

Supplementary Online Content

Fowler VG, Allenn KB, Moreira ED, et al. Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery: a randomized trial. *JAMA*. doi:10.1001/jama.2013.3010

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. All Vaccinated Subjects With Serious Adverse Events (SAE) Regardless of Causality Anytime During the Study

Subjects With Serious Adverse Events
(Incidence > 0% in One or More Vaccination Groups)
(All Vaccinated Subjects)(Duration of Study)

	V710 60 mcg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Vaccinated Subjects with follow-up	3,958		3,967		7,925	
with ≥1 SAE	291	(7.4)	274	(6.9)	565	(7.1)
without any SAE	3,667	(92.6)	3,693	(93.1)	7,360	(92.9)
Blood and lymphatic system disorders	4	(0.1)	5	(0.1)	9	(0.1)
Anaemia	3	(0.1)	3	(0.1)	6	(0.1)
Febrile neutropenia	1	(0.0)	0	(0.0)	1	(0.0)
Microcytic anaemia	0	(0.0)	1	(0.0)	1	(0.0)
Pancytopenia	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac disorders	108	(2.7)	94	(2.4)	202	(2.5)
Acute coronary syndrome	1	(0.0)	0	(0.0)	1	(0.0)
Acute myocardial infarction	6	(0.2)	11	(0.3)	17	(0.2)
Angina pectoris	3	(0.1)	1	(0.0)	4	(0.1)
Angina unstable	4	(0.1)	1	(0.0)	5	(0.1)
Arrhythmia	1	(0.0)	2	(0.1)	3	(0.0)
Atrial fibrillation	4	(0.1)	1	(0.0)	5	(0.1)
Atrioventricular block second degree	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac arrest	18	(0.5)	21	(0.5)	39	(0.5)
Cardiac failure	12	(0.3)	6	(0.2)	18	(0.2)
Cardiac failure acute	2	(0.1)	0	(0.0)	2	(0.0)
Cardiac failure chronic	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac failure congestive	5	(0.1)	5	(0.1)	10	(0.1)
Cardiac tamponade	1	(0.0)	2	(0.1)	3	(0.0)
Cardiac valve disease	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac ventricular disorder	1	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	8	(0.2)	2	(0.1)	10	(0.1)
Cardiogenic shock	23	(0.6)	18	(0.5)	41	(0.5)
Cardiopulmonary failure	1	(0.0)	1	(0.0)	2	(0.0)
Coronary artery disease	2	(0.1)	1	(0.0)	3	(0.0)
Ischaemic cardiomyopathy	1	(0.0)	0	(0.0)	1	(0.0)
Left ventricular dysfunction	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac disorders	108	(2.7)	94	(2.4)	202	(2.5)
Left ventricular failure	1	(0.0)	0	(0.0)	1	(0.0)
Low cardiac output syndrome	2	(0.1)	1	(0.0)	3	(0.0)
Myocardial infarction	3	(0.1)	8	(0.2)	11	(0.1)
Pericardial haemorrhage	1	(0.0)	0	(0.0)	1	(0.0)
Right ventricular failure	2	(0.1)	5	(0.1)	7	(0.1)
Sinus arrest	0	(0.0)	1	(0.0)	1	(0.0)
Ventricle rupture	2	(0.1)	0	(0.0)	2	(0.0)
Ventricular arrhythmia	1	(0.0)	1	(0.0)	2	(0.0)
Ventricular dysfunction	2	(0.1)	0	(0.0)	2	(0.0)
Ventricular failure	0	(0.0)	1	(0.0)	1	(0.0)
Ventricular fibrillation	3	(0.1)	1	(0.0)	4	(0.1)
Ventricular tachyarrhythmia	1	(0.0)	0	(0.0)	1	(0.0)
Ventricular tachycardia	1	(0.0)	1	(0.0)	2	(0.0)

	V710 60 mcg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Congenital, familial and genetic disorders	0	(0.0)	1	(0.0)	1	(0.0)
Cerebral arteriovenous malformation haemorrhagic	0	(0.0)	1	(0.0)	1	(0.0)
Eye disorders	0	(0.0)	1	(0.0)	1	(0.0)
Blindness	0	(0.0)	1	(0.0)	1	(0.0)
Gastrointestinal disorders	9	(0.2)	6	(0.2)	15	(0.2)
Anal haemorrhage	1	(0.0)	0	(0.0)	1	(0.0)
Diarrhoea	0	(0.0)	1	(0.0)	1	(0.0)
Diverticular perforation	1	(0.0)	0	(0.0)	1	(0.0)
Duodenal ulcer haemorrhage	1	(0.0)	0	(0.0)	1	(0.0)
Gastric ulcer	1	(0.0)	0	(0.0)	1	(0.0)
Gastrointestinal haemorrhage	3	(0.1)	3	(0.1)	6	(0.1)
Intestinal infarction	1	(0.0)	0	(0.0)	1	(0.0)
Intestinal ischaemia	1	(0.0)	2	(0.1)	3	(0.0)
General disorders and administration site conditions	46	(1.2)	28	(0.7)	74	(0.9)
General disorders and administration site conditions	46	(1.2)	28	(0.7)	74	(0.9)
Chest pain	3	(0.1)	2	(0.1)	5	(0.1)
Death	3	(0.1)	4	(0.1)	7	(0.1)
Device dislocation	1	(0.0)	0	(0.0)	1	(0.0)
Device leakage	1	(0.0)	0	(0.0)	1	(0.0)
Multi-organ failure	31	(0.8)	17	(0.4)	48	(0.6)
Organ failure	0	(0.0)	1	(0.0)	1	(0.0)
Sudden cardiac death	3	(0.1)	2	(0.1)	5	(0.1)
Sudden death	3	(0.1)	2	(0.1)	5	(0.1)
Systemic inflammatory response syndrome	1	(0.0)	0	(0.0)	1	(0.0)
Hepatobiliary disorders	1	(0.0)	2	(0.1)	3	(0.0)
Cholelithiasis	1	(0.0)	0	(0.0)	1	(0.0)
Cytolytic hepatitis	0	(0.0)	1	(0.0)	1	(0.0)
Hepatic failure	0	(0.0)	1	(0.0)	1	(0.0)
Infections and infestations	85	(2.1)	78	(2.0)	163	(2.1)
Bacteraemia	1	(0.0)	0	(0.0)	1	(0.0)
Campylobacter gastroenteritis	0	(0.0)	1	(0.0)	1	(0.0)
Candida sepsis	0	(0.0)	1	(0.0)	1	(0.0)
Cellulitis staphylococcal	0	(0.0)	1	(0.0)	1	(0.0)
Clostridium difficile colitis	1	(0.0)	0	(0.0)	1	(0.0)
Diarrhoea infectious	1	(0.0)	0	(0.0)	1	(0.0)
Endocarditis	1	(0.0)	2	(0.1)	3	(0.0)
Endocarditis pseudomonas	1	(0.0)	0	(0.0)	1	(0.0)
Endocarditis staphylococcal	2	(0.1)	4	(0.1)	6	(0.1)
Enterococcal sepsis	1	(0.0)	0	(0.0)	1	(0.0)
Fungal endocarditis	1	(0.0)	0	(0.0)	1	(0.0)
Klebsiella infection	1	(0.0)	0	(0.0)	1	(0.0)
Mediastinitis	3	(0.1)	1	(0.0)	4	(0.1)
Pneumonia	5	(0.1)	6	(0.2)	11	(0.1)
Pneumonia bacterial	1	(0.0)	0	(0.0)	1	(0.0)
Pneumonia staphylococcal	4	(0.1)	8	(0.2)	12	(0.2)

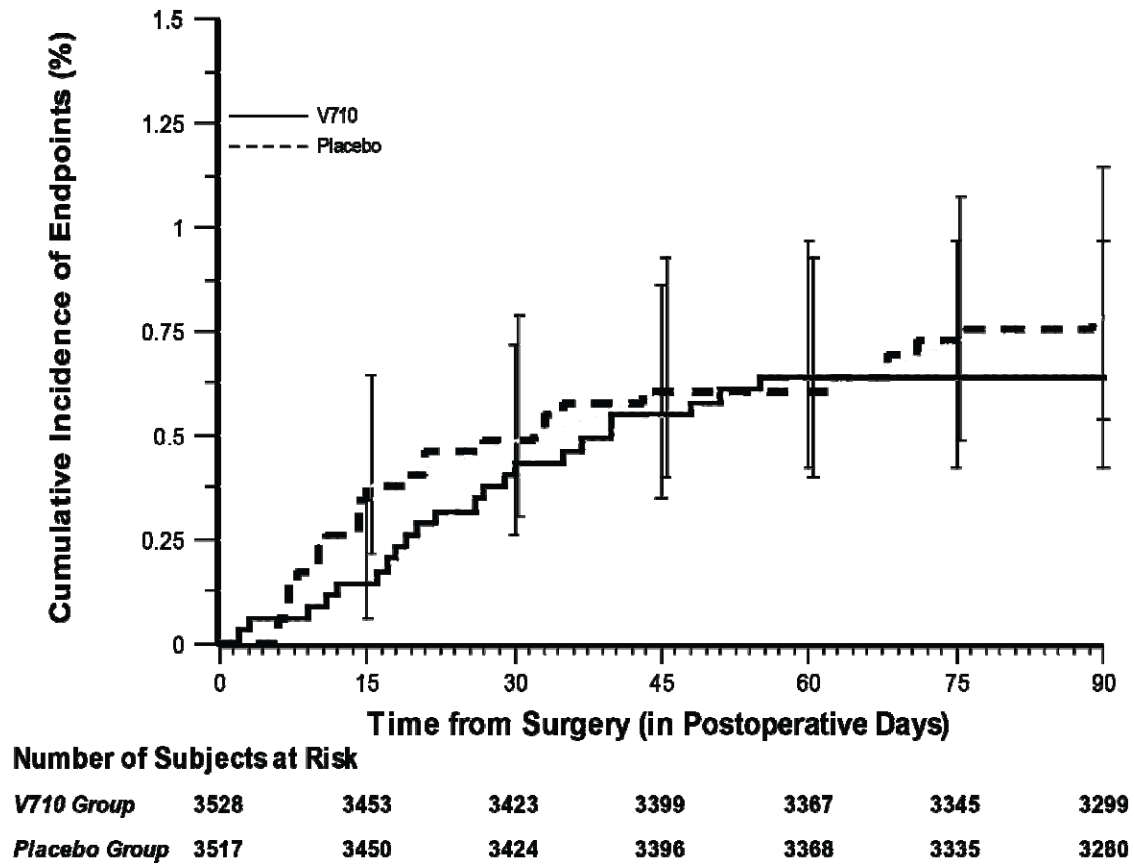
	V710 60 mcg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Infections and infestations	85	(2.1)	78	(2.0)	163	(2.1)
Postoperative wound infection	2	(0.1)	1	(0.0)	3	(0.0)
Prostatic abscess	1	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sepsis	1	(0.0)	0	(0.0)	1	(0.0)
Pyonephrosis	1	(0.0)	0	(0.0)	1	(0.0)
Respiratory tract infection	1	(0.0)	1	(0.0)	2	(0.0)
Sepsis	3	(0.1)	2	(0.1)	5	(0.1)
Septic shock	7	(0.2)	5	(0.1)	12	(0.2)
Skin infection	1	(0.0)	0	(0.0)	1	(0.0)
Staphylococcal abscess	1	(0.0)	2	(0.1)	3	(0.0)
Staphylococcal bacteraemia	18	(0.5)	19	(0.5)	37	(0.5)
Staphylococcal infection	5	(0.1)	5	(0.1)	10	(0.1)
Staphylococcal mediastinitis	8	(0.2)	9	(0.2)	17	(0.2)
Staphylococcal osteomyelitis	1	(0.0)	1	(0.0)	2	(0.0)
Staphylococcal sepsis	3	(0.1)	2	(0.1)	5	(0.1)
Staphylococcal skin infection	0	(0.0)	2	(0.1)	2	(0.0)
Streptococcal sepsis	1	(0.0)	0	(0.0)	1	(0.0)
Tracheobronchitis	4	(0.1)	1	(0.0)	5	(0.1)
Urosepsis	0	(0.0)	1	(0.0)	1	(0.0)
Wound infection	2	(0.1)	0	(0.0)	2	(0.0)
Wound infection bacterial	2	(0.1)	0	(0.0)	2	(0.0)
Wound infection staphylococcal	25	(0.6)	27	(0.7)	52	(0.7)
Injury, poisoning and procedural complications	13	(0.3)	6	(0.2)	19	(0.2)
Abdominal injury	1	(0.0)	0	(0.0)	1	(0.0)
Anastomotic ulcer	0	(0.0)	1	(0.0)	1	(0.0)
Brain herniation	1	(0.0)	0	(0.0)	1	(0.0)
Cardiac valve replacement complication	0	(0.0)	1	(0.0)	1	(0.0)
Contusion	0	(0.0)	1	(0.0)	1	(0.0)
Hip fracture	1	(0.0)	0	(0.0)	1	(0.0)
Intraoperative cerebral artery occlusion	1	(0.0)	0	(0.0)	1	(0.0)
Operative haemorrhage	3	(0.1)	0	(0.0)	3	(0.0)
Injury, poisoning and procedural complications	13	(0.3)	6	(0.2)	19	(0.2)
Post procedural haemorrhage	1	(0.0)	2	(0.1)	3	(0.0)
Postoperative thoracic procedure complication	2	(0.1)	0	(0.0)	2	(0.0)
Postoperative wound complication	1	(0.0)	0	(0.0)	1	(0.0)
Rib fracture	0	(0.0)	1	(0.0)	1	(0.0)
Subdural haematoma	1	(0.0)	1	(0.0)	2	(0.0)
Vasoplegia syndrome	1	(0.0)	0	(0.0)	1	(0.0)
Investigations	2	(0.1)	2	(0.1)	4	(0.1)
Blood creatinine increased	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac output decreased	1	(0.0)	1	(0.0)	2	(0.0)
Troponin T increased	1	(0.0)	0	(0.0)	1	(0.0)
Metabolism and nutrition disorders	2	(0.1)	0	(0.0)	2	(0.0)
Diabetes mellitus	1	(0.0)	0	(0.0)	1	(0.0)
Metabolic acidosis	1	(0.0)	0	(0.0)	1	(0.0)
Musculoskeletal and connective tissue disorders	0	(0.0)	1	(0.0)	1	(0.0)
Bone fistula	0	(0.0)	1	(0.0)	1	(0.0)

	V710 60 mcg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	(0.2)	7	(0.2)	14	(0.2)
Acute myeloid leukaemia	1	(0.0)	0	(0.0)	1	(0.0)
Brain neoplasm	1	(0.0)	0	(0.0)	1	(0.0)
Bronchial carcinoma	0	(0.0)	1	(0.0)	1	(0.0)
Chronic lymphocytic leukaemia	1	(0.0)	0	(0.0)	1	(0.0)
Colon cancer	1	(0.0)	0	(0.0)	1	(0.0)
Gastric cancer	1	(0.0)	0	(0.0)	1	(0.0)
Lymphoma	0	(0.0)	1	(0.0)	1	(0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7	(0.2)	7	(0.2)	14	(0.2)
Metastatic renal cell carcinoma	0	(0.0)	1	(0.0)	1	(0.0)
Multiple myeloma	0	(0.0)	1	(0.0)	1	(0.0)
Neoplasm malignant	1	(0.0)	0	(0.0)	1	(0.0)
Pancreatic carcinoma	0	(0.0)	1	(0.0)	1	(0.0)
Rectal cancer	0	(0.0)	1	(0.0)	1	(0.0)
Renal neoplasm	0	(0.0)	1	(0.0)	1	(0.0)
Thyroid cancer	1	(0.0)	0	(0.0)	1	(0.0)
Nervous system disorders	17	(0.4)	18	(0.5)	35	(0.4)
Basal ganglia infarction	1	(0.0)	0	(0.0)	1	(0.0)
Brain stem haemorrhage	0	(0.0)	1	(0.0)	1	(0.0)
Brain stem infarction	1	(0.0)	0	(0.0)	1	(0.0)
Carotid artery stenosis	1	(0.0)	0	(0.0)	1	(0.0)
Cerebral disorder	1	(0.0)	0	(0.0)	1	(0.0)
Cerebral haemorrhage	2	(0.1)	2	(0.1)	4	(0.1)
Cerebral infarction	1	(0.0)	0	(0.0)	1	(0.0)
Cerebral ischaemia	1	(0.0)	0	(0.0)	1	(0.0)
Cerebrovascular accident	2	(0.1)	3	(0.1)	5	(0.1)
Dizziness exertional	0	(0.0)	1	(0.0)	1	(0.0)
Encephalitis	0	(0.0)	1	(0.0)	1	(0.0)
Haemorrhage intracranial	1	(0.0)	1	(0.0)	2	(0.0)
Haemorrhagic stroke	1	(0.0)	1	(0.0)	2	(0.0)
Hypoxic-ischaemic encephalopathy	0	(0.0)	1	(0.0)	1	(0.0)
Intraventricular haemorrhage	0	(0.0)	1	(0.0)	1	(0.0)
Ischaemic stroke	1	(0.0)	2	(0.1)	3	(0.0)
Loss of consciousness	1	(0.0)	0	(0.0)	1	(0.0)
Presyncope	0	(0.0)	2	(0.1)	2	(0.0)
Syncope	2	(0.1)	3	(0.1)	5	(0.1)
Transient ischaemic attack	1	(0.0)	0	(0.0)	1	(0.0)
Psychiatric disorders	0	(0.0)	1	(0.0)	1	(0.0)
Panic attack	0	(0.0)	1	(0.0)	1	(0.0)
Renal and urinary disorders	5	(0.1)	5	(0.1)	10	(0.1)
Renal failure	0	(0.0)	3	(0.1)	3	(0.0)
Renal failure acute	4	(0.1)	2	(0.1)	6	(0.1)
Renal failure chronic	1	(0.0)	0	(0.0)	1	(0.0)
Reproductive system and breast disorders	1	(0.0)	0	(0.0)	1	(0.0)
Epididymitis	1	(0.0)	0	(0.0)	1	(0.0)

	V710 60 mcg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	18	(0.5)	14	(0.4)	32	(0.4)
Acute respiratory distress syndrome	0	(0.0)	1	(0.0)	1	(0.0)
Acute respiratory failure	1	(0.0)	0	(0.0)	1	(0.0)
Chronic obstructive pulmonary disease	1	(0.0)	0	(0.0)	1	(0.0)
Dyspnoea	3	(0.1)	0	(0.0)	3	(0.0)
Hydropneumothorax	0	(0.0)	1	(0.0)	1	(0.0)
Pneumonia aspiration	1	(0.0)	2	(0.1)	3	(0.0)
Pulmonary congestion	0	(0.0)	1	(0.0)	1	(0.0)
Pulmonary embolism	3	(0.1)	1	(0.0)	4	(0.1)
Pulmonary fibrosis	0	(0.0)	1	(0.0)	1	(0.0)
Pulmonary mass	1	(0.0)	0	(0.0)	1	(0.0)
Pulmonary oedema	0	(0.0)	1	(0.0)	1	(0.0)
Respiratory arrest	1	(0.0)	0	(0.0)	1	(0.0)
Respiratory failure	8	(0.2)	6	(0.2)	14	(0.2)
Vascular disorders	15	(0.4)	25	(0.6)	40	(0.5)
Aneurysm ruptured	1	(0.0)	0	(0.0)	1	(0.0)
Aortic aneurysm	0	(0.0)	1	(0.0)	1	(0.0)
Aortic aneurysm rupture	0	(0.0)	1	(0.0)	1	(0.0)
Aortic dissection	0	(0.0)	1	(0.0)	1	(0.0)
Aortic rupture	1	(0.0)	1	(0.0)	2	(0.0)
Vascular disorders	15	(0.4)	25	(0.6)	40	(0.5)
Aortic stenosis	2	(0.1)	0	(0.0)	2	(0.0)
Arterial thrombosis	0	(0.0)	1	(0.0)	1	(0.0)
Arteriosclerosis obliterans	1	(0.0)	0	(0.0)	1	(0.0)
Circulatory collapse	3	(0.1)	9	(0.2)	12	(0.2)
Deep vein thrombosis	1	(0.0)	0	(0.0)	1	(0.0)
Embolism	0	(0.0)	1	(0.0)	1	(0.0)
Haemorrhage	3	(0.1)	2	(0.1)	5	(0.1)
Hypertensive crisis	1	(0.0)	0	(0.0)	1	(0.0)
Hypovolaemic shock	1	(0.0)	4	(0.1)	5	(0.1)
Shock	0	(0.0)	1	(0.0)	1	(0.0)
Shock haemorrhagic	1	(0.0)	3	(0.1)	4	(0.1)

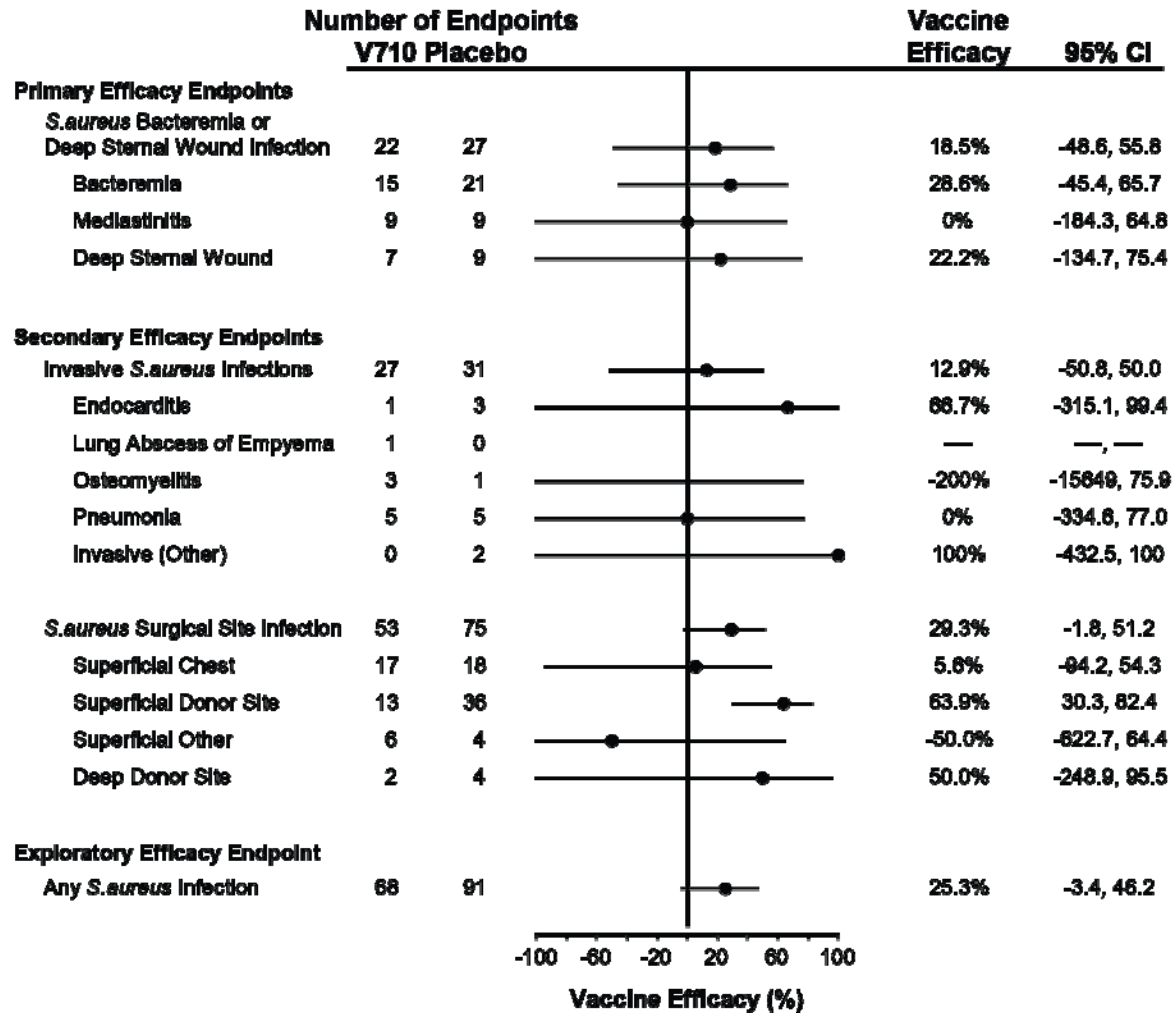
The table presents the number of patients with the specified adverse events. A subject is only counted once for each applicable row and column. Adverse event terms are from MedDRA 14.0.

eFigure 1. Kaplan-Meier Plot of Postoperative Time to an Adjudicated Primary Endpoint



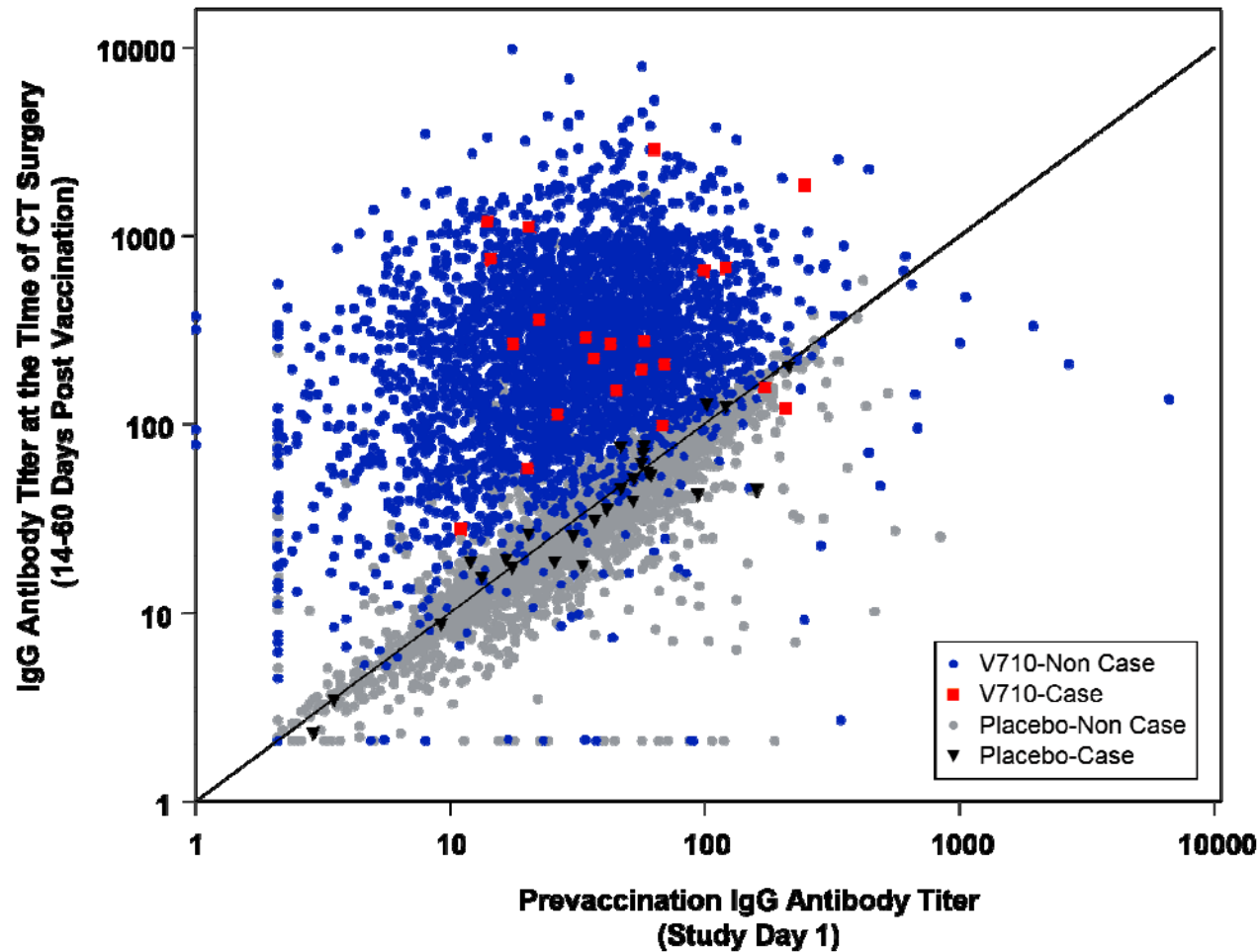
The bars show the 95% confidence intervals around the point estimates at each time point.

eFigure 2. Forest Plot of Vaccine Efficacy Against Primary, Secondary, and Exploratory Outcomes



The differences between endpoint rates for the V710 minus placebo group (vaccine efficacy) are shown on the graph. No difference between groups is referenced by the vertical axis of neutrality. All participants at a single site (including 1 patient with an adjudicated primary endpoint in the V710 group) were excluded from the analyses prior to unblinding the data because of questionable clinical practices discovered during quality-assurance audits. The efficacy analyses included 3528 subjects in the V710 arm and 3517 subjects in the placebo arm. The circles represent the point estimates of vaccine efficacy for the indicated endpoint(s), and the bracketing lines show the corresponding 95% confidence intervals [CI]. The lower bound of the 95% CI being >20% (for primary) or >0% (for secondary/exploratory) implies that the efficacy is significantly greater than the prespecified criterion (20% for primary hypothesis; 0% for secondary/exploratory hypotheses, only to be tested if the primary hypothesis is satisfied) and allows for a conclusion of vaccine efficacy with respect to the given endpoint. ‡ Includes all primary cases and any cases meeting the definition of an invasive *S. aureus* infection or a *S. aureus* surgical-site infection. § Includes all primary and secondary cases as well as any other *S. aureus* infections.

eFigure 3. Comparison of Serum IgG Antibody Titers against Iron Surface Determinant B at the Time of Surgery (14-60 Days after Vaccination) to Prevaccination Levels for V710 and Placebo Recipients by Whether the Patient Reached an Adjudicated Primary Endpoint



Both axes are drawn on a log scale. Anti-IsdB IgG titers are expressed as $\mu\text{g/mL}$. The diagonal line of neutrality shows where IgG titers would be the same at both time points. Points above and to the left of the diagonal line indicate antibody levels that had increased from the time of vaccination to the time of surgery. In contrast to the placebo group, anti-IsdB IgG titers at the time of surgery in V710 recipients were consistently higher than their baseline prevaccination levels, confirming the immunogenicity of the vaccine. Anti-IsdB IgG levels in V710 recipients who developed *S. aureus* infections were distributed similarly to the titers in V710 recipients who did not develop a *S. aureus* infection, suggesting that vaccine non-responsiveness was not the underlying reason for vaccine failure.

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