test will be used to compare the number of study cases in the group receiving V710 versus the placebo group. The null hypothesis that the vaccine efficacy (VE)=20% versus the alternative that the VE>20% will be tested at the one-sided 2.5% significance level (where VE=1–RR, with RR being the relative risk of the vaccine compared with placebo). The statistical success criterion corresponds to the lower bound

of the two-sided 95% confidence interval for vaccine efficacy being >20%. Appropriate multiplicity adjustments will be made for the planned interim analyses using exact binomial calculations (Jennison and Turnbull [19]).

The secondary efficacy hypotheses will be tested in a similar fashion, but using a one-sided test for efficacy >0%.

The distribution of methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) pathogens will also be tabulated for each treatment group for each efficacy endpoint. Exploratory analyses to assess the impact of age (18-59 years, ≥60 years) on efficacy will also be conducted.

3.5.5.3 Analysis of Vaccine Immunogenicity

All immunogenicity analyses are exploratory in this study. At the time of hospitalization for surgery (Day 14 to Day 60 following vaccination), postoperative Day 45, and postoperative Day 90, the proportion of subjects with a positive immune response (response proportion), the GMT, and the GMFR in titer from baseline will be descriptively summarized (including 95% confidence intervals) for each group, using the FAS population. Differences in the response proportions and fold-differences in GMTs between the groups (and corresponding 95% confidence intervals) will also be calculated. Fold-differences in GMTs will be calculated using a longitudinal data analysis (LDA) method proposed by Liang and Zeger [20]. This LDA model includes both baseline and post-baseline log titers (i.e., natural logarithm of the individual titers) as response variables. The repeated measures model will include terms for treatment, time, and the interaction of treatment by time (with a restriction of the same baseline mean across treatment groups). Time will be treated as a categorical variable so that no restriction is imposed on the trajectory of the mean over time. An unstructured covariance matrix will be used to model the correlation among the repeated measures.

Summaries of the immune response proportions, GMTs, and GMFRs (from baseline) on postoperative Day 180, Day 270, and Day 360 will also be summarized by vaccination group for the subset of subjects (N=~400) followed for long-term immune response.

3.5.5.4 Analysis of Vaccine Safety

Safety and tolerability of V710 will be assessed by evaluation of all relevant safety parameters. All subjects who are vaccinated and have any safety follow-up data will be included in the safety analyses and summaries. The primary safety endpoint of the study will be based on the incidence rate of vaccine-related serious adverse experiences observed through postoperative Day 180 in each vaccination group. Any adverse experiences considered by the primary investigator to be both: (1) Serious (based on criteria outlined in Table 3-1, and (2) possibly, probably, or definitely related to V710/placebo, will count towards this primary safety analysis. Due to the potential for differing follow-up times among patients for this safety endpoint, the risk of the vaccine-related serious adverse experiences will be characterized by the incidence rate based on person-time data (i.e., number of patients with vaccine-related serious adverse

experiences per 1000 person years). A point estimate of the risk difference (V710-Placebo) of having a vaccine-related serious adverse experience accounting for the potential differential follow-up among patients will be calculated, and a corresponding two-tailed 95% confidence interval will be obtained using the method for analysis of Poisson rates given by Miettinen and Nurminen [21].

To provide an overall safety assessment during the 14-day follow-up period, safety measures such as the proportion of patients with (1) any adverse experience, (2) any injection-site adverse experience, (3) any systemic adverse experience, (4) any serious adverse experience, and (5) any discontinuation due to an adverse experience will be summarized for both vaccination groups. The risk differences on these overall safety parameters between the two groups and the corresponding two-sided 95% CI on the risk difference will be provided using the asymptotic methods proposed by Miettinen and Nurminen [21].

For adverse experiences specifically prompted for on the VRC, such as elevated temperatures, injection-site swelling, redness, and tenderness (through Day 5 postvaccination), the risk differences between the two groups, the 95% CIs, and the corresponding p-values will be provided. For other adverse experiences that are reported in ≥1% of subjects in either group, the risk difference and 95% CI will be provided. Additionally, the number and percentages will be provided for all reported adverse experiences.

3.5.6 Multiplicity

The protocol will test a single, primary efficacy null hypothesis and the study will be considered successful if it is rejected. However, as there are multiple interim efficacy analyses, appropriate adjustments (based on exact binomial calculations) for multiplicity (Jennison and Turnbull [19]) will be made to control the Type I error due to this factor (see Section 3.5.7 and Section 3.5.8 for details).

3.5.7 Sample Size and Power

For the primary efficacy hypothesis, 107 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections are required. With an assumed vaccine efficacy of 60%, a 1:1 randomization ratio, and a one-sided α of 0.025, the study will have an overall power of ~92.3% to conclude that the true VE>20%.

The power was calculated using exact methodology described in Jennison and Turnbull [19], which accounts for the interim analysis plan described below and adjusts for multiplicity.

To accrue the required 107 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections occurring at any time during the 90-day postoperative period, an enrollment of ~15,000 patients will be required. This is based on the assumption that the incidence of this composite endpoint in the placebo group during the 90-day postoperative period is ~1.14% for the remainder of the study, the VE is 60%, the

randomization ratio is 1:1, and that ~5% of the patients will be non-evaluable. The incidence rate estimate is based on the blinded rate of primary endpoints observed in all subjects prior to Protocol Amendment 003-02. As this is an event-driven and group-sequential study, enrollment number may vary depending on the primary endpoint rate and potential early stop for futility or success.

If the event rate is much lower, more patients may be enrolled, following discussion and approval from the MSMC (and other Merck Management committees).

3.5.8 Interim Efficacy Analyses

The efficacy data from this study will be evaluated on an interim basis. The interim analyses will evaluate whether there is overwhelming efficacy and/or very poor efficacy (i.e., futility) with respect to the end-of-study success criterion. Three interim analyses and one final analysis are planned:

1. ***Stage 1:*** (the first interim analysis) at 24 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections;
2. ***Stage 2:*** (the second interim analysis) at 48 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections;
3. ***Stage 3:*** (the third interim analysis) at 77 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections;
4. ***Final Stage:*** (the final analysis) at 107 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections;

Futility will be assessed at *Stage 1* and *Stage 2*, whereas both futility and efficacy will be assessed at *Stage 3* and the *Final Stage*. It is noted, however, that the overall Type I error for the study would will still be maintained at the one-sided α=0.025 level even if the futility boundaries were ignored at each stage. Also note that even though the efficacy criterion for stopping at the second interim analysis (<11 cases in the vaccine group, as defined in Protocol Amendment 003-01) was removed in Protocol Amendment 003-02, the amount of alpha-spend associated with that efficacy look (0.0564%) was retained to maintain the overall alpha-adjustment as originally planned in Protocol Amendment 003-01.

Table 3-2 lists the stopping boundaries (based on the number of cases observed in the vaccine group) and the probability of stopping given varying assumed vaccine efficacies and a 1:1 randomization ratio. For example, at the time of the first futility analysis at *Stage 1* (24 cases), the probability of stopping the trial for futility (i.e., observe ≥13 cases in the vaccine group) is 41.9% if the true efficacy is 0%, and 0.7% if the true efficacy is 60%. Likewise, at the time of the second futility analysis (48 cases) at *Stage 2*, the cumulative probability of stopping the trial for futility (i.e., observe ≥13 cases in the vaccine group at *Stage 1* or ≥22 cases in the vaccine group at *Stage 2*) is 78.1% if the true efficacy is 0%, and 1.3% if the true efficacy is 60%.

If 22 cases (60.0% efficacy) were observed in the vaccine group at *Stage 3*, the study would stop for success and the 95% multiplicity-adjusted confidence interval for vaccine efficacy would be (33.0%, 76.7%). Likewise, if 37 cases (47.1% efficacy) were observed in the vaccine group at the final analysis, the success criterion would be met and the 95% multiplicity-adjusted confidence interval for vaccine efficacy would be (20.2%, 65.8%).

Due to the logistics of the study, it is important to note that there is a chance that there may not be exactly the number of cases that are listed for each *Stage* at the interim analyses. The *Stage 1* interim analysis of futility alone will be based on the first 24 cases of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections occurring in patients in the FAS population observed in the study. Tiebreaking rules will be used in the event that several *S. aureus* cases are reported simultaneously at the time of this analysis. For the *Stage 2* and *Stage 3* interim analyses, all available cases satisfying the primary endpoint definition occurring in patients in the FAS population will be included. In the event that more cases are available, the stopping rules in Table 3-2 may no longer be appropriate for maintaining Type I error and thus new boundaries would be needed. Details for determining the new boundaries as well as the tiebreaking rules for *Stage 1* will be provided in the SAP. For the final analysis, all cases meeting the FAS population definition will be included in the primary efficacy analysis.

A SPONSOR Unblinded Statistician will perform the interim analyses. Results of the analyses will be confirmed by the DSMB with ultimate approval to stop enrollment in the study from the MSMC.

Table 3-2

Impact of Stopping Criteria on Testing an Efficacy Lower Bound >20%

Stages	Targeted Cases	Observed Vaccine Cases Futility/ Failure[†]	Observed Vaccine Cases for Success[‡]	Efficacy = 0%		Efficacy = 20%		Efficacy = 50%		Efficacy = 60%		Efficacy = 70%		Efficacy = 80%	
				Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)
1	24	>12		41.94		22.50		2.84		0.74		0.09		<0.01	
2	48	>21		78.06		50.56	0.06[§]	6.30		1.35		0.13		<0.01	
3	77	>31	<23	95.17	0.01	75.91	0.34[§]	10.94	22.36	1.96	55.69	0.14	89.73	<0.01	99.71
Final	107	>37	<38	99.91	0.09	97.58	2.42[§]	35.76	64.20	7.69	92.30	0.35	99.65	<0.01	99.99

[†] Futility corresponds to observed efficacy <0% in the vaccine group at Stage 1, observed efficacy <22% in the vaccine group at Stage 2, observed efficacy <32% in the vaccine group at Stage 3, and observed efficacy <47% in the vaccine group at the Final analysis.

[‡] Success corresponds to observed efficacy ≥60% in the vaccine group at Stage 3, and observed efficacy >47% in the vaccine group at the Final analysis.

[§] Though the efficacy criterion for stopping at the second interim analysis (<11 cases in the vaccine group, as defined in Protocol Amendment 003-01) was removed in Protocol Amendment 003-02, the amount of alpha-spend associated with that efficacy look (0.0564%) was retained to maintain the overall alpha-adjustment as originally planned in Protocol Amendment 003-01.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL MATERIALS

For studies using Controlled Substances, all Federal, State, Province, Country, etc., regulations must be adhered to in regard to the shipping, storage, handling, and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc. laws in which the study is being conducted.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be administered only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount administered to the subjects/patients, and the amount remaining at the conclusion of the study. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all unused clinical supplies must be returned as indicated on the Contact Information page(s). U.S. sites should follow instructions for the Clinical Supplies Return Form (V464) and contact the SPONSOR representative for review of shipment and form before shipping. Sites outside of the U.S. should check with local country Merck personnel for appropriate documentation that needs to be completed for vaccine accountability.

3.6.1 Patient and Replacement Supply Information

The clinical materials (V710, diluent for V710 reconstitution [0.45% saline solution], and placebo [0.9% normal saline solution]) will be packaged to support an enrollment of ~15,000 patients. The clinical supplies will be managed via an Interactive Voice Response System (IVRS) and will be packaged according to a component ID schedule generated by a member of the SPONSOR not directly involved with the conduct of the study.

3.6.2 Clinical Supply Descriptions

The investigational clinical materials will be provided by the SPONSOR as summarized in Table 3-3.

The reconstituted V710 will appear as a clear, colorless to slightly yellow liquid. If the appearance is not as described, the reconstituted V710 should be disposed of as biohazard waste, and this should be documented on the appropriate vaccine accountability log in the Administrative Binder. In such a case, the site staff will use IVRS to assign a replacement vial of V710 to be reconstituted and administered (see Section 3.6.8).

Table 3-3

Clinical Material Descriptions

Product Name & Dosage	Dosage Form	Dosing Instructions	Storage Conditions
Merck 0657nI *S. aureus* Vaccine (V710) 60 µg/0.5 mL dose	Lyophilized powder for IM injection	Administer per protocol	Store at 2 to 8º C, protect from light.
Saline Solution (0.9%) for Placebo (0.5-mL dose)	Sterile solution for IM injection	Administer per protocol	Store at room temperature (~15 to 30º C).
Saline Diluent (0.45%) for Reconstitution of V710	Sterile Solution ~0.75-0.85 mL per vial	For reconstitution of V710	Store at room temperature (~15 to 30º C).

3.6.3 Primary Packaging and Labeling Information

V710 and Placebo (Normal Saline Solution [0.9%])

V710 and placebo (normal saline solution [0.9%]) will be packaged in vials with a single-panel or multilingual booklet label. The vial label text may include the following:

- Lot Trace ID No.
- Component ID No.
- Product name and potency (if required)
- Dosage Form
- Re-evaluation date (if needed)
- Dosing Instructions
- Storage Conditions
- Compound ID/Protocol No.
- Country Regulatory Requirements
- SPONSOR Address (if applicable)
- Translation Key (if applicable)

Diluent for Reconstitution of V710 (Saline [0.45%] Solution)

The diluent (0.45%) for reconstitution of V710 will be packaged in vials with an open single-panel or multilingual booklet label. The vial label text may include the following:

- Lot Trace ID No.
- Component ID No.
- Product Name
- Dosage Form
- Re-evaluation date (if needed)
- Dosing Instructions
- Storage Conditions
- Compound ID/Protocol No.
- Country Regulatory Requirements
- SPONSOR Address (if applicable)
- Translation Key (if applicable)

3.6.4 Secondary Packaging and Labeling Information (Kits)

The clinical materials for this study will not be provided in kits.

3.6.5 Clinical Materials Disclosure/Unblinding

IVRS will be used to perform emergency unblinding of patients and to unmask clinical material identity (i.e., V710 or placebo). The SPONSOR will not provide disclosure envelopes with the clinical supplies. Information regarding the identification of the clinical materials is to be unmasked only if necessary for the welfare of the patient (i.e., knowledge of the exact treatment group administered to the patient is necessary for treatment of a serious adverse experience). Prior to unblinding a patient, every effort should be made to contact the SPONSOR Clinical Monitor. Any patient unblinding that occurs at the investigator site must be documented.

3.6.6 Storage and Handling Requirements

The clinical materials will be shipped to the site from the SPONSOR in insulated containers. The SPONSOR reserves the right to ship the clinical material with temperature monitoring devices and/or refrigerated (with temperature monitoring devices and cold packs). The vials containing the lyophilized V710 should be removed from the insulated shipping container and placed in a refrigerator maintained at 2 to 8º C immediately after arrival at the investigator site. The V710 should remain refrigerated until the time of reconstitution for administration. The vials containing diluent (0.45% saline solution for reconstitution of V710) and placebo (0.9% normal saline solution) are to be stored at room temperature (~15 to 30º C).

The refrigerator used to store the lyophilized V710 at the investigator site must be monitored by the site staff for temperature consistency within the acceptable storage temperature range (2 to 8º C). Documentation of the temperature monitoring must be maintained by the site staff on an ongoing basis.

The storage range of ~15 to 30º C for the vaccine diluent (0.45% saline solution for reconstitution of V710) and placebo (0.9% saline solution) is recommended.

3.6.7 Standard Policies and Return of Clinical Supplies

Because V710 and placebo will be provided in different formulations, certain member(s) of the site staff (study coordinator and/or pharmacist) will be unblinded to treatment groups. The unblinded person(s) will be responsible for receiving all clinical supply shipments, monitoring the ongoing clinical supply accountability (temperature), and preparing and administering the clinical supplies to all patients. In order to avoid bias, the unblinded person(s) will have limited contact with the study patients following administration of V710/placebo (i.e., the unblinded person(s) will not be involved in any postvaccination efficacy or safety assessment procedures). The unblinded person(s) must also not disclose any information regarding the allocation of the clinical supplies (V710 or placebo) to any blinded member of the site staff. Conversely, no blinded member of the site staff should have contact with the clinical supplies at any point during the course of the study.

The clinical materials are to be administered only in accordance with the protocol. The investigator is responsible for assigning unblinded person(s) to keep accurate records of the clinical materials received from the SPONSOR, the amount administered to patients, and the amount remaining at the conclusion of the study. The SPONSOR Clinical Research Personnel should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all unused clinical materials must be returned to the SPONSOR as indicated on the Contact Information page(s) of the Administrative Binder. U.S.-based investigator sites should follow the instructions for the Clinical Supplies Return Form and contact the SPONSOR representative for review of the shipment and return form prior to returning clinical materials. International sites should check with local country SPONSOR personnel for appropriate documentation that must be completed for vaccine accountability.

3.6.8 Distribution of Clinical Supplies to Investigator Sites and Assignment to Patients

Only the unblinded site person(s) (unblinded study coordinator and/or unblinded pharmacist) will have access to IVRS to allocate patients, assign the clinical materials to patients, and manage the distribution of additional clinical materials (resupply shipments). In the event that an assigned vial cannot be administered to a patient (e.g., broken or damaged vials, or vials not administered in the protocol-specified time period), the unblinded person(s) will also use IVRS to obtain a replacement vial for that patient. The unblinded person(s) accessing IVRS will be assigned an individual unique personal identification number (PIN). That person must use only their assigned PIN to access IVRS and they must not share their assigned PIN with anyone, especially blinded members of the study staff.

The primary investigator will have access to IVRS only to perform emergency unblinding of patients. Prior to emergency unblinding of a patient, the primary investigator should follow the instructions outlined in Section 3.2.6.

No blinded member of the site staff should have contact with the clinical supplies at any point during the course of the study, and therefore will not be provided with IVRS access.

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding the collection and storage of biological specimens for this protocol is provided in Section 3.2.4.7.

Additional information will be provided by the SPONSOR in the study Administrative Binder.

Product: V710 1
Protocol/Amendment No.: 003-02

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

By signing this protocol, the investigator affirms to the SPONSOR that information furnished to the investigator by the SPONSOR will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethics Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the SPONSOR, and subsidiaries, affiliates and agents of the SPONSOR, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies
In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects/patients, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the SPONSOR.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study,

provide all data, and upon completion or termination of the clinical study submit any other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPONSOR as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the SPONSOR prematurely terminates a particular trial site, the SPONSOR will promptly notify that site's IRB/IEC.

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. in the United States for

these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of the Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank. In accordance with the criteria set forth in the FDA "Guidance for Industry: Information Program on Clinical Trials for Serious or Life Threatening Conditions," Mar-2002, Merck, as SPONSOR of this study, has reviewed this protocol, determined that it meets the criteria for submission to the Clinical Trials Data Bank, and will submit the information necessary to fulfill this requirement.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

As this study is part of a multicenter trial, publications derived from this study should include input from the investigator(s) and SPONSOR personnel. Such input should be reflected in publication authorship, and whenever possible, preliminary agreement regarding the strategy for order of authors' names should be established before conducting the study. Subsequent to the multicenter publication, or 24 months after completion of the study, whichever comes first, an investigator and/or his/her colleagues may publish the results for their study site independently. However, the SPONSOR does not recommend separate publication of individual study site results due to scientific concerns.

The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication guidelines.

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6. APPENDICES

6.1 Society of Thoracic Surgeons (STS) Risk Scores For Major Infection Following Cardiothoracic Surgery

As part of the screening process for each patient, specific preoperative variables will be collected in order to calculate a Society of Thoracic Surgeons (STS) score for the risk of major infections following cardiothoracic surgery. These variables will be recorded by the study staff via electronic data capture (EDC). A total STS risk score will be calculated based on adding up all the individual risk factors collected by the study staff during patient screening based on the criteria outlined in Table 6-1 [18].

Table 6-1

Society of Thoracic Surgeons (STS) Bedside Risk Score Assessment

Preoperative Variable	Definition	Risk Score†
Age (for each 5 years of age over 55 years)	Add 1 point for each 5 year period, starting at age 60 years.	1 point
Body mass index (BMI) 30 to 40 kg/m^2	BMI equals a person's weight (in kilograms) divided by height (in meters) squared. (BMI=weight [kg]/height^2[m]).	4 points
BMI 40+ kg/m^2	BMI equals a person's weight (in kilograms) divided by height (in meters) squared. (BMI=weight [kg]/height^2[m]).	9 points
Diabetes mellitus	Confirmed diagnosis of insulin-dependent or non-insulin dependent diabetes mellitus, regardless of duration of disease or need for anti-diabetic agents. Does not include gestational diabetes.	3 points
Renal failure	• Defined as meeting <u>one</u> of the following two criteria: – Documented history of renal failure, and/or – History of creatinine >2.0 mg/dL. • Prior renal transplant patients are not included as pre-op renal failure unless since transplantation their creatinine has been or currently is >2.0 mg/dL.	4 points
Congestive heart failure (CHF)	• History of congestive heart within the last 2 weeks • CHF can be diagnosed based on history and physical exam, or by <u>one</u> of the following criteria: – Paroxysmal nocturnal dyspnea – Dyspnea on exertion due to heart failure – Chest X-Ray (CXR) showing pulmonary congestion – Pedal edema or dyspnea and receiving diuretics or digoxin	3 points

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Table 6-1 (Cont.)

Society of Thoracic Surgeons (STS) Bedside Risk Score Assessment

Preoperative Variable	Definition	Risk Score†
Peripheral vascular disease (PVD)	Defined as meeting one of the following criteria: • Claudication either with exertion or rest; • Amputation for arterial insufficiency; • Aorto-iliac occlusive disease reconstruction; • Peripheral vascular bypass surgery, angioplasty, or stent; • Documented abdominal aortic aneurysm (AAA), AAA repair, or stent; • Positive non-invasive testing documented. Does not include procedures such as vein stripping, carotid disease, or procedures above the diaphragm	2 points
Female gender	Female gender	2 points
Chronic lung disease	Defined as either mild, moderate, or severe chronic lung disease per the following classification: • Mild: FEV1 60-75% of predicted, and/or on chronic inhaled or oral bronchodilator therapy. • Moderate: FEV1 50- 59% of predicted, and/or on chronic steroid therapy aimed at lung disease. • Severe: FEV1 <50% predicted, and/or room air pO2 < 60 or room air pCO2 > 50	2 points
Cardiogenic shock	Patient in a clinical state of hypoperfusion according to one of the 2 following criteria: • Systolic blood pressure (SBP) <80 mm Hg and/or cardiac Index (CI) <1.8 despite maximal treatment • IV inotropes and/or intraaortic balloon pump (IABP) necessary to maintain SBP >80 mm Hg and/or CI > 1.8.	6 points
Myocardial infarction (MI)	Prior or current history of MI	2 points
Concomitant Surgery	Multiple surgical procedures planned (e.g., coronary bypass graft surgery & valvular repair/replacement)	4 points
† A patient's total risk score is calculated by adding the total points for all risk factors present.		

Example: A 72 year-old woman (BMI 32) with known history of diabetes mellitus and a baseline serum creatinine of 2.4 mg/dL requires mitral valve replacement. A 2-vessel coronary bypass graft is also planned for that time. The patient has no prior or active history of MI, cardiogenic shock, CHF, chronic lung disease, or PVD.

STS score:	Age 72 years	2 points
	BMI 32	4 points
	Diabetes mellitus	3 points
	Renal failure	4 points
	Female gender	2 points
	Concomitant surgery	4 points
		19 points

6.2 Guidelines for Antimicrobial Prophylaxis in the Preoperative Period

Antimicrobial Prophylaxis

All patients included in this pivotal study will be mandated to receive preoperative antibiotic prophylaxis. Studies have shown that preoperative antibiotic administration reduces the risk of postoperative infections by as much as 5-fold.

Some general principles for antimicrobial prophylaxis use include the following:

- A single 1-day (<24 hour) course of antimicrobial therapy is usually sufficient
- Therapy should be administered as close to incision as possible (i.e., within 60 minutes of incision). A commonly accepted technique is to administer the antibiotic after anesthetic induction but before skin incision. If vancomycin is administered for prophylaxis, some guidelines recommend that prophylaxis be given within 120 minutes of incision.
- Usually a single-dose administration is sufficient in the operating room. A second dose may be considered in the operating room if the operation exceeds ~3 hours or at intervals of 1-2 times the half-life of the drug

Recommended antimicrobial choices, doses, routes, and dose interval are included in Table 6-2. These specific antimicrobial regimens are recommendations, not requirements. Every patient should receive appropriate antimicrobial prophylaxis based on local and/or regional practices.

Table 6-2

Prophylactic Antimicrobials for Cardiothoracic Surgery

Drug	Standard Dose	Recommended Dose Interval, in Hours (assuming normal renal function)[†]	Additional Comments
Recommended Drugs			
Cefazolin	1-2 g IV	2-5	
Cefuroxime	1.5 g IV	3-4	
Alternative Drugs			
Clindamycin	600-900 mg IV	3-6	If the patient has a β-lactam allergy
Vancomycin	1 g IV		If the patient has a β-lactam allergy OR patients with known MRSA colonization

[†] Administer first dose as close to incision as possible (within 60 minutes of incision). A single 1-day (<24 hour) course of antimicrobial therapy is usually sufficient; in fact, a single-dose administration may be sufficient for short procedures (<3 hours).

Other Non-Antimicrobial Measures

All patients will receive all other preoperative and perioperative standard-of-care measures provided at their specific investigative sites/institutions (i.e., all other non-antimicrobial measures to reduce postoperative infections), regardless of the treatment group they have been assigned.

Included among these strategies may be the following:

- Preoperative measures:
  - Skin preparation with topical antiseptics
  - Clipping (rather than shaving) the skin
  - Avoidance of hair removal

- Perioperative measures:
  - Reduction of traffic in operating room during surgery
  - Laminar-flow ventilation in the operating room
  - Reduced timing of operation
  - Minimization of electrocautery
  - Aggressive fluid resuscitation during surgery
  - Supplemental oxygen administration during surgery
  - Aggressive perioperative glucose control in diabetics to reduce perioperative hyperglycemia

For many of these non-antimicrobial measures, additional clinical research is needed before definitive recommendations can be made [21; 22]. The one exception may be perioperative glucose control; considerable evidence suggests that aggressive perioperative control of blood sugar with intravenous insulin may reduce surgical-site infections in patients undergoing cardiac surgery.

Information based on AHA/ACC Guidelines for CABG Surgery [22] and the Advisory Statement for the National Surgical Infection Prevention Project [23].

6.3 Definitions of Nosocomial *Staphylococcus aureus* Infections

The following tables provide a listing of all the anticipated *S. aureus* infections in this study and the requirements needed to fulfill that specific diagnosis. The initial table (Table 6-3) is based on the criteria for the primary efficacy endpoint for the study (*S. aureus* bacteremia and *S. aureus* deep sternal wound infections). The following 2 tables (Tables 6-4 and 6-5) are representative of the 2 secondary efficacy endpoints for the study: invasive *S. aureus* infections and *S. aureus* surgical site infections. The final section includes other potential *S. aureus* infections not covered by the primary or secondary efficacy endpoints, but may represent additional infections which might be covered under the exploratory efficacy endpoint (i.e., any *S. aureus* infection).

All definitions are based on criteria set forth in the Centers for Disease Control (CDC) Definitions for Nosocomial Infections [14].

Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the proportion of patients with evidence of *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections at any time through postoperative Day 90. For this study, a *S. aureus* deep sternal wound infection includes *S. aureus* mediastinitis or a *S. aureus* deep incisional surgical site infection involving the sternal wound. The definitions of *S. aureus* bacteremia, *S. aureus* mediastinitis, or a *S. aureus* deep incisional surgical site infection involving the sternal wound are included in Table 6-3 below.

Table 6-3

Definitions for *S. aureus* Bacteremia and Mediastinitis
(Primary Efficacy Endpoint)

Category	Specific Site of Infection	Requirements
Bloodstream Infection	*S. aureus* bacteremia	Defined as ≥1 positive blood culture for *S. aureus* (regardless of the presence of clinical symptoms)
Surgical Site Infection (Cardiovascular System)	*S. aureus* mediastinitis	Defined as any infection that meets 1 of the following 2 criteria: 1. A positive *S. aureus* culture from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration; **OR** 2. Patient meets the following 2 criteria: • Purulent discharge from the mediastinal area (i.e., from mediastinal fluid or tissue and not only from more anterior sites [including skin, subcutaneous tissue, fascial layer, or muscle layer]) positive on culture for *S. aureus*, **AND** • At least one of the following signs or symptoms with no other recognized cause: - Fever (>38ºC [or >100.4ºF]) - Chest pain - Sternal instability - Radiographic evidence on either chest X-ray/CT of mediastinal widening
Surgical Site Infection (Sternal Wound)	Deep incisional *S. aureus* surgical site infection involving the sternal wound	Defined as any infection that meets the following 2 criteria: • *S. aureus* organisms isolated from an aseptically obtained culture of deep soft tissue (involving the fascial or muscle layers) but not from mediastinal tissue or fluid, **AND** • The patient has at least one of the following: 1. Purulent drainage from the deep incision (from fascial or muscle layers, but not from mediastinal space) 2. Sternal wound spontaneously dehisces or is deliberately opened by the surgeon 3. The patient has at least one of the following signs or symptoms: fever (>38˚ C or >100.4ºF), chest pain, or chest tenderness 4. An abscess or other evidence of infection involving the fascial or muscle layers is found on direct examination, during reoperation, or by histopathologic or radiologic examination (a stitch abscess, which is defined as minimal inflammation and discharge confined to the point of suture penetration, or other abscesses anterior to the fascial layers do not qualify)

Secondary Efficacy Endpoints

Secondary efficacy endpoints for this study include the following:

- Any invasive *S. aureus* infection through postoperative Day 90.
- Any *S. aureus* surgical site infection through postoperative Day 90.

Invasive *S. aureus* Infections

The definitions of invasive *S. aureus* infections are included in Table 6-4 below.

Table 6-4

Definitions for Invasive *S. aureus* Infections
(Secondary Efficacy Endpoint)

Category	Specific Site of Infection	Requirements
Bloodstream Infection	*S. aureus* bacteremia	See Table 6-3 above
Lung	*S. aureus* pneumonia	Defined as culture isolation of *S. aureus* from a specimen obtained by transtracheal aspirate, bronchial brushing, or bronchoscopic/lung biopsy in one of the following 2 patient settings: 1. Patient with rales or dullness to percussion on physical examination of the chest, OR 2. Patient with a chest radiographic examination showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion. **NOTE:** Findings from serial chest X-rays may be more helpful than a single X-ray. An expectorated sputum culture is not useful by itself in the diagnosis of pneumonia but may help identify the etiologic agent and provide useful antimicrobial susceptibility data.
Lung	*S. aureus* lung abscess	Defined as either: 1. Culture isolation of *S. aureus* from a specimen obtained aseptically from a lung abscess during surgical operation, OR 2. Culture isolation of *S. aureus* from a specimen obtained aseptically from a lung abscess via bronchoscopic/lung biopsy in a patient with an abscess cavity seen on radiographic examination of lung.
Lung	*S. aureus* empyema	Defined as either: 1. Culture isolation of *S. aureus* from a pleural fluid specimen obtained aseptically from a surgical operation, OR 2. Culture isolation of *S. aureus* from a pleural fluid specimen obtained aseptically from a needle aspiration (i.e., thoracentesis) or a newly-placed chest tube drain.
Bone or Joint	*S. aureus* osteomyelitis	Defined as culture isolation of *S. aureus* from a bone specimen obtained aseptically during surgical operation or from needle aspiration.
Bone or Joint	*S. aureus* septic arthritis or bursitis	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from the joint space or bursa during surgical operation or from needle aspiration (i.e., arthrocentesis).

Table 6-4 (Cont.)

Definitions for Invasive *S. aureus* Infections
(Secondary Efficacy Endpoint)

Category	Specific Site of Infection	Requirements
Bone or Joint	*S. aureus* vertebral disc space infection	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from the vertebral disc space during surgical operation or from needle aspiration (i.e., spinal arthrocentesis).
Central Nervous System	*S. aureus* intracranial infection (brain abscess, subdural or epidural infection, or encephalitis)	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from either brain tissue, dura, or associated abscess tissue during surgical operation or from a transcranial needle aspiration (i.e., brain biopsy).
Central Nervous System	*S. aureus* meningitis or ventriculitis	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from the cerebrospinal fluid (CSF) tissue during surgical operation, lumbar puncture, or newly-placed CSF drain/shunt.
Central Nervous System	*S. aureus* spinal abscess without meningitis (abscess of the spinal epidural or subdural space, without involvement of the cerebrospinal fluid or adjacent bone structures)	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically at surgical operation or at autopsy from an abscess in the spinal epidural or subdural space.
Cardiovascular System	*S. aureus* intravascular (arterial or venous) infection (also known as arteritis, veinitis, or septic thrombophlebitis)	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from large arteries or veins removed during a surgical operation *but in whom no S. aureus organisms were cultured from the blood.* **NOTE**: Intravascular infections with *S. aureus* organisms also cultured from the blood should be referred to as *S. aureus* bacteremia.

Table 6-4 (Cont.)

Definitions for Invasive *S. aureus* Infections
(Secondary Efficacy Endpoint)

Category	Specific Site of Infection	Requirements
Cardiovascular System	*S. aureus* endocarditis	Defined as one of the following: 1. *S. aureus* microorganisms demonstrated by culture of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; 2. Persistently positive blood cultures for *S. aureus* (≥2 positive cultures of samples drawn > 12 hours apart, OR all of 3 or a majority of ≥4 separate cultures of blood) with 1 of the following 2 criteria: • Evidence of endocardial involvement as one of the following: - Echocardiogram positive for endocarditis, OR - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, OR - Abscess, OR - New partial dehiscence of prosthetic valve. • New valvular regurgitation. 3. Persistently positive blood cultures for *S. aureus* (≥2 positive cultures of samples drawn > 12 hours apart, OR all of 3 or a majority of ≥4 separate cultures of blood) with 3 of the following: • Predisposition, predisposing heart condition, or injection drug use. • Fever (temperature >38˚C). • Vascular phenomena: major arterial emboli, septic lung infarcts, mycotic aneurysm, intracranial or conjunctival hemorrhages, & Janeway lesions. • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.

Table 6-4 (Cont.)

Definitions for Invasive *S. aureus* Infections
(Secondary Efficacy Endpoint)

Category	Specific Site of Infection	Requirements
Cardiovascular System	*S. aureus* myocarditis or pericarditis	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from the pericardial tissue or pericardial fluid either by needle aspiration or during a surgical operation.
Cardiovascular System	*S. aureus* mediastinitis	See Table 6-3 above.
Gastrointestinal System	*S. aureus* intraabdominal infection (including tissue or abscess infection in the stomach, appendix, gallbladder, bile ducts, liver, spleen, pancreas, small or large intestine, peritoneum, subphrenic or subdiaphragmatic space or other intraabdominal tissue or other area not specified)	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from purulent material from the intraabdominal space (either from tissue, intraabdominal fluid, or abscess) obtained during a surgical operation or needle aspiration.
Genitourinal System	*S. aureus* retroperitoneal infection (including tissue or abscess infection in the kidney, adrenal gland, or tissues surrounding the retroperitoneal or perinephric spaces)	Defined as culture isolation of *S. aureus* from a specimen obtained aseptically from purulent material from the retroperitoneal space (either from tissue, intraabdominal fluid, or abscess) obtained during a surgical operation or needle aspiration.

S. aureus Surgical Site Infections

The definitions of *S. aureus* surgical site infections (SSI) are included in Table 6-5 below. This includes all SSI caused by *S. aureus*, including the following 3 categories:

- **Superficial incisional SSI**: Infection involves only skin and subcutaneous tissue at the incision site

- **Deep incisional SSI**: Infection involves or extends into the fascial and muscle layers at the incision site

- **Organ/space SSI:** An organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection (see Table 6-5 below).

Table 6-5

Definitions for *S. aureus* Surgical Site Infections (SSI)
(Secondary Efficacy Endpoint)

Category	Specific Types	Requirements
Superficial Incisional SSI	• Superficial *S. aureus* SSI at chest incision site • Superficial *S. aureus* SSI at leg (donor or harvest) incision site • Superficial *S. aureus* SSI at site of catheter placement (chest tube, tracheostomy, etc.)	A superficial-incisional *S. aureus* SSI must meet the following criteria: 1. Infection involves only skin and subcutaneous tissue of the incision, AND 2. *S. aureus* organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision or localized site, AND 3. The patient has at least one of the following: • Purulent draining from the superficial incision or localized site. • At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat. • Superficial incision is deliberately opened by surgeon. **NOTE**: A stitch abscess (defined as minimal inflammation and discharge confined to the point of suture penetration) should not be reported as a superficial SSI. **NOTE**: Efforts should be made to report all culture specimens from superficial incisions as incisional drainage. *Infection that involves both superficial and deep incision sites should be reported as deep incisional SSI.*

Table 6-5 (Cont.)

Definitions for *S. aureus* Surgical Site Infections (SSI)
(Secondary Efficacy Endpoint)

Category	Specific Types	Requirements
Deep Incisional SSI	• Deep *S. aureus* SSI at chest incision site (involving the sternal wound) • Deep *S. aureus* SSI at leg (donor or harvest) incision site • Deep *S. aureus* SSI at site of catheter placement (chest tube, tracheostomy, etc.)	A deep-incisional *S. aureus* SSI must meet the following criteria: 1. Infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision, AND 2. *S. aureus* organisms isolated from an aseptically obtained culture of fluid or tissue from the deep soft tissue (fascial and muscle layers) but not from organ/space component of surgical site, AND 3. The patient has at least one of the following: • Purulent drainage from the deep incision but not from the organ/space component of the surgical site. • A deep incision spontaneously dehisces or is deliberately opened by a surgeon • The patient has at least one of the following signs or symptoms: fever (>38˚ C [>100.4ºF]), or localized pain or tenderness. • An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination. **NOTE**: Efforts should be made to report all culture specimens from superficial incisions should be reported as incisional drainage. *Infection that involves both superficial and deep incision sites should be reported as deep incisional SSI.*

Table 6-5 (Cont.)

Definitions for *S. aureus* Surgical Site Infections (SSI)
(Secondary Efficacy Endpoint)

Category	Specific Types	Requirements
Organ/Space SSI	1. *S. aureus* mediastinitis 2. *S. aureus* myocarditis or pericarditis 3. *S. aureus* endocarditis 4. *S. aureus* breast abscess or mastitis 5. *S. aureus* osteomyelitis or joint/disc/bursa space 6. *S. aureus* intraabdominal space infection 7. *S. aureus* brain abscess or dura infection 8. *S. aureus* meningitis or ventriculitis 9. *S. aureus* spinal abscess without meningitis 10. *S. aureus* arterial or venous infection	A organ/space *S. aureus* 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. *S. aureus* organisms isolated from an aseptically obtained culture of fluid or tissue from the organ/space component of the surgical site, AND 3. The patient has at least one of the following: • Purulent drainage from a drain that is placed through a stab wound into the organ/space. • Abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

Exploratory Efficacy Endpoint

Any *S. aureus* Infection

In addition to all the conditions outlined in Tables 6-3, 6-4, and 6-5 other potential *S. aureus* infections include the following (by specific site codes), provided a positive culture for *S. aureus* was obtained from the involved site:

1. Urinary tract:
   - Symptomatic urinary tract infection due to *S. aureus*
   - Urethritis due to *S. aureus*
2. Ear, Eye, Nose or Throat, or Mouth:
   - Conjunctivitis or other eye infection due to *S. aureus*
   - Otitis externa due to *S. aureus*
   - Otitis media or interna due to *S. aureus*
   - Mastoiditis due to *S. aureus*
   - Oral cavity infection (of mouth, tongue, or gums) due to *S. aureus*
   - Pharyngitis, laryngitis, or epiglottitis due to *S. aureus*
3. Gastrointestinal Tract:
   - Gastroenteritis (including gastritis, enteritis, or colitis) due to *S. aureus*
4. Lower Respiratory Tract:
   - Bronchitis, tracheobronchitis, bronchiolitis, or tracheitis due to *S. aureus* (without evidence of pneumonia)
   - *S. aureus* respiratory infection not fulfilling the criteria for *S. aureus* pneumonia defined in Table 6-4: (e.g., culture isolation of *S. aureus* from an expectorated sputum specimen in the setting of either rales/dullness to percussion on physical examination of the chest, OR patient with a chest radiographic examination showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion)
5. Reproductive Tract:
   - Infections of the female reproductive tract due to *S. aureus* (cervix, vagina, uterus, or ovaries)
   - Infections of the male reproductive tract due to *S. aureus* (epididymis, testes, or prostate)

6. Skin and Soft Tissues (not involving prior site of surgery):
    - Furuncle or boils due to *S. aureus*
    - Cellulitis due to *S. aureus*
    - Soft tissue infections due to *S. aureus* (necrotizing fascitis, infectious gangrene, necrotizing cellulitis, infectious myositis, lymphadenitis, or lymphangitis)
    - Decubitus ulcer due to *S. aureus*
    - Breast abscess or mastitis due to *S. aureus*

Other *S. aureus* infections which are not mentioned above may also qualify if a positive culture for *S. aureus* is obtained and its presence is indicative of infection, not colonization.

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7. ATTACHMENTS

Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., Code of Conduct for Clinical Trials

Merck Sharp & Dohme Corp.,
a Subsidiary of Merck & Co., Inc.,
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. ("Merck") conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of patient safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies will be consistent with standards established by the Declaration of Helsinki and in compliance with all local and/or national regulations and directives.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (e.g., Medical School Grant Program), which are not under the control of Merck.

II. Scientific Issues

A. Study Conduct

1. Study Design

Except for pilot or estimation studies, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

The design and conduct of a study (i.e., patient population, duration, statistical power) must be adequate to address the specific purpose of the study. Research subjects must meet protocol entry criteria to be enrolled in the study.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance in Merck studies, as well as budgetary considerations. Prior to study initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Study sites are monitored to assess compliance with the study protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency: data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud and/or misconduct are suspected, the issue is investigated: when necessary, the clinical site will be closed and, if appropriate, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of studies it conducts. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the study, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the study results and conclusions. Merck funding of a study will be acknowledged in publications.

III. Patient Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect patient safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or local medical director (non-U.S. studies) will approve the patient informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that patient welfare is of primary importance. Potential patients will be informed of the risks and benefits of, as well as alternatives to, study participation. At a minimum, study designs will take into account the local standard of care. Patients are never denied access to appropriate medical care based on participation in a Merck clinical study.

All participation in Merck clinical trials is voluntary. Patients are enrolled only after providing informed consent for participation. Patients may withdraw from a Merck study at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding patient confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck studies. Merck does not pay incentives to enroll patients in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for patient referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible patients.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the study. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck studies will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g. to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an attachment to the study protocol, and in signing the protocol, agree to support these ethical and scientific standards.

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8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

8.2 INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in the SAFETY MEASUREMENTS section of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE