Clinical trial results:
A Phase 2B, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate The Safety And Efficacy Of Staphylococcus Aureus 4 Antigen Vaccine (SA4Ag) In Adults Undergoing Elective Open Posterior Spinal Fusion Procedures With Multilevel Instrumentation

Summary

EudraCT number	2014-002644-40
Trial protocol	ES GB DE HU AT SE BG
Global end of trial date	27 June 2019

Results information

Result version number	v2 (current)
This version publication date	27 December 2020
First version publication date	21 June 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	B3451002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02388165
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Staphylococcus (S.) aureus 4-antigen (SA4Ag) in the prevention of postoperative S. aureus Bloodstream Infection (BSI) and/or deep incisional or organ/space surgical-site infection (SSI) occurring within 90 days of elective open posterior spinal fusion procedures with multilevel instrumentation, in adults aged 18 to less than (<) 86 years.

To describe the safety and tolerability of a single vaccination of SA4Ag in adults aged 18 to <86 years undergoing elective open posterior spinal fusion procedures with multilevel instrumentation, by measuring local reactions, systemic events, and adverse events (AEs).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	8 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Canada: 174
Country: Number of subjects enrolled	France: 275
Country: Number of subjects enrolled	Germany: 101
Country: Number of subjects enrolled	Hungary: 87
Country: Number of subjects enrolled	Japan: 560
Country: Number of subjects enrolled	Spain: 324
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 1836
Worldwide total number of subjects	3417
EEA total number of subjects	847

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1660
From 65 to 84 years	1748
85 years and over	9

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 3450 subjects were enrolled and randomized in the study. Out of 3450, only 3417 subjects received the investigational product.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Staphylococcus aureus 4-antigen (SA4Ag)

Arm description:

Subjects randomized to SA4Ag received a single dose of 0.5 milliliter (mL) SA4Ag vaccine intramuscularly, 10 to 60 days prior to their scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical procedure.

Arm type	Experimental
Investigational medicinal product name	Staphylococcus aureus 4-antigen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects randomized to SA4Ag received a single dose of 0.5 mL SA4Ag vaccine intramuscularly, 10 to 60 days prior to their scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical procedure.

Arm title	Placebo

Arm description:

Subjects randomized to this arm received placebo containing the vaccine excipients reconstituted in 0.5mL water for injection. It was administered via intramuscular injection, 10 to 60 days prior to scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects randomized to this arm received placebo containing the vaccine excipients reconstituted in 0.5mL water for injection. It was administered via intramuscular injection, 10 to 60 days prior to scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical

Number of subjects in period 1	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo
Started	1708	1709
Completed	1599	1594
Not completed	109	115
Consent withdrawn by subject	26	27
No longer meet eligibility criteria	33	38
Death	13	10
Study terminated by sponsor	5	5
Adverse event	3	5
Unspecified	10	10
Lost to follow-up	19	20

Baseline characteristics

Reporting groups	
Reporting group title	Staphylococcus aureus 4-antigen (SA4Ag)
Reporting group description:	
Subjects randomized to SA4Ag received a single dose of 0.5 milliliter (mL) SA4Ag vaccine intramuscularly, 10 to 60 days prior to their scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical procedure.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to this arm received placebo containing the vaccine excipients reconstituted in 0.5mL water for injection. It was administered via intramuscular injection, 10 to 60 days prior to scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical	

Reporting group values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo	Total
Number of subjects	1708	1709	3417
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	824	836	1660
From 65-84 years	880	868	1748
85 years and over	4	5	9
Age Continuous Units: Years			
arithmetic mean	62.7	62.6	
standard deviation	± 12.3	± 12.6	-
Sex: Female, Male Units: Subjects			
Female	950	940	1890
Male	758	769	1527
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	295	290	585
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	90	111	201
White	1295	1283	2578
More than one race	0	0	0
Unknown or Not Reported	28	25	53
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	69	69	138

Not Hispanic or Latino	1634	1639	3273
Unknown or Not Reported	5	1	6

End points

End points reporting groups

Reporting group title	Staphylococcus aureus 4-antigen (SA4Ag)

Reporting group description:

Subjects randomized to SA4Ag received a single dose of 0.5 milliliter (mL) SA4Ag vaccine intramuscularly, 10 to 60 days prior to their scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical procedure.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to this arm received placebo containing the vaccine excipients reconstituted in 0.5mL water for injection. It was administered via intramuscular injection, 10 to 60 days prior to scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical

Primary: Number of Subjects With Postoperative Staphylococcus Aureus Bloodstream Infection (BSI) and/or Surgical-site Infection (SSI-including Deep Incisional or Organ/Space) Occurring Within 90 Days After Spinal Surgery

End point title	Number of Subjects With Postoperative Staphylococcus Aureus Bloodstream Infection (BSI) and/or Surgical-site Infection (SSI-including Deep Incisional or Organ/Space) Occurring Within 90 Days After Spinal Surgery

End point description:

BSI: clinical infection involving a recognized pathogen (S. aureus) cultured from >=1 blood cultures or commensal organism cultured from >=2 blood cultures. SSI: surgical site infection. Types of SSI in this measure: Deep incisional SSI=infection in deep soft tissues of incision (fascial, muscle layers), Organ space SSI=infection in any part of body (excluding skin incision, fascia or muscle layers) opened/manipulated during surgery. Overall Number of subjects with postoperative BSI and/or SSI (deep incisional or organ/space) confirmed by event adjudication committee were reported. A subject may have met criteria for both BSI and SSI (deep incisional or organ/space). Per-protocol efficacy population: all eligible subjects, vaccinated as randomized, underwent surgery per study criteria within 9-90 days (inclusive) post vaccination (expanded from 10-60 days in protocol), had no infection/malignancy at surgery and no major protocol violations prior to S. aureus infection.

End point type	Primary

End point timeframe:

Day of surgery (Day 1) up to Day 90

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1544	1547		
Units: Subjects	14	14		

Statistical analyses

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo

Number of subjects included in analysis	3091
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	VE
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-126.3
upper limit	55.81

Notes:

[1] - Vaccine Efficacy (VE): calculated as 1-(P/[1-P]*100), where P is the number of SA4Ag cases divided by the total number of cases. The confidence interval (CI) was calculated using the Clopper-Pearson method.

Primary: Percentage of Subjects With Local Reactions Within 10 Days After Vaccination

End point title	Percentage of Subjects With Local Reactions Within 10 Days After Vaccination

End point description:

Local reactions were recorded using an electronic diary (e-diary). Local reactions included redness, swelling and pain at the injection site. Redness and swelling were categorized as mild (2.5 to 5.0 centimeters [cm]), moderate (5.5 to 10.0 cm) and, severe (greater than or equal to [>=] 10.5 cm). Pain at the injection site was defined as mild (did not interfere with activity), moderate (interfered with activity), and severe (prevented daily activity). Subjects may be represented in more than 1 row. Here, “Any” for redness, swelling, pain at the injection site represents any grade of these local reactions among mild, moderate or severe. Safety population: all subjects who received investigational product in this study. Here, "Overall Number of Subjects Analysed, N" signifies number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

Within 10 days after Vaccination

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1692	1685		
Units: Percentage of subjects				
number (confidence interval 95%)				
Redness: Any	9.2 (7.9 to 10.7)	0.9 (0.5 to 1.5)		
Redness: Mild	5.3 (4.2 to 6.4)	0.9 (0.5 to 1.5)		
Redness: Moderate	3.1 (2.4 to 4.1)	0.1 (0.0 to 0.3)		
Redness: Severe	0.8 (0.5 to 1.4)	0.0 (0.0 to 0.2)		
Swelling: Any	8.0 (6.7 to 9.4)	1.0 (0.6 to 1.6)		
Swelling: Mild	4.6 (3.6 to 5.7)	0.7 (0.4 to 1.2)		
Swelling: Moderate	2.7 (2.0 to 3.6)	0.3 (0.1 to 0.7)		
Swelling: Severe	0.7 (0.4 to 1.2)	0.0 (0.0 to 0.2)		
Pain at the injection site: Any	24.1 (22.1 to 26.2)	8.4 (7.1 to 9.9)		
Pain at the injection site: Mild	19.2 (17.4 to 21.2)	7.0 (5.8 to 8.3)		

Pain at the injection site: Moderate	4.3 (3.4 to 5.4)	1.3 (0.8 to 2.0)		
Pain at the injection site: Severe	0.6 (0.3 to 1.1)	0.1 (0.0 to 0.4)		

Statistical analyses

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Redness: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	9.8

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Redness: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	5.6

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Redness: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo

Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	4

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Redness: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.4

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Swelling: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	8.4

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo

Statistical analysis description: Swelling: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	5

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Swelling: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	3.3

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Swelling: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.2

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Pain at the injection site: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.3
upper limit	18.1

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Pain at the injection site: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	14.5

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Pain at the injection site: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	4.2

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Pain at the injection site: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1

Primary: Percentage of Subjects With Systemic Events Within 10 Days After Vaccination

End point title	Percentage of Subjects With Systemic Events Within 10 Days After Vaccination

End point description:

Systemic reactions:fever, fatigue, headache, diarrhea, vomiting, muscle pain and joint pain, recorded using an e-diary. Fever graded:38.0-38.4 degree Celsius(C), 38.5-38.9 degree C, 39.0-40.0 degree C and greater than(>)40.0 degree C. Vomiting graded: mild(1-2 times in 24 hours), moderate(>2 times in 24 hours), severe(required intravenous hydration). Diarrhea: graded as mild(2-3 loose stools in 24 hours), moderate(4-5 loose stools in 24 hours), severe(>=6 loose stools in 24 hours). Headache, fatigue, muscle pain and joint pain graded: mild(no interference with activity), moderate(some interference with activity) and severe(prevented daily routine activity). Subjects may be represented in >1 row. Here"any" for fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain represents any grade of these systemic reactions among mild, moderate or severe. Safety population:all subjects who received investigational product in study. "N":number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

Within 10 days after Vaccination

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1692	1685		
Units: Percentage of subjects				
number (confidence interval 95%)				
Fever: Any	2.0 (1.4 to 2.8)	1.4 (0.9 to 2.0)		
Fever: 38.0 degree C to 38.4 degree C	1.3 (0.8 to 2.0)	0.9 (0.5 to 1.5)		
Fever: 38.5 degree C to 38.9 degree C	0.5 (0.2 to 0.9)	0.4 (0.2 to 0.9)		
Fever: 39.0 degree C to 40.0 degree C	0.2 (0.0 to 0.5)	0.1 (0.0 to 0.3)		

Fever: >40.0 degree C	0.1 (0.0 to 0.3)	0.0 (0.0 to 0.2)		
Fatigue: Any	43.3 (40.9 to 45.7)	40.4 (38.1 to 42.8)		
Fatigue: Mild	14.0 (12.4 to 15.8)	12.6 (11.1 to 14.3)		
Fatigue: Moderate	24.9 (22.8 to 27.0)	23.6 (21.6 to 25.7)		
Fatigue: Severe	4.4 (3.4 to 5.5)	4.2 (3.3 to 5.2)		
Headache: Any	32.4 (30.2 to 34.7)	31.2 (29.0 to 33.5)		
Headache: Mild	17.7 (15.9 to 19.6)	18.0 (16.2 to 19.9)		
Headache: Moderate	13.5 (11.9 to 15.3)	12.0 (10.5 to 13.6)		
Headache: Severe	1.2 (0.8 to 1.9)	1.2 (0.8 to 1.9)		
Diarrhea: Any	17.0 (15.2 to 18.8)	16.0 (14.3 to 17.9)		
Diarrhea: Mild	13.0 (11.4 to 14.7)	12.2 (10.7 to 13.9)		
Diarrhea: Moderate	3.4 (2.6 to 4.4)	2.9 (2.2 to 3.8)		
Diarrhea: Severe	0.5 (0.2 to 1.0)	0.9 (0.5 to 1.5)		
Vomiting: Any	2.7 (1.9 to 3.5)	3.3 (2.5 to 4.2)		
Vomiting: Mild	2.4 (1.7 to 3.2)	2.6 (1.9 to 3.5)		
Vomiting: Moderate	0.3 (0.1 to 0.7)	0.7 (0.3 to 1.2)		
Vomiting: Severe	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)		
Muscle pain: Any	27.9 (25.8 to 30.1)	26.2 (24.1 to 28.4)		
Muscle pain: Mild	10.1 (8.7 to 11.6)	9.3 (8.0 to 10.8)		
Muscle pain: Moderate	15.7 (14.0 to 17.5)	14.6 (12.9 to 16.4)		
Muscle pain: Severe	2.1 (1.5 to 2.9)	2.3 (1.7 to 3.2)		
Joint pain: Any	27.5 (25.4 to 29.7)	25.8 (23.7 to 28.0)		
Joint pain: Mild	9.6 (8.3 to 11.1)	8.0 (6.7 to 9.3)		
Joint pain: Moderate	16.1 (14.4 to 17.9)	16.1 (14.4 to 18.0)		
Joint pain: Severe	1.8 (1.2 to 2.5)	1.7 (1.2 to 2.5)		

Statistical analyses

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fever: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.6

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fever: 38.0 degree C to 38.4 degree C	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	1.2

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fever: 38.5 degree C to 38.9 degree C	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.6

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fever: 39.0 degree C to 40.0 degree C	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo

Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.5

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fever: >40.0 degree C	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.3

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fatigue: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	6.2

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo

Statistical analysis description: Fatigue: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	3.7

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fatigue: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	4.2

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Fatigue: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.6

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Headache: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.443
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	4.4

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Headache: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	2.3

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Headache: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	3.8

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Headache: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.8

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Diarrhea: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.462
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	3.4

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Diarrhea: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	3

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Diarrhea: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.7

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Diarrhea: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.2

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Vomiting: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo

Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.5

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Vomiting: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.8

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Vomiting: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.1

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo

Statistical analysis description: Muscle pain: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	4.7

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Muscle pain: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	2.8

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Muscle pain: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.5

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Muscle pain: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.8

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Joint pain: Any	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentage of subjects
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	4.6

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Joint pain: Mild	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	3.6

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Statistical analysis description: Joint pain: Moderate	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	2.4

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag)
Statistical analysis description: Joint pain: Severe	
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1

Primary: Number of Subjects With Adverse Events (AEs) From Vaccination Until The Day of Surgery (Day 1)

End point title	Number of Subjects With Adverse Events (AEs) From Vaccination Until The Day of Surgery (Day 1)[2]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study vaccine without regard to possibility of causal relationship. AEs including serious as well non-serious AEs. Safety population: all subjects who received investigational product in this study.

End point type	Primary

End point timeframe:

From vaccination up to Day of surgery (Day 1) (10-60 days after vaccination)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis has been performed for this endpoint

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1708	1709		
Units: Subjects	213	178		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events (AEs) From Vaccination Until First Postoperative Evaluation on Day 42

End point title	Number of Subjects With Adverse Events (AEs) From Vaccination Until First Postoperative Evaluation on Day 42[3]

End point description:

An AE was any untoward medical occurrence in a subject who received study vaccine without regard to possibility of causal relationship. AEs including serious as well non-serious AEs. Safety population: all subjects who received investigational product in this study.

End point type	Primary

End point timeframe:

From vaccination until Day 42 after surgery (52-102 days after vaccination)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis has been performed for this endpoint

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1708	1709		
Units: Subjects	1198	1213		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events (AEs) From The Day of Surgery (Day 1) Until First Postoperative Evaluation on Day 42

End point title	Number of Subjects With Adverse Events (AEs) From The Day of Surgery (Day 1) Until First Postoperative Evaluation on Day

	42[4]

End point description:

An AE was any untoward medical occurrence in a subject who received study vaccine without regard to possibility of causal relationship. AEs including serious as well non-serious AEs. Safety population: all subjects who received investigational product in this study.

End point type	Primary

End point timeframe:

Day of surgery (Day 1) up to Day 42 after surgery

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis has been performed for this endpoint

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1708	1709		
Units: Subjects	1136	1167		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Newly Diagnosed Chronic Medical Disorders From First Postoperative Evaluation on Day 42 Until Last Postoperative Evaluation on Day 180

End point title	Number of Subjects With Newly Diagnosed Chronic Medical Disorders From First Postoperative Evaluation on Day 42 Until Last Postoperative Evaluation on Day 180[5]

End point description:

A newly diagnosed chronic medical disorder was defined as a disease or medical condition, not previously identified, that was expected to be persistent or otherwise long-lasting in its effects. Safety population: all subjects who received investigational product in this study.

End point type	Primary

End point timeframe:

Day 42 up to Day 180 (up to 138 days)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis has been performed for this endpoint

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1708	1709		
Units: Subjects	29	41		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Serious Adverse Events (SAEs) From Vaccination Until Last Postoperative Evaluation on Day 180

End point title	Number of Subjects With Serious Adverse Events (SAEs) From Vaccination Until Last Postoperative Evaluation on Day 180[6]

End point description:

An AE was any untoward medical occurrence in a subject who received study vaccine without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death, initial or prolonged inpatient hospitalization, life-threatening experience (immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly. Safety population: all subjects who received investigational product in this study.

End point type	Primary

End point timeframe:

From vaccination up to Day 180 after surgery (190-240 days after vaccination)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis has been performed for this endpoint

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1708	1709		
Units: Subjects	403	424		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Serious Adverse Events (SAEs) From Vaccination Until Day of Surgery (Day 1)

End point title	Number of Subjects With Serious Adverse Events (SAEs) From Vaccination Until Day of Surgery (Day 1)[7]

End point description:

An AE was any untoward medical occurrence in a subject who received study vaccine without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death, initial or prolonged inpatient hospitalization, life-threatening experience (immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly. Safety population: all subjects who received investigational product in this study.

End point type	Primary

End point timeframe:

From vaccination up to Day of surgery (Day 1) (10-60 days after vaccination)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis has been performed for this endpoint

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1708	1709		
Units: Subjects	27	26		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Serious Adverse Events (SAEs) From The Day of Surgery (Day 1) Until Last Postoperative Evaluation on Day 180

End point title	Number of Subjects With Serious Adverse Events (SAEs) From The Day of Surgery (Day 1) Until Last Postoperative Evaluation on Day 180[8]

End point description:

An AE was any untoward medical occurrence in a subject who received study vaccine without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death, initial or prolonged inpatient hospitalization, life-threatening experience (immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly. Safety population: all subjects who received investigational product in this study.

End point type	Primary

End point timeframe:

Day of surgery (Day 1) up to Day 180 after surgery

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis has been performed for this endpoint

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1708	1709		
Units: Subjects	384	401		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Postoperative S. Aureus Blood Stream Infection (BSI) and/or Surgical-site Infection (SSI-including Deep Incisional or Organ/Space) Occurring Within 180 Days After Surgery

End point title	Number of Subjects With Postoperative S. Aureus Blood Stream Infection (BSI) and/or Surgical-site Infection (SSI-including Deep Incisional or Organ/Space) Occurring Within 180 Days After Surgery

End point description:

BSI: clinical infection involving a recognized pathogen (S. aureus) cultured from >=1 blood cultures or

commensal organism cultured from >=2 blood cultures. SSI: surgical site infection. Types of SSI in this measure: Deep incisional SSI=infection in deep soft tissues of incision (fascial, muscle layers); Organ space SSI=infection in any part of body (excluding skin incision, fascia or muscle layers) opened or manipulated during surgery. Overall number of subjects with postoperative BSI and/or SSI (deep incisional or organ/space), confirmed by event adjudication committee were reported. A subject may have met criteria for both BSI and SSI (deep incisional or organ/space). Per-protocol efficacy population: all eligible subjects, vaccinated as randomized, underwent surgery per study criteria within 9-90 days (inclusive) post vaccination (expanded from 10-60 days in protocol), had no infection/malignancy at surgery and no major protocol violations prior to S. aureus infection.

End point type	Secondary

End point timeframe:

Day of surgery (Day 1) up to Day 180 after surgery

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1544	1547		
Units: Subjects	14	14		

Statistical analyses

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3091
Analysis specification	Pre-specified
Analysis type	superiority[9]
Parameter estimate	VE
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-126.3
upper limit	55.81

Notes:

[9] - VE: calculated as 1-(P/[1-P]*100), where P is the number of SA4Ag cases divided by the total number of cases. The CI was calculated using the Clopper-Pearson method.

Secondary: Number of Subjects With any Postoperative S. Aureus Surgical-site Infection (SSI-Superficial, Deep Incisional or Organ/Space) Occurring Within 90 Days After Surgery

End point title	Number of Subjects With any Postoperative S. Aureus Surgical-site Infection (SSI-Superficial, Deep Incisional or Organ/Space) Occurring Within 90 Days After Surgery

End point description:

SSI: surgical site infection. Types of SSI in this measure: Superficial SSI: infection involving skin and subcutaneous tissue of incision, Deep incisional SSI: infection involving deep soft tissues of incision (fascial and muscle layers), Organ/space SSI: infection involving any part of body, (excluding skin incision, fascia, or muscle layers) opened/manipulated during surgery. Overall number of subjects with postoperative SSI (including superficial, deep incisional and/or organ/space SSI) confirmed by event adjudication committee were reported. Per-protocol efficacy population: all eligible subjects, vaccinated

as randomized, underwent surgery per study-defined criteria within 9-90 days post vaccination (expanded from 10-60 days in protocol), had no infection/malignancy at surgery and no major protocol violations prior to S. aureus infection.

End point type	Secondary

End point timeframe:

Day of surgery (Day 1) up to Day 90 after surgery

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1544	1547		
Units: Subjects	24	22		

Statistical analyses

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3091
Analysis specification	Pre-specified
Analysis type	superiority[10]
Parameter estimate	VE
Point estimate	-9.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-104.06
upper limit	41.41

Notes:

[10] - VE: calculated as 1-(P/[1-P]*100), where P is the number of SA4Ag cases divided by the total number of cases. The CI was calculated using the Clopper-Pearson method.

Secondary: Number of Subjects With Any Postoperative S. Aureus Surgical-site Infection (SSI-Superficial, Deep Incisional or Organ/Space) Occurring Within 180 Days After Surgery

End point title	Number of Subjects With Any Postoperative S. Aureus Surgical-site Infection (SSI-Superficial, Deep Incisional or Organ/Space) Occurring Within 180 Days After Surgery

End point description:

SSI: surgical site infection. Types of SSI in this measure: Superficial SSI: infection involving skin and subcutaneous tissue of incision, Deep incisional SSI: infection involving deep soft tissues of incision (fascial and muscle layers), Organ/space SSI: infection involving any part of body, (excluding skin incision, fascia, or muscle layers) opened/manipulated during surgery. Overall number of subjects with postoperative SSI (including superficial, deep incisional and/or organ/space SSI) confirmed by event adjudication committee were reported. Per-protocol efficacy population: all eligible subjects, vaccinated as randomized, underwent surgery per study-defined criteria within 9-90 days post vaccination (expanded from 10-60 days in protocol), had no infection/malignancy at surgery and no major protocol violations prior to S. aureus infection.

End point type	Secondary

End point timeframe:

Day of surgery (Day 1) up to Day 180 after surgery

End point values	Staphylococcus aureus 4-antigen (SA4Ag)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1544	1547		
Units: Subjects	25	23		

Statistical analyses

Statistical analysis title	Staphylococcus aureus 4-antigen (SA4Ag) Vs Placebo
Comparison groups	Staphylococcus aureus 4-antigen (SA4Ag) v Placebo
Number of subjects included in analysis	3091
Analysis specification	Pre-specified
Analysis type	superiority[11]
Parameter estimate	VE
Point estimate	-8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100.42
upper limit	40.8

Notes:

[11] - VE: calculated as 1-(P/[1-P]*100), where P is the number of SA4Ag cases divided by the total number of cases. The CI was calculated using the Clopper-Pearson method.

Adverse events information

Timeframe for reporting adverse events:

SAE and non-SAE: From vaccination up to Day 180 (190-240 days after vaccination). Local and systemic reactions: within 10 days after vaccination (systematic assessment).

Adverse event reporting additional description:

Safety population. The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject or one subject may have experienced both a serious and non-serious event during the analysis population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects randomized to this arm received placebo containing the vaccine excipients reconstituted in 0.5mL water for injection. It was administered via intramuscular injection, 10 to 60 days prior to scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical

Reporting group title	Staphylococcus aureus 4-antigen (SA4Ag)

Reporting group description:

Subjects randomized to SA4Ag received a single dose of 0.5 mL SA4Ag vaccine intramuscularly, 10 to 60 days prior to their scheduled surgery. Subjects were followed from vaccination up to 6 months after their spinal surgical procedure.

Serious adverse events	Placebo	Staphylococcus aureus 4-antigen (SA4Ag)	
Total subjects affected by serious adverse events			
subjects affected / exposed	424 / 1709 (24.81%)	403 / 1708 (23.59%)	
number of deaths (all causes)	10	13	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone neoplasm			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric neoplasm			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of ampulla of vater			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinum neoplasm			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloid leukaemia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal meningioma benign			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	19 / 1709 (1.11%)	21 / 1708 (1.23%)	
occurrences causally related to treatment / all	0 / 19	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	3 / 1709 (0.18%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	10 / 1709 (0.59%)	13 / 1708 (0.76%)	
occurrences causally related to treatment / all	0 / 10	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	3 / 1709 (0.18%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labile blood pressure			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 1709 (0.00%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arthrodesis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle flap operation			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fusion surgery			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calcinosis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	5 / 1709 (0.29%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of device insertion			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysplasia			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrosis			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site reaction			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 1709 (0.18%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	3 / 1709 (0.18%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	7 / 1709 (0.41%)	6 / 1708 (0.35%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical failure			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erectile dysfunction			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic haemorrhage			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	4 / 1709 (0.23%)	7 / 1708 (0.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic pneumonia			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemothorax			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	4 / 1709 (0.23%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal oedema			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal ulceration			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	17 / 1709 (0.99%)	22 / 1708 (1.29%)	
occurrences causally related to treatment / all	0 / 17	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infarction			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 1709 (0.12%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	7 / 1709 (0.41%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract oedema			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	4 / 1709 (0.23%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium tremens			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	7 / 1709 (0.41%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	6 / 1709 (0.35%)	11 / 1708 (0.64%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	6 / 1709 (0.35%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device fastener issue			
subjects affected / exposed	1 / 1709 (0.06%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device loosening			
subjects affected / exposed	2 / 1709 (0.12%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant subsidence			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	4 / 1709 (0.23%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			

subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Adjacent segment degeneration			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia postoperative			
subjects affected / exposed	3 / 1709 (0.18%)	8 / 1708 (0.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic injury			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac function disturbance postoperative			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			

subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device deployment issue			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dispensing error			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dural tear			
subjects affected / exposed	9 / 1709 (0.53%)	9 / 1708 (0.53%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure to communicable disease			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	1 / 1709 (0.06%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 1709 (0.18%)	9 / 1708 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatback syndrome			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	3 / 1709 (0.18%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft complication			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart injury			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haematoma			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incomplete spinal fusion			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			

subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	5 / 1709 (0.29%)	6 / 1708 (0.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	3 / 1709 (0.18%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post laminectomy syndrome			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural constipation			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural discharge			
subjects affected / exposed	2 / 1709 (0.12%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	7 / 1709 (0.41%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative delirium			
subjects affected / exposed	3 / 1709 (0.18%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	7 / 1709 (0.41%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	3 / 1709 (0.18%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	9 / 1709 (0.53%)	7 / 1708 (0.41%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomeningocele			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	4 / 1709 (0.23%)	6 / 1708 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	2 / 1709 (0.12%)	6 / 1708 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury cauda equina			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	4 / 1709 (0.23%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urethral injury			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular injury			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous injury			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	4 / 1709 (0.23%)	5 / 1708 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Spinal muscular atrophy			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 1709 (0.23%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute right ventricular failure			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	10 / 1709 (0.59%)	12 / 1708 (0.70%)	
occurrences causally related to treatment / all	0 / 10	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 1709 (0.23%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Coronary artery disease			
subjects affected / exposed	4 / 1709 (0.23%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery occlusion			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 1709 (0.12%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sinus node dysfunction			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	3 / 1709 (0.18%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fistula			

subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	5 / 1709 (0.29%)	5 / 1708 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal cord paralysis			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased vibratory sense			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	5 / 1709 (0.29%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paresis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Loss of consciousness			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miller Fisher syndrome			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis			
subjects affected / exposed	0 / 1709 (0.00%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			

subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	4 / 1709 (0.23%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 1709 (0.06%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sedation			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord disorder			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal epidural haematoma			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 1709 (0.29%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	4 / 1709 (0.23%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 1709 (0.23%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normocytic anaemia			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet disorder			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal incontinence			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anorectal disorder			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	4 / 1709 (0.23%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1709 (0.06%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	5 / 1709 (0.29%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 1709 (0.06%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	3 / 1709 (0.18%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 1709 (0.06%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 1709 (0.47%)	6 / 1708 (0.35%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder disorder			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neck obstruction			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurogenic bladder			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 1709 (0.18%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthropathy			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	7 / 1709 (0.41%)	8 / 1708 (0.47%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone disorder			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture nonunion			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	2 / 1709 (0.12%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			

subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	3 / 1709 (0.18%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint instability			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kyphosis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	3 / 1709 (0.18%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal disorder			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	12 / 1709 (0.70%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 13	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 1709 (0.06%)	7 / 1708 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyositis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	3 / 1709 (0.18%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scoliosis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal deformity			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal instability			
subjects affected / exposed	3 / 1709 (0.18%)	5 / 1708 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal ligament ossification			
subjects affected / exposed	0 / 1709 (0.00%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			

subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal segmental dysfunction			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 1709 (0.06%)	4 / 1708 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	2 / 1709 (0.12%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	3 / 1709 (0.18%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial disease carrier			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 1709 (0.12%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 1709 (0.23%)	5 / 1708 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site abscess			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lice infestation			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site joint infection			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 1709 (0.70%)	19 / 1708 (1.11%)	
occurrences causally related to treatment / all	0 / 12	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	32 / 1709 (1.87%)	27 / 1708 (1.58%)	
occurrences causally related to treatment / all	0 / 33	0 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 1709 (0.12%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	10 / 1709 (0.59%)	11 / 1708 (0.64%)	
occurrences causally related to treatment / all	0 / 10	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	3 / 1709 (0.18%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 1709 (0.06%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	7 / 1709 (0.41%)	6 / 1708 (0.35%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 1709 (0.06%)	2 / 1708 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	5 / 1709 (0.29%)	5 / 1708 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection bacterial			
subjects affected / exposed	3 / 1709 (0.18%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection fungal			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	3 / 1709 (0.18%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uncoded System Organ Class			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis septic shock			

subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 1709 (0.18%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	2 / 1709 (0.12%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 1709 (0.00%)	1 / 1708 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 1709 (0.06%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	3 / 1709 (0.18%)	3 / 1708 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 1709 (0.06%)	0 / 1708 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	Staphylococcus aureus 4-antigen (SA4Ag)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1489 / 1709 (87.13%)	1530 / 1708 (89.58%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 1709 (1.17%)	15 / 1708 (0.88%)	
occurrences (all)	20	15	
Hypotension			
subjects affected / exposed	84 / 1709 (4.92%)	79 / 1708 (4.63%)	
occurrences (all)	89	81	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	13 / 1709 (0.76%)	18 / 1708 (1.05%)	
occurrences (all)	13	18	
Pyrexia 1			
subjects affected / exposed	114 / 1709 (6.67%)	121 / 1708 (7.08%)	
occurrences (all)	118	130	
Oedema peripheral			

subjects affected / exposed	29 / 1709 (1.70%)	22 / 1708 (1.29%)	
occurrences (all)	30	23	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 1709 (0.94%)	156 / 1708 (9.13%)	
occurrences (all)	16	156	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	681 / 1709 (39.85%)	732 / 1708 (42.86%)	
occurrences (all)	681	732	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	142 / 1709 (8.31%)	408 / 1708 (23.89%)	
occurrences (all)	142	408	
Pyrexia 2			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 1709 (1.35%)	34 / 1708 (1.99%)	
occurrences (all)	23	34	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	17 / 1709 (0.99%)	135 / 1708 (7.90%)	
occurrences (all)	17	135	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	21 / 1709 (1.23%)	10 / 1708 (0.59%)	
occurrences (all)	21	10	
Cough			
subjects affected / exposed	19 / 1709 (1.11%)	8 / 1708 (0.47%)	
occurrences (all)	19	8	
Hypoxia			
subjects affected / exposed	35 / 1709 (2.05%)	24 / 1708 (1.41%)	
occurrences (all)	35	27	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	63 / 1709 (3.69%)	68 / 1708 (3.98%)	
occurrences (all)	65	68	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	108 / 1709 (6.32%)	109 / 1708 (6.38%)	
occurrences (all)	108	111	
Dural tear			
subjects affected / exposed	73 / 1709 (4.27%)	60 / 1708 (3.51%)	
occurrences (all)	75	61	
Fall			
subjects affected / exposed	44 / 1709 (2.57%)	60 / 1708 (3.51%)	
occurrences (all)	48	61	
Incision site pain			
subjects affected / exposed	63 / 1709 (3.69%)	67 / 1708 (3.92%)	
occurrences (all)	64	69	
Procedural pain			
subjects affected / exposed	84 / 1709 (4.92%)	92 / 1708 (5.39%)	
occurrences (all)	85	92	
Wound complication			
subjects affected / exposed	21 / 1709 (1.23%)	19 / 1708 (1.11%)	
occurrences (all)	21	19	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	30 / 1709 (1.76%)	32 / 1708 (1.87%)	
occurrences (all)	31	33	
Nervous system disorders			
Headache 1			
subjects affected / exposed	26 / 1709 (1.52%)	33 / 1708 (1.93%)	
occurrences (all)	27	33	
Dizziness			
subjects affected / exposed	35 / 1709 (2.05%)	30 / 1708 (1.76%)	
occurrences (all)	36	33	
Hypoaesthesia			
subjects affected / exposed	38 / 1709 (2.22%)	50 / 1708 (2.93%)	
occurrences (all)	40	55	

Paraesthesia			
subjects affected / exposed	12 / 1709 (0.70%)	24 / 1708 (1.41%)	
occurrences (all)	12	26	
Headache 2			
alternative assessment type: Systematic			
subjects affected / exposed	526 / 1709 (30.78%)	549 / 1708 (32.14%)	
occurrences (all)	526	549	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	122 / 1709 (7.14%)	97 / 1708 (5.68%)	
occurrences (all)	128	98	
Blood loss anaemia			
subjects affected / exposed	42 / 1709 (2.46%)	58 / 1708 (3.40%)	
occurrences (all)	43	60	
Leukocytosis			
subjects affected / exposed	20 / 1709 (1.17%)	18 / 1708 (1.05%)	
occurrences (all)	20	18	
Thrombocytopenia			
subjects affected / exposed	23 / 1709 (1.35%)	26 / 1708 (1.52%)	
occurrences (all)	23	26	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	192 / 1709 (11.23%)	201 / 1708 (11.77%)	
occurrences (all)	194	202	
Diarrhoea 1			
subjects affected / exposed	30 / 1709 (1.76%)	31 / 1708 (1.81%)	
occurrences (all)	30	32	
Vomiting 1			
subjects affected / exposed	67 / 1709 (3.92%)	80 / 1708 (4.68%)	
occurrences (all)	71	84	
Nausea			
subjects affected / exposed	140 / 1709 (8.19%)	162 / 1708 (9.48%)	
occurrences (all)	140	174	
Diarrhoea 2			
alternative assessment type: Systematic			

subjects affected / exposed	270 / 1709 (15.80%)	287 / 1708 (16.80%)	
occurrences (all)	270	287	
Vomiting 2			
alternative assessment type: Systematic			
subjects affected / exposed	55 / 1709 (3.22%)	45 / 1708 (2.63%)	
occurrences (all)	55	45	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	33 / 1709 (1.93%)	27 / 1708 (1.58%)	
occurrences (all)	33	27	
Erythema			
subjects affected / exposed	61 / 1709 (3.57%)	57 / 1708 (3.34%)	
occurrences (all)	83	79	
Rash			
subjects affected / exposed	15 / 1709 (0.88%)	21 / 1708 (1.23%)	
occurrences (all)	15	21	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	59 / 1709 (3.45%)	58 / 1708 (3.40%)	
occurrences (all)	62	59	
Acute kidney injury			
subjects affected / exposed	13 / 1709 (0.76%)	24 / 1708 (1.41%)	
occurrences (all)	15	24	
Musculoskeletal and connective tissue disorders			
Arthralgia 1			
subjects affected / exposed	29 / 1709 (1.70%)	27 / 1708 (1.58%)	
occurrences (all)	32	30	
Back pain			
subjects affected / exposed	36 / 1709 (2.11%)	39 / 1708 (2.28%)	
occurrences (all)	40	40	
Muscular weakness			
subjects affected / exposed	24 / 1709 (1.40%)	25 / 1708 (1.46%)	
occurrences (all)	25	28	
Muscle spasms			

subjects affected / exposed	30 / 1709 (1.76%)	21 / 1708 (1.23%)	
occurrences (all)	31	22	
Musculoskeletal pain			
subjects affected / exposed	20 / 1709 (1.17%)	24 / 1708 (1.41%)	
occurrences (all)	21	25	
Pain in extremity			
subjects affected / exposed	59 / 1709 (3.45%)	55 / 1708 (3.22%)	
occurrences (all)	64	60	
Myalgia (muscle pain)			
alternative assessment type: Systematic			
subjects affected / exposed	442 / 1709 (25.86%)	472 / 1708 (27.63%)	
occurrences (all)	442	472	
Arthralgia 2			
alternative assessment type: Systematic			
subjects affected / exposed	435 / 1709 (25.45%)	465 / 1708 (27.22%)	
occurrences (all)	435	465	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	23 / 1709 (1.35%)	28 / 1708 (1.64%)	
occurrences (all)	24	29	
Urinary tract infection			
subjects affected / exposed	103 / 1709 (6.03%)	96 / 1708 (5.62%)	
occurrences (all)	113	102	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	18 / 1709 (1.05%)	24 / 1708 (1.41%)	
occurrences (all)	18	24	
Hyperglycaemia			
subjects affected / exposed	25 / 1709 (1.46%)	28 / 1708 (1.64%)	
occurrences (all)	25	29	
Hyponatraemia			
subjects affected / exposed	20 / 1709 (1.17%)	22 / 1708 (1.29%)	
occurrences (all)	20	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2015	Protocol Amendment 2: 1. All invasive infections were adjudicated by the event adjudication committee (EAC); previously only those associated with S. aureus were to be adjudicated (change requested by the EAC). 2. Any preexisting spinal instrumentation or tissue removed during a revisional surgical procedure, must be cultured (to detect preexisting pathogens) 3. Spinal steroids added to concomitant medications (may have an effect on the immune response). 4. Added missing text to criteria for vertebral disc space infection and superficial SSI (previous omissions). Appendix 3: Added collection of data regarding composition of implanted devices (request by investigators).
01 June 2016	Protocol Amendment 3: 1. Clarified the remit of the endpoint adjudication committee (EAC); ie, the remit of the EAC is not restricted to S. aureus infections. 2. Refined evaluation periods for protocol-defined infections and organ failure events. 2. Amended an exclusion criterion (No. 19) to exclude subjects with indwelling central nervous system shunts and implanted devices. 3. Added details of periodic checks for study futility that will be performed prior to the interim analysis. This includes the data monitoring committee's role in these assessments.
05 February 2018	Protocol amendment 4: 1. Changed the expected number of enrolled subjects from 2600 to 6000 and target number of endpoint cases changed from 42 to 48. 2. Amended an exclusion criterion to clarify that subjects with rheumatologic disorders that are not being treated with immunosuppressant medications can enter the study. 3. Modified interim analysis case count from 21 to 24; removed all REFs to hierarchical testing of proof of principle/high-level efficacy. 4. Modified sample size and power calculations based on increased sample size, primary endpoint case count, VE and incidence rates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported