



Clinical trial results:

A Phase 3, Placebo-Controlled, Randomised, Observer-Blinded Study to Evaluate the Efficacy, Safety, And Tolerability of a Clostridium Difficile Vaccine in Adults 50 Years of Age and Older

Summary

EudraCT number	2016-003866-14
Trial protocol	SK BG SE HU BE CZ GB DE FI PT ES PL FR
Global end of trial date	21 December 2021

Results information

Result version number	v1 (current)
This version publication date	16 December 2022
First version publication date	16 December 2022

Trial information

Trial identification

Sponsor protocol code	B5091007
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03090191
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, 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	11 February 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that Pfizer's C difficile vaccine is effective in reducing the incidence of a first primary episode of CDI and to evaluate the safety profile of Pfizer's C difficile vaccine as measured by the percentage of subjects reporting local reactions and systemic events, Adverse Events (AEs), and Serious Adverse Events (SAEs).

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 Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 118
Country: Number of subjects enrolled	Australia: 258
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Bulgaria: 868
Country: Number of subjects enrolled	Canada: 449
Country: Number of subjects enrolled	Chile: 37
Country: Number of subjects enrolled	Colombia: 456
Country: Number of subjects enrolled	Czechia: 141
Country: Number of subjects enrolled	Germany: 301
Country: Number of subjects enrolled	Spain: 204
Country: Number of subjects enrolled	Finland: 119
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	United Kingdom: 224
Country: Number of subjects enrolled	Hungary: 600
Country: Number of subjects enrolled	Japan: 1062
Country: Number of subjects enrolled	Korea, Republic of: 175
Country: Number of subjects enrolled	Peru: 61
Country: Number of subjects enrolled	Poland: 671
Country: Number of subjects enrolled	Portugal: 75

Country: Number of subjects enrolled	Slovakia: 369
Country: Number of subjects enrolled	Sweden: 185
Country: Number of subjects enrolled	Taiwan: 89
Country: Number of subjects enrolled	United States: 10899
Worldwide total number of subjects	17440
EEA total number of subjects	3612

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)	5925
From 65 to 84 years	11184
85 years and over	331

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 18095 subjects signed the informed consent form (ICF). Among that 560 subjects did not meet all eligibility criteria, were not randomised and vaccinated. Overall, 17535 subjects were randomised. Among those, 17440 subjects received at least 1 dose of 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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Clostridium difficile Vaccine

Arm description:

Subjects received Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.

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

Dosage and administration details:

Subjects received 200 microgram total toxoid per dose intramuscularly.

Arm title	Placebo
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Arm description:

Subjects received placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6.

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

Dosage and administration details:

Subjects received Normal saline solution of 0.9 percent [%] sodium chloride intramuscularly.

Number of subjects in period 1	Clostridium difficile Vaccine	Placebo
Started	8722	8718
Vaccinated at Month 0 (Dose 1)	8722	8718
Vaccinated at Month 1 (Dose 2)	8311	8331
Vaccinated at Month 6 (Dose 3)	7894	7967
Completed	5532	5575
Not completed	3190	3143
Adverse event, serious fatal	368	358
Physician decision	77	66
Consent withdrawn by subject	2160	2133
Adverse event, non-fatal	87	72
Site terminated	7	8
Unspecified	66	60
Lost to follow-up	382	394
Protocol deviation	43	52

Baseline characteristics

Reporting groups

Reporting group title	Clostridium difficile Vaccine
Reporting group description:	
Subjects received Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6.	

Reporting group values	Clostridium difficile Vaccine	Placebo	Total
Number of subjects	8722	8718	17440
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)	2962	2963	5925
From 65-84 years	5597	5587	11184
85 years and over	163	168	331
Age Continuous			
Units: Years			
arithmetic mean	68.0	68.1	
standard deviation	± 7.5	± 7.5	-
Sex: Female, Male			
Units: Subjects			
Female	4472	4501	8973
Male	4250	4217	8467
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	53	54	107
Asian	754	725	1479
Native Hawaiian or Other Pacific Islander	20	14	34
Black or African American	663	666	1329
White	6891	6922	13813
More than one race	327	322	649
Unknown or Not Reported	14	15	29
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1119	1143	2262
Not Hispanic or Latino	7546	7515	15061
Unknown or Not Reported	57	60	117

End points

End points reporting groups

Reporting group title	Clostridium difficile Vaccine
Reporting group description: Subjects received Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6.	

Primary: Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 3

End point title	Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 3
End point description: CDI definition 1 for a primary episode of CDI(no previous CDI onset in prior 8 weeks)defined as either a) presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7]) in 24 or fewer consecutive hours,stool sample positive for toxin B gene(by polymerase chain reaction[PCR]) and positive for toxin A and/or toxin B,as measured in central laboratory;or b)Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically;and corresponding stool sample positive for toxin B gene(via PCR)as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of investigational product to which they were randomised and had no major protocol violations up to and including 14 days after dose 3. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.	
End point type	Primary
End point timeframe: From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)	

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7707	7805		
Units: Episodes	17	25		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
Statistical analysis description: Vaccine efficacy(VE)=100*(1-infection rate ratio[IRR]),IRR=calculated ratio of first primary CDI incidence between Clostridium difficile vaccine group and placebo group. 96.4% CI was estimated using Clopper-Pearson-Method	
Comparison groups	Clostridium difficile Vaccine v Placebo

Number of subjects included in analysis	15512
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
Parameter estimate	Vaccine efficacy
Point estimate	31
Confidence interval	
level	Other: 96.4 %
sides	2-sided
lower limit	-38.7
upper limit	66.6

Notes:

[1] - Lower bound of confidence interval greater than 20% demonstrate vaccine efficacy.

Primary: Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 2

End point title	Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 2
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End point description:

CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks) defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7]) in 24 or fewer consecutive hours, and stool sample positive for toxin B gene(by polymerase chain reaction [PCR]) and positive for toxin A and/or toxin B, as measured in central laboratory; or b)Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample positive for toxin B gene (via PCR) as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Primary
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End point timeframe:

From 14 days after Dose 2 to the end of the surveillance period (mean follow-up after dose 2 was 36 months)

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8139	8184		
Units: Episodes	24	34		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
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Statistical analysis description:

Vaccine efficacy(VE)=100*(1-infection rate ratio[IRR]),IRR=calculated ratio of first primary CDI incidence between Clostridium difficile vaccine group and placebo group. 96.4% CI was estimated using Clopper-Pearson-Method.

Comparison groups	Clostridium difficile Vaccine v Placebo
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Number of subjects included in analysis	16323
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
Parameter estimate	Vaccine efficacy
Point estimate	28.6
Confidence interval	
level	Other: 96.4 %
sides	2-sided
lower limit	-28.4
upper limit	61

Notes:

[2] - Lower bound of confidence interval greater than 20% demonstrate vaccine efficacy.

Primary: Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 1

End point title	Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 1 ^[3]
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End point description:

Local reactions included redness, swelling and pain at injection site. These were recorded by subjects in an electronic diary (e-diary). Redness and swelling were measured and recorded in measuring device units. One measuring device unit= 0.5 centimeter (cm) and graded as mild: 2.5 to 5.0 cm, moderate: greater than (>) 5.0 to 10.0 cm, severe: >10.0 cm. Grade 4 indicated necrosis or exfoliative dermatitis for redness and necrosis for swelling. Pain at injection site was graded as mild: did not interfere with daily activity, moderate: interfered with daily activity, severe: prevented daily activity. Grade 4 indicated emergency room visit or hospitalisation. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Primary
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End point timeframe:

Within 7 days after Dose 1 at Month 0

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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8558	8510		
Units: Percentage of subjects				
number (confidence interval 95%)				
Redness: Mild	1.5 (1.3 to 1.8)	0.6 (0.4 to 0.7)		
Redness: Moderate	0.5 (0.4 to 0.7)	0.3 (0.2 to 0.4)		
Redness: Severe	0.4 (0.3 to 0.6)	0.2 (0.1 to 0.3)		
Redness: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Swelling: Mild	1.5 (1.3 to 1.8)	0.5 (0.3 to 0.7)		
Swelling: Moderate	0.9 (0.8 to 1.2)	0.3 (0.2 to 0.5)		
Swelling: Severe	0.3 (0.2 to 0.5)	0.1 (0.0 to 0.2)		
Swelling: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Pain at injection site: Mild	17.5 (16.7 to 18.3)	6.2 (5.7 to 6.8)		
Pain at injection site: Moderate	2.2 (1.9 to 2.5)	0.8 (0.6 to 1.0)		
Pain at injection site: Severe	0.1 (0.0 to 0.2)	0.1 (0.1 to 0.2)		
Pain at injection site: Grade 4	0 (0.0 to 0.0)	0.1 (0.0 to 0.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 2

End point title	Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 2 ^[4]
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End point description:

Local reactions included redness, swelling and pain at injection site. These were recorded by subjects in an e-diary. Redness and swelling were measured and recorded in measuring device units. One measuring device unit= 0.5 cm and graded as mild: 2.5 to 5.0 cm, moderate: > 5.0 to 10.0 cm, severe: >10.0 cm. Grade 4 indicated necrosis or exfoliative dermatitis for redness and necrosis for swelling. Pain at injection site was graded as mild: did not interfere with daily activity, moderate: interfered with daily activity, severe: prevented daily activity. Grade 4 indicated emergency room visit or hospitalisation. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Primary
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End point timeframe:

Within 7 days after Dose 2 at Month 1

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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8041	8039		
Units: Percentage of subjects				
number (confidence interval 95%)				
Redness: Mild	2.6 (2.2 to 2.9)	0.3 (0.2 to 0.5)		
Redness: Moderate	2.2 (1.9 to 2.6)	0.2 (0.1 to 0.3)		
Redness: Severe	0.9 (0.7 to 1.2)	0.1 (0.0 to 0.1)		
Redness: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Swelling: Mild	3.2 (2.8 to 3.6)	0.3 (0.2 to 0.53)		
Swelling: Moderate	3.0 (2.6 to 3.4)	0.2 (0.1 to 0.3)		
Swelling: Severe	0.9 (0.7 to 1.1)	0.1 (0.0 to 0.2)		
Swelling: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Pain at injection site: Mild	23.0 (22.1 to 23.9)	4.3 (3.9 to 4.8)		
Pain at injection site: Moderate	4.5 (4.0 to 4.9)	0.7 (0.5 to 0.9)		
Pain at injection site: Severe	0.2 (0.1 to 0.3)	0.1 (0.0 to 0.1)		
Pain at injection site: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 3

End point title	Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 3 ^[5]
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End point description:

Local reactions included redness, swelling and pain at injection site. These were recorded by subjects in an e-diary. Redness and swelling were measured and recorded in measuring device units. One measuring device unit= 0.5 cm and graded as mild: 2.5 to 5.0 cm, moderate: > 5.0 to 10.0 cm, severe: >10.0 cm. Grade 4 indicated necrosis or exfoliative dermatitis for redness and necrosis for swelling. Pain at injection site was graded as mild: did not interfere with daily activity, moderate: interfered with daily activity, severe: prevented daily activity. Grade 4 indicated emergency room visit or hospitalisation. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Primary
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End point timeframe:

Within 7 days after Dose 3 at Month 6

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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7526	7569		
Units: Percentage of subjects				
number (confidence interval 95%)				
Redness: Mild	2.6 (2.3 to 3.0)	0.4 (0.2 to 0.5)		
Redness: Moderate	2.4 (2.1 to 2.8)	0.2 (0.1 to 0.4)		
Redness: Severe	0.7 (0.5 to 0.9)	0.1 (0.0 to 0.1)		
Redness: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Swelling: Mild	3.5 (3.1 to 3.9)	0.3 (0.2 to 0.5)		
Swelling: Moderate	3.3 (2.9 to 3.7)	0.2 (0.1 to 0.4)		
Swelling: Severe	0.8 (0.6 to 1.1)	0 (0.0 to 0.0)		
Swelling: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Pain at injection site: Mild	21.0 (20.1 to 21.9)	3.6 (3.2 to 4.1)		
Pain at injection site: Moderate	4.5 (4.0 to 5.0)	0.8 (0.6 to 1.0)		
Pain at injection site: Severe	0.2 (0.1 to 0.4)	0.1 (0.0 to 0.1)		
Pain at injection site: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 1

End point title	Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 1 ^[6]
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End point description:

Systemic events included fever, fatigue, headache, joint pain, muscle pain and vomiting. These were recorded by subjects in an e-diary. Fever was categorised as: mild: (38.0 to 38.4 degree Celsius [deg C]), moderate: (38.5 to 38.9 deg C), severe (39.0 to 40.0 deg C), potentially life threatening (> 40.0 deg C). Fatigue, headache, joint pain and muscle pain were graded as mild: did not interfere with activity, moderate: some interference with activity, severe: prevented daily activity, grade 4: emergency room visit or hospitalisation. Vomiting was graded as mild: 1 to 2 times in 24 hours, moderate: >2 times in 24 hours, severe: required intravenous hydration, grade 4: emergency room visit or hospitalisation for hypotensive shock. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Primary
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End point timeframe:

Within 7 days after Dose 1 at Month 0

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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8558	8510		
Units: Percentage of subjects				
number (confidence interval 95%)				
Headache: Mild	11.6 (10.9 to 12.3)	10.1 (9.4 to 10.7)		
Headache: Moderate	5.8 (5.3 to 6.3)	5.4 (4.9 to 5.9)		
Headache: Severe	0.5 (0.4 to 0.7)	0.6 (0.5 to 0.8)		
Headache: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Vomiting: Mild	1.1 (0.8 to 1.3)	0.7 (0.5 to 0.9)		
Vomiting: Moderate	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.3)		
Vomiting: Severe	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)		
Vomiting: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
New or worsening muscle pain: Mild	5.2 (4.7 to 5.7)	3.9 (3.5 to 4.3)		
New or worsening muscle pain: Moderate	5.7 (5.2 to 6.2)	5.6 (5.1 to 6.1)		
New or worsening muscle pain: Severe	0.6 (0.4 to 0.8)	0.6 (0.5 to 0.8)		
New or worsening muscle pain: Grade 4	0.1 (0.0 to 0.1)	0 (0.0 to 0.0)		
New or worsening joint pain: Mild	4.0 (3.6 to 4.5)	3.3 (2.9 to 3.7)		
New or worsening joint pain: Moderate	5.2 (4.7 to 5.7)	5.0 (4.5 to 5.5)		
New or worsening joint pain: Severe	0.5 (0.4 to 0.7)	0.5 (0.3 to 0.6)		
New or worsening joint pain: Grade 4	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Fever: 38.0-38.4 deg C	0.5 (0.3 to 0.6)	0.4 (0.3 to 0.5)		
Fever: 38.5-38.9 deg C	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.3)		
Fever: 39.0-40.0 deg C	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)		
Fever: >40.0 deg C	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)		
Fatigue: Mild	11.6 (10.9 to 12.3)	10.2 (9.6 to 10.9)		
Fatigue: Moderate	10.6 (10.0 to 11.3)	10.4 (9.7 to 11.0)		
Fatigue: Severe	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.5)		
Fatigue: Grade 4	0.1 (0.0 to 0.1)	0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 2

End point title	Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 2 ^[7]
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End point description:

Systemic events included fever, fatigue, headache, joint pain, muscle pain and vomiting. These were recorded by subjects in an e-diary. Fever was categorised as: mild: (38.0 to 38.4 deg C), moderate: (38.5 to 38.9 deg C), severe (39.0 to 40.0 deg C), potentially life threatening (> 40.0 deg C). Fatigue, headache, joint pain and muscle pain were graded as mild: did not interfere with activity, moderate: some interference with activity, severe: prevented daily activity, grade 4: emergency room visit or hospitalisation. Vomiting was graded as mild: 1 to 2 times in 24 hours, moderate: >2 times in 24 hours, severe: required intravenous hydration, grade 4: emergency room visit or hospitalisation for hypotensive shock. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point and "number analysed" signifies subjects evaluable for specific rows.

End point type	Primary
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End point timeframe:

Within 7 days after Dose 2 at Month 1

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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8041	8039		
Units: Percentage of subjects				
number (confidence interval 95%)				
Fatigue: Mild(n=8041, 8039)	10.2 (9.6 to 10.9)	7.8 (7.2 to 8.4)		
Fatigue: Moderate(n=8041, 8039)	9.4 (8.7 to 10.0)	9.0 (8.4 to 9.6)		
Fatigue: Severe(n=8041, 8039)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)		
Fatigue: Grade 4(n=8041, 8039)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Headache: Mild(n=8041, 8039)	10.1 (9.4 to 10.8)	8.3 (7.7 to 9.0)		
Headache: Moderate(n=8041, 8039)	5.1 (4.6 to 5.6)	5.5 (5.0 to 6.1)		
Headache: Severe(n=8041, 8039)	0.5 (0.4 to 0.7)	0.4 (0.3 to 0.6)		
Headache: Grade 4(n=8041, 8039)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Vomiting: Mild(n=8041, 8039)	0.8 (0.6 to 1.0)	0.7 (0.5 to 0.9)		
Vomiting: Moderate(n=8041, 8039)	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.3)		
Vomiting: Severe(n=8041, 8039)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Vomiting: Grade 4(n=8041, 8039)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
New or worsening muscle pain:Mild(n=8041,8039)	4.8 (4.3 to 5.3)	3.2 (2.9 to 3.6)		
New or worsening muscle pain:Moderate(n=8041,8039)	5.1 (4.6 to 5.6)	4.2 (3.8 to 4.7)		
New or worsening muscle pain:Severe(n=8041,8039)	0.5 (0.4 to 0.7)	0.6 (0.4 to 0.8)		
New or worsening muscle pain:Grade 4(n=8041,8039)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
New or worsening joint pain: Mild(n=8041, 8039)	3.8 (3.4 to 4.2)	2.9 (2.6 to 3.3)		

New or worsening joint pain: Moderate (n=8041,8039)	4.6 (4.1 to 5.0)	3.9 (3.5 to 4.4)		
New or worsening joint pain: Severe (n=8041,8039)	0.4 (0.3 to 0.6)	0.5 (0.3 to 0.6)		
New or worsening joint pain: Grade 4 (n=8041,8039)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Fever: 38.0-38.4 deg C (n=8041,8038)	0.4 (0.3 to 0.6)	0.4 (0.3 to 0.6)		
Fever: 38.5-38.9 deg C (n=8041,8038)	0.2 (0.1 to 0.3)	0.1 (0.0 to 0.2)		
Fever: 39.0-40.0 deg C (n=8041,8038)	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.3)		
Fever: >40.0 deg C (n=8041, 8038)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 3

End point title	Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 3 ^[8]
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End point description:

Systemic events included fever, fatigue, headache, joint pain, muscle pain and vomiting. These were recorded by subjects in an e-diary. Fever was categorised as: mild: (38.0 to 38.4 deg C), moderate: (38.5 to 38.9 deg C), severe (39.0 to 40.0 deg C), potentially life threatening (> 40.0 deg C). Fatigue, headache, joint pain and muscle pain were graded as mild: did not interfere with activity, moderate: some interference with activity, severe: prevented daily activity, grade 4: emergency room visit or hospitalisation. Vomiting was graded as mild: 1 to 2 times in 24 hours, moderate: >2 times in 24 hours, severe: required intravenous hydration, grade 4: emergency room visit or hospitalisation for hypotensive shock. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point and "number analysed" signifies subjects evaluable for specific rows.

End point type	Primary
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End point timeframe:

Within 7 days after Dose 3 at Month 6

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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7526	7569		
Units: Percentage of subjects				
number (confidence interval 95%)				
Fatigue: Mild (n=7526,7569)	9.2 (8.6 to 9.9)	7.0 (6.4 to 7.6)		
Fatigue: Moderate (n=7526,7569)	9.4 (8.7 to 10.0)	8.0 (7.4 to 8.6)		
Fatigue: Severe (n=7526,7569)	0.8 (0.6 to 1.0)	0.8 (0.6 to 1.0)		
Fatigue: Grade 4 (n=7526,7569)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Headache: Mild (n=7526,7569)	8.4 (7.8 to 9.0)	7.9 (7.3 to 8.5)		
Headache: Moderate (n=7526,7569)	5.7 (5.1 to 6.2)	4.7 (4.2 to 5.2)		
Headache: Severe (n=7526,7569)	0.3 (0.2 to 0.5)	0.5 (0.3 to 0.6)		
Headache: Grade 4 (n=7526,7569)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Vomiting: Mild (n=7526,7569)	0.6 (0.5 to 0.8)	0.5 (0.4 to 0.7)		

Vomiting: Moderate(n=7526,7569)	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.3)		
Vomiting: Severe(n=7526,7569)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Vomiting: Grade 4(n=7526,7569)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
New or worsening muscle pain:Mild(n=7526,7569)	4.0 (3.5 to 4.4)	2.5 (2.2 to 2.9)		
New or worsening muscle pain:Moderate(n=7526,7569)	4.8 (4.3 to 5.3)	4.1 (3.6 to 4.6)		
New or worsening muscle pain:Severe(n=7526,7569)	0.5 (0.3 to 0.7)	0.5 (0.3 to 0.7)		
New or worsening muscle pain:Grade 4(n=7526,7569)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
New or worsening joint pain:Mild(n=7526,7569)	3.0 (2.6 to 3.4)	2.5 (2.2 to 2.9)		
New or worsening joint pain:Moderate(n=7526,7569)	4.4 (3.9 to 4.8)	3.6 (3.2 to 4.0)		
New or worsening joint pain:Severe(n=7526,7569)	0.4 (0.3 to 0.6)	0.4 (0.3 to 0.5)		
New or worsening joint pain:Grade 4(n=7526,7569)	0.1 (0.0 to 0.1)	0 (0.0 to 0.0)		
Fever: 38.0-38.4 deg C(n=7525,7569)	0.4 (0.3 to 0.6)	0.2 (0.1 to 0.4)		
Fever: 38.5-38.9 deg C(n=7525,7569)	0.1 (0.1 to 0.2)	0.1 (0.0 to 0.2)		
Fever: 39.0-40.0 deg C(n=7525,7569)	0.1 (0.1 to 0.2)	0.1 (0.0 to 0.2)		
Fever: >40.0 deg C(n=7525,7569)	0.1 (0.0 to 0.1)	0.1 (0.1 to 0.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Adverse Events (AEs)

End point title	Number of Subjects Reporting Adverse Events (AEs) ^[9]
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End point description:

An AE was defined as any untoward medical occurrence in a subjects who received investigational product without regard to possibility of causal relationship. AEs included both serious and all non-serious adverse events. An SAE was defined as any untoward medical occurrence at any dose that resulted in any of the following outcomes: death; life-threatening (immediate risk of death); required inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); congenital anomaly/birth defect; or that was considered as an important medical event. AEs included both SAEs and all Non-SAEs (except local and systemic events). Safety analysis population included all subjects who received at least 1 dose of the investigational product.

End point type	Primary
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End point timeframe:

From Day 1 of Dose 1 to 1 Month after Dose 3 (7 Months)

Notes:

[9] - 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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8722	8718		
Units: Subjects				
Any AEs	4161	4050		
Non-Serious AEs	3913	3791		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Serious Adverse Events (SAEs)

End point title	Number of Subjects Reporting Serious Adverse Events
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End point description:

An SAE was defined as any untoward medical occurrence at any dose that resulted in any of the following outcomes: death; life-threatening (immediate risk of death); required inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); congenital anomaly/birth defect; or that was considered as an important medical event. Safety analysis population included all participants who received at least 1 dose of the investigational product.

End point type	Primary
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End point timeframe:

From Day 1 of Dose 1 up to 6 months after Dose 3 (up to Month 12)

Notes:

[10] - 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: Only descriptive data was planned for this endpoint.

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8722	8718		
Units: Subjects	719	722		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of all Episodes of CDI (Definition 1 and 2) After Dose 3

End point title	Number of all Episodes of CDI (Definition 1 and 2) After Dose 3
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End point description:

CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks),CDI definition 2 for recurrent episode(episode occurred 8 weeks or less after onset of previous episode[provided symptoms of previous episode resolved])were both defined as either a)presence of diarrhea,(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours,stool sample positive for toxin B gene(by PCR),positive for toxin A and/or B,measured in central laboratory;or b)Pseudomembranous colitis diagnosed at colonoscopy, surgery, histopathologically; corresponding stool sample positive for toxin B gene(via PCR)measured in central laboratory.Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of investigational product to which they were randomized had no major protocol violations up to and including 14 days after dose 3. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Secondary
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End point timeframe:

From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7707	7805		
Units: Episodes	28	32		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
Statistical analysis description: VE = 100*(1 - Hazard Ratio). 98.2% CI was estimated using Proportional Means Model.	
Comparison groups	Clostridium difficile Vaccine v Placebo
Number of subjects included in analysis	15512
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Vaccine efficacy
Point estimate	11.1
Confidence interval	
level	Other: 98.2 %
sides	2-sided
lower limit	-110.7
upper limit	62.5

Secondary: Time to Resolution for Subjects With First Primary Episodes of CDI (Definition 1) After Dose 3

End point title	Time to Resolution for Subjects With First Primary Episodes of CDI (Definition 1) After Dose 3
End point description: Resolution of event was last day on which event was recorded in e-diary or date the event ends if it was unresolved during subject diary-recording period(end date collected on case report form[CRF]).CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks) defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7]) in 24 or fewer consecutive hours, and stool sample positive for toxin B gene(by polymerase chain reaction [PCR]) and positive for toxin A and/or toxin B, as measured in central laboratory; or b)Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample positive for toxin B gene (via PCR) as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-3 analysis population was analysed. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end	
End point type	Secondary
End point timeframe: From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)	

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	24		
Units: Days				
median (full range (min-max))	1.0 (1 to 18)	4.0 (1 to 183)		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
Comparison groups	Clostridium difficile Vaccine v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0172
Method	Wilcoxon Rank Sum Test (2-sided)

Secondary: Proportion of Subjects who Required Medical Attention During First Primary Episode of CDI (Definition 1) After Dose 3

End point title	Proportion of Subjects who Required Medical Attention During First Primary Episode of CDI (Definition 1) After Dose 3
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End point description:

CDI definition 1 for a primary episode of CDI (no previous CDI onset in prior 8 weeks) defined as either a) presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours, and stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (via PCR) as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of the investigational product to which they were randomised and had no major protocol violations up to and including 14 days after dose 3. Here, "Overall Number of Subjects Analyzed" signifies subjects evaluable for this end point.

End point type	Secondary
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End point timeframe:

From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	25		
Units: Proportion of subjects				
number (not applicable)	0	0.440		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
Comparison groups	Clostridium difficile Vaccine v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratio of proportions
Point estimate	0
Confidence interval	
level	Other: 98.2 %
sides	2-sided
lower limit	0
upper limit	0.81

Secondary: Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 3

End point title	Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 3
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End point description:

CDI definition 2 for recurrent episode(an episode of CDI that occurred 8 weeks or less after onset of a previous CDI episode[provided symptoms of previous episode had resolved]),defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours; stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (by PCR) as measured in central laboratory. Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of the investigational product to which they were randomised and had no major protocol violations up to and including 14 days after dose 3. Here, "Overall Number of Subjects Analyzed" signifies subjects evaluable for this end point.

End point type	Secondary
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End point timeframe:

From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7707	7805		
Units: Subjects	5	3		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
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Statistical analysis description:

Vaccine efficacy(VE)=100*(1-infection rate ratio[IRR]),IRR=calculated ratio of recurrent CDI incidence between Clostridium difficile vaccine group and placebo group. 98.2% CI was estimated using Clopper-Pearson-Method.

Comparison groups	Clostridium difficile Vaccine v Placebo
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Number of subjects included in analysis	15512
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Vaccine efficacy
Point estimate	-69.3
Confidence interval	
level	Other: 98.2 %
sides	2-sided
lower limit	-1533.1
upper limit	75.6

Secondary: Number of all Episodes of CDI (Definition 1 and 2) After Dose 2

End point title	Number of all Episodes of CDI (Definition 1 and 2) After Dose 2
End point description:	<p>CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks),CDI definition 2 for recurrent episode(episode occurred 8 weeks or less after onset of previous episode[provided symptoms of previous episode resolved])were both defined as either a)presence of diarrhea,(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours,stool sample positive for toxin B gene(by PCR),positive for toxin A and/or B,measured in central laboratory;or</p> <p>b)Pseudomembranous colitis diagnosed at colonoscopy, surgery, histopathologically; corresponding stool sample positive for toxin B gene(via PCR)measured in central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.</p>
End point type	Secondary
End point timeframe:	<p>From 14 days after Dose 2 to the end of the surveillance period (mean follow-up after dose 2 was 36 months)</p>

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8139	8184		
Units: Episodes	37	44		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
Statistical analysis description:	<p>VE = 100*(1 - Hazard Ratio). 98.2% CI was estimated using Proportional Means Model</p>
Comparison groups	Clostridium difficile Vaccine v Placebo

Number of subjects included in analysis	16323
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Vaccine efficacy
Point estimate	14.9
Confidence interval	
level	Other: 98.2 %
sides	2-sided
lower limit	-74.6
upper limit	58.5

Secondary: Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 2

End point title	Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 2
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End point description:

CDI definition 2 for recurrent episode(an episode of CDI that occurred 8 weeks or less after onset of a previous CDI episode[provided symptoms of previous episode had resolved]),defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours; stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (by PCR) as measured in central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Secondary
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End point timeframe:

From 14 days after Dose 2 to the end of the surveillance period (mean follow-up after dose 2 was 36 months)

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8139	8184		
Units: Subjects	6	3		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
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Statistical analysis description:

VE = 100*(1 - IRR), where IRR= the calculated ratio of recurrent CDI incidence between the Clostridium difficile vaccine group and the placebo group. 98.2% CI was estimated using Clopper-Pearson-Method.

Comparison groups	Clostridium difficile Vaccine v Placebo
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Number of subjects included in analysis	16323
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Vaccine efficacy
Point estimate	-102.4
Confidence interval	
level	Other: 98.2 %
sides	2-sided
lower limit	-1770.1
upper limit	67.2

Secondary: Number of First Primary Episode of CDI (Definition 1) After Dose 2 and Before Dose 3

End point title	Number of First Primary Episode of CDI (Definition 1) After Dose 2 and Before Dose 3
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End point description:

CDI definition 1 for a primary episode of CDI (no previous CDI onset in the prior 8 weeks) was defined as either a) presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours, and stool sample that was positive for the toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in the central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for the toxin B gene (via PCR) as measured in the central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Secondary
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End point timeframe:

From 14 days after Dose 2 to Dose 3 or the day the third vaccination was expected (168 days after Dose 2) for subjects who received only 2 doses

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8139	8184		
Units: Episodes	7	8		

Statistical analyses

Statistical analysis title	Clostridium difficile vaccine versus Placebo
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Statistical analysis description:

Vaccine efficacy (VE) = $100 \times (1 - \text{infection rate ratio [IRR]})$, IRR = calculated ratio of first primary CDI incidence between Clostridium difficile vaccine group and placebo group. 98.2% CI was estimated using Clopper-Pearson-Method.

Comparison groups	Clostridium difficile Vaccine v Placebo
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Number of subjects included in analysis	16323
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Vaccine efficacy
Point estimate	12
Confidence interval	
level	Other: 98.2 %
sides	2-sided
lower limit	-246.7
upper limit	78.5

Secondary: Number of Subjects With Recurrent Episode of CDI (Definition 2) After Dose 2 and Before Dose 3

End point title	Number of Subjects With Recurrent Episode of CDI (Definition 2) After Dose 2 and Before Dose 3
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End point description:

CDI definition 2 for recurrent episode(an episode of CDI that occurred 8 weeks or less after onset of a previous CDI episode[provided symptoms of previous episode had resolved]),defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours; stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (by PCR) as measured in central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

End point type	Secondary
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End point timeframe:

From 14 days after Dose 2 to Dose 3 or the day the third vaccination was expected (168 days after Dose 2) for subjects who received only 2 doses

End point values	Clostridium difficile Vaccine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8139	8184		
Units: Subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

LR and SE(added in other AEs):within 7days after each dose(systematic assessment);SAEs:Day1upto 6months after last dose(up to12months);other AEs:Day1upto1month after last dose(upto7months);All-Cause mortality:Day1 upto 6months after last dose(upto12months)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However,what is presented are distinct events.An event may be categorised as serious in one subject and non-serious in another,or a subject may have experienced both a serious and non-serious event.Safety analysis population included all subjects who received at least 1 dose of investigational product.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Clostridium difficile Vaccine
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Reporting group description:

Participants were randomized to receive a single dose of Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.

Reporting group title	Placebo
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Reporting group description:

Participants were randomized to receive a single dose of placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6.

Serious adverse events	Clostridium difficile Vaccine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	719 / 8722 (8.24%)	722 / 8718 (8.28%)	
number of deaths (all causes)	369	362	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
B-cell lymphoma			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell small lymphocytic lymphoma stage III			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	3 / 8722 (0.03%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign breast neoplasm			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of bladder			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 8722 (0.01%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			
subjects affected / exposed	2 / 8722 (0.02%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endometrial cancer recurrent			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal metastasis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	4 / 8722 (0.05%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lung neoplasm malignant			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to abdominal cavity			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to lung			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to lymph nodes			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to peritoneum			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myxofibrosarcoma			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal cancer metastatic			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal neoplasm			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 8722 (0.00%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer stage I			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	7 / 8722 (0.08%)	7 / 8718 (0.08%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			

subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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 of skin			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 8722 (0.00%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			

subjects affected / exposed	3 / 8722 (0.03%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic stenosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 8722 (0.02%)	7 / 8718 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Extremity necrosis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	5 / 8722 (0.06%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	5 / 8722 (0.06%)	8 / 8718 (0.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 8722 (0.01%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian steal syndrome			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vein disorder			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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			
Adverse drug reaction			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	6 / 8722 (0.07%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	25 / 8722 (0.29%)	32 / 8718 (0.37%)	
occurrences causally related to treatment / all	0 / 27	0 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of device insertion			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug interaction			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site haematoma			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site pain			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site swelling			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	4 / 8722 (0.05%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	3 / 8722 (0.03%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pacemaker generated arrhythmia			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic mass			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical failure			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Physical assault			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Heavy menstrual bleeding			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	11 / 8722 (0.13%)	12 / 8718 (0.14%)	
occurrences causally related to treatment / all	0 / 11	0 / 14	
deaths causally related to treatment / all	0 / 4	0 / 6	
Aspiration			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asthma			
subjects affected / exposed	7 / 8722 (0.08%)	6 / 8718 (0.07%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
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	33 / 8722 (0.38%)	43 / 8718 (0.49%)	
occurrences causally related to treatment / all	0 / 37	0 / 44	
deaths causally related to treatment / all	0 / 9	0 / 12	
Cough			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 8722 (0.07%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			

subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 8722 (0.03%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypersensitivity pneumonitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	6 / 8722 (0.07%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasal septum deviation			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 8722 (0.06%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 8722 (0.11%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 10	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
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	3 / 8722 (0.03%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory acidosis			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	9 / 8722 (0.10%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 8722 (0.01%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizoaffective disorder			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device loosening			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lead dislodgement			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Bile duct stone			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholangitis acute			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis sclerosing			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	3 / 8722 (0.03%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cholecystitis acute			
subjects affected / exposed	3 / 8722 (0.03%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	3 / 8722 (0.03%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder rupture			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic lesion			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate increased			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal function test abnormal			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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			
Accidental overdose			
subjects affected / exposed	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia postoperative			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	4 / 8722 (0.05%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod sting			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone contusion			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Combined tibia-fibula fracture			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	4 / 8722 (0.05%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial bones fracture			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	6 / 8722 (0.07%)	10 / 8718 (0.11%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 8722 (0.00%)	7 / 8718 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	2 / 8722 (0.02%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Heat exhaustion			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat stroke			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	3 / 8722 (0.03%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Humerus fracture			
subjects affected / exposed	4 / 8722 (0.05%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site swelling			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intentional product misuse			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	6 / 8722 (0.07%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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 / 8722 (0.00%)	1 / 8718 (0.01%)	
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 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal foreign body			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck injury			

subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural discharge			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory distress			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpolypectomy syndrome			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	5 / 8722 (0.06%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	5 / 8722 (0.06%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 2	
Sciatic nerve injury			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
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 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Traumatic haemothorax			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular procedure complication			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wound decomposition			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			

subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arnold-Chiari malformation			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial septal defect			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal dystrophy			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hereditary motor and sensory neuropathy			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobile caecum syndrome			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute left ventricular failure			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	20 / 8722 (0.23%)	8 / 8718 (0.09%)	
occurrences causally related to treatment / all	0 / 20	0 / 8	
deaths causally related to treatment / all	0 / 6	0 / 2	
Angina pectoris			
subjects affected / exposed	9 / 8722 (0.10%)	13 / 8718 (0.15%)	
occurrences causally related to treatment / all	0 / 10	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	4 / 8722 (0.05%)	9 / 8718 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	12 / 8722 (0.14%)	15 / 8718 (0.17%)	
occurrences causally related to treatment / all	0 / 12	0 / 17	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrial flutter			
subjects affected / exposed	4 / 8722 (0.05%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	3 / 8722 (0.03%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 8722 (0.03%)	6 / 8718 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 11	0 / 20	
Cardiac failure acute			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 3	
Cardiac failure chronic			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	14 / 8722 (0.16%)	17 / 8718 (0.19%)	
occurrences causally related to treatment / all	0 / 16	0 / 17	
deaths causally related to treatment / all	0 / 10	0 / 6	
Cardiac failure			

subjects affected / exposed	13 / 8722 (0.15%)	10 / 8718 (0.11%)	
occurrences causally related to treatment / all	0 / 15	0 / 11	
deaths causally related to treatment / all	0 / 9	0 / 8	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 5	
Cardiogenic shock			
subjects affected / exposed	3 / 8722 (0.03%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 4	
Cardiovascular disorder			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	13 / 8722 (0.15%)	8 / 8718 (0.09%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 4	0 / 2	
Coronary artery insufficiency			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	1 / 8722 (0.01%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	12 / 8722 (0.14%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 12	0 / 4	
deaths causally related to treatment / all	0 / 14	0 / 8	
Myocardial injury			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 8722 (0.02%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	3 / 8722 (0.03%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 8722 (0.02%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	2 / 8722 (0.02%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carotid artery disease			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral artery stenosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	11 / 8722 (0.13%)	7 / 8718 (0.08%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 11	0 / 1	
Cerebrovascular disorder			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cervical radiculopathy			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	3 / 8722 (0.03%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	4 / 8722 (0.05%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	6 / 8722 (0.07%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Lacunar infarction			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital neuralgia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Presyncope			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stroke			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spondylitic myelopathy			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	11 / 8722 (0.13%)	13 / 8718 (0.15%)	
occurrences causally related to treatment / all	0 / 11	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	8 / 8722 (0.09%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke-Korsakoff syndrome			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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 macrocytic			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	6 / 8722 (0.07%)	8 / 8718 (0.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Immune thrombocytopenia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	3 / 8722 (0.03%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiretinal membrane			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	5 / 8722 (0.06%)	6 / 8718 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer perforation			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Change of bowel habit			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	4 / 8722 (0.05%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 8722 (0.03%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematochezia			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	3 / 8722 (0.03%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			

subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Oesophagitis haemorrhagic			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	8 / 8722 (0.09%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilla of Vater stenosis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 8722 (0.02%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	4 / 8722 (0.05%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulite			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	2 / 8722 (0.02%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic ulcer			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen planus			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer haemorrhage			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 8722 (0.10%)	18 / 8718 (0.21%)	
occurrences causally related to treatment / all	0 / 10	0 / 19	
deaths causally related to treatment / all	0 / 2	0 / 3	
Calculus urinary			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contracted bladder			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	4 / 8722 (0.05%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incontinence			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower urinary tract symptoms			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	5 / 8722 (0.06%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-ureteric obstruction			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal tubular necrosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcapsular renal haematoma			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric reflux			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 8722 (0.05%)	9 / 8718 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	4 / 8722 (0.05%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthropathy			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (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	4 / 8722 (0.05%)	9 / 8718 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondropathy			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture malunion			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint stiffness			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	2 / 8722 (0.02%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	18 / 8722 (0.21%)	15 / 8718 (0.17%)	
occurrences causally related to treatment / all	0 / 18	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacral pain			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal instability			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	4 / 8722 (0.05%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondyloarthropathy			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial disorder			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendinous contracture			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 8722 (0.02%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	3 / 8722 (0.03%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	12 / 8722 (0.14%)	11 / 8718 (0.13%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	23 / 8722 (0.26%)	18 / 8718 (0.21%)	
occurrences causally related to treatment / all	0 / 24	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic sinusitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis escherichia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 8722 (0.02%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related sepsis			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	8 / 8722 (0.09%)	7 / 8718 (0.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture infection			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gas gangrene			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic fever with renal syndrome			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic fever			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter infection			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	6 / 8722 (0.07%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	5 / 8722 (0.06%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis fungal			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	12 / 8722 (0.14%)	11 / 8718 (0.13%)	
occurrences causally related to treatment / all	0 / 12	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Parotitis			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	38 / 8722 (0.44%)	39 / 8718 (0.45%)	
occurrences causally related to treatment / all	0 / 40	0 / 40	
deaths causally related to treatment / all	0 / 5	0 / 6	
Post procedural infection			

subjects affected / exposed	3 / 8722 (0.03%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 8722 (0.00%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 8722 (0.02%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyuria			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	16 / 8722 (0.18%)	16 / 8718 (0.18%)	
occurrences causally related to treatment / all	0 / 16	0 / 16	
deaths causally related to treatment / all	0 / 6	0 / 3	
Septic arthritis staphylococcal			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 8722 (0.03%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8722 (0.01%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	13 / 8722 (0.15%)	10 / 8718 (0.11%)	
occurrences causally related to treatment / all	0 / 13	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 3	
Urosepsis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
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	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Alcoholic ketoacidosis			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	8 / 8722 (0.09%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 9	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	0 / 8722 (0.00%)	4 / 8718 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	4 / 8722 (0.05%)	5 / 8718 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	2 / 8722 (0.02%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 8722 (0.02%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 8722 (0.02%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertriglyceridaemia			

subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	1 / 8722 (0.01%)	3 / 8718 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemia			
subjects affected / exposed	4 / 8722 (0.05%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 8722 (0.03%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoosmolar state			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 8722 (0.00%)	2 / 8718 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			

subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactose intolerance			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 8722 (0.00%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 8722 (0.01%)	0 / 8718 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 8722 (0.01%)	1 / 8718 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Clostridium difficile Vaccine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5702 / 8722 (65.37%)	4314 / 8718 (49.48%)	
Nervous system disorders			
Headache (HEADACHE)			
alternative assessment type: Systematic			
subjects affected / exposed	2615 / 8722 (29.98%)	2323 / 8718 (26.65%)	
occurrences (all)	2615	2323	
General disorders and administration site conditions			
Fatigue (FATIGUE)			
alternative assessment type: Systematic			

subjects affected / exposed	3240 / 8722 (37.15%)	2820 / 8718 (32.35%)	
occurrences (all)	3240	2820	
Injection site pain (PAIN) alternative assessment type: Systematic			
subjects affected / exposed	3596 / 8722 (41.23%)	1056 / 8718 (12.11%)	
occurrences (all)	3596	1056	
Injection site swelling (SWELLING) alternative assessment type: Systematic			
subjects affected / exposed	1846 / 8722 (21.16%)	414 / 8718 (4.75%)	
occurrences (all)	1846	414	
Skin and subcutaneous tissue disorders Injection site erythema (REDNESS) alternative assessment type: Systematic			
subjects affected / exposed	1879 / 8722 (21.54%)	653 / 8718 (7.49%)	
occurrences (all)	1879	653	
Musculoskeletal and connective tissue disorders Arthralgia (JOINT PAIN) alternative assessment type: Systematic			
subjects affected / exposed	1583 / 8722 (18.15%)	1354 / 8718 (15.53%)	
occurrences (all)	1583	1354	
Myalgia (MUSCLE PAIN) alternative assessment type: Systematic			
subjects affected / exposed	1856 / 8722 (21.28%)	1487 / 8718 (17.06%)	
occurrences (all)	1856	1487	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2020	Clarified that if an SAE was reported after subject Visit 6, all the requirements will apply, including the respect of the reporting timelines as if the SAE occurred within the reporting period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported