Clinical trial results:
BACILLUS CALMETTE-GUÉRIN VACCINATION TO PREVENT SERIOUS RESPIRATORY TRACT INFECTION AND COVID-19 IN VULNERABLE ELDERLY – AN ADAPTIVE RANDOMIZED CONTROLLED TRIAL

Summary

EudraCT number	2020-003470-47
Trial protocol	NL
Global end of trial date	22 July 2021

Results information

Result version number	v1 (current)
This version publication date	03 August 2022
First version publication date	03 August 2022

Trial information

Trial identification

Sponsor protocol code	74730.041.20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04537663
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UMCU
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584CX
Public contact	N.L.J. (Nicolette) van Sluis, UMCU Utrecht , N.L.J.vanSluis@umcutrecht.nl
Scientific contact	C.H. (Henri) van Werkhoven, UMCU Utrecht , c.h.vanwerkhoven@umcutrecht.nl

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	03 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:
To determine in vulnerable elderly the effect of BCG vaccination on the adaptive primary endpoint, based on the accrual of events:
- the incidence of COVID-19 (selected as primary endpoint), or
- the incidence of clinically relevant RTI (potentially including COVID-19) (selected as secondary endpoint)

Protection of trial subjects:

Safety Follow up after injection by weekly calls

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2020
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	Netherlands: 6112
Worldwide total number of subjects	6112
EEA total number of subjects	6112

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)	1355
From 65 to 84 years	4627

85 years and over	130

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in hospitals and were eligible for enrollment in the trial if they were 60 years of age or older and at risk of severe COVID-19, had no contra-indications for BCG-vaccination, and did not have a documented COVID-19 infection prior to enrollment. Participants who had previously received BCG at any age were eligible.

Pre-assignment

Screening details:

Hospitals screened for patients with chronic underlying disease or recent hospitalization or major surgery and checked eligibility criteria, or GPs referred patients, or participants self-referred to the study team.

Period 1

Period 1 title	overal trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Vaccinations are prepared in a double blind set up- Placebo/ active vaccin

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

0.1 mL of BCG (Danish strain 1331, SSI, Denmark) via intradermal injection preferrably in the left upper arm

Arm type	Active comparator
Investigational medicinal product name	BCG Vaccination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

eenmalig 0,11ml (=0,1ml + 0,01ml overmaat) intradermaal toedienen
Aangevraagd #JC BCG-PRIME
BCG SSI PDR+SOLV
0,75 MG/ML
(98171291)
……
flacons
#JC BCG-PRIME
PLACEBO NACL
(98171348)

Arm title	Placebo

Arm description:

0.1 mL saline placebo via intradermal injection preferrably in the left upper arm

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

eenmalig 0,11ml (=0,1ml + 0,01ml overmaat) intradermaal toedienen
Aangevraagd #JC BCG-PRIME
BCG SSI PDR+SOLV
0,75 MG/ML
(98171291)
……
flacons
#JC BCG-PRIME
PLACEBO NACL
(98171348)

Number of subjects in period 1	Active	Placebo
Started	3058	3054
Primary endpoint analysis	3045	3040
Completed	3017	3007
Not completed	41	47
Adverse event, serious fatal	13	18
Consent withdrawn by subject	21	27
Physician decision	6	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Active
Reporting group description:	
0.1 mL of BCG (Danish strain 1331, SSI, Denmark) via intradermal injection preferrably in the left upper arm	
Reporting group title	Placebo
Reporting group description:	
0.1 mL saline placebo via intradermal injection preferrably in the left upper arm	

Reporting group values	Active	Placebo	Total
Number of subjects	3058	3054	6112
Age categorical			
Age strata			
Units: Subjects			
60-69 years	1576	1565	3141
70-79 years	1254	1260	2514
80+ years	228	229	457
Age continuous			
Age			
Units: years			
median	69	69	
inter-quartile range (Q1-Q3)	65 to 74	65 to 74	-
Gender categorical			
Sex			
Units: Subjects			
Female	1125	1150	2275
Male	1933	1904	3837
History of BCG vaccination			
Having received BCG prior to the trial at any age			
Units: Subjects			
Yes	495	413	908
No	2267	2358	4625
Unknown	296	283	579

Subject analysis sets

Subject analysis set title	All subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomized and consenting to the intervention	

Reporting group values	All subjects		
Number of subjects	6112		
Age categorical			
Age strata			
Units: Subjects			
60-69 years	3141		

70-79 years	2514		
80+ years	457		

Age continuous			
Age			
Units: years			
median	69		
inter-quartile range (Q1-Q3)	65 to 74		
Gender categorical			
Sex			
Units: Subjects			
Female	2275		
Male	3837		
History of BCG vaccination			
Having received BCG prior to the trial at any age			
Units: Subjects			
Yes	908		
No	4625		
Unknown	579		

End points

End points reporting groups

Reporting group title	Active
Reporting group description:	
0.1 mL of BCG (Danish strain 1331, SSI, Denmark) via intradermal injection preferrably in the left upper arm	
Reporting group title	Placebo
Reporting group description:	
0.1 mL saline placebo via intradermal injection preferrably in the left upper arm	
Subject analysis set title	All subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomized and consenting to the intervention	

Primary: Cumulative incidence of COVID-19 - primary analysis

End point title	Cumulative incidence of COVID-19 - primary analysis
End point description:	
Participants potentially meeting one of the two candidate primary endpoints will be adjudicated by a blinded committee. Each episode can be classified as COVID-19 or clinically relevant RTI or both. The number of primary endpoints will be continuously monitored and a decision will be made according to a straightforward prespecified process. When the number of COVID-19 episodes first reaches its target of 67 episodes, COVID-19 will be declared primary endpoint and will be analyzed.	
End point type	Primary
End point timeframe:	
From randomization until at least 67 episodes of COVID-19 in unique individuals were identified.	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3058	3054		
Units: percentage				
number (not applicable)				
COVID-19	57	50		
No COVID-19	3001	3004		

Statistical analyses

Statistical analysis title	Cumulative incidence
Statistical analysis description:	
Reported as the cumulative incidence by treatment arm. Competing risk analysis using Fine and Gray regression with mortality as potential competing event and adjusted for site of enrolment, age (categorized as 60-69, 70-79 and ≥ 80 years), chronic cardiovascular disease (including hypertension), diabetes mellitus (type 1 and 2), and chronic pulmonary disease. The effect was reported as a sub-distribution hazard ratio (SDHR) with 95% CI.	
Comparison groups	Active v Placebo

Number of subjects included in analysis	6112
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.65

Notes:

[1] - Fine and Gray regression

Primary: Cumulative incidence of COVID-19 - final analysis

End point title	Cumulative incidence of COVID-19 - final analysis

End point description:

After the primary analysis the DSMB recommended continuation of the trial without unblinding. This analysis includes all primary endpoints of the total 6-month study duration.

End point type	Primary

End point timeframe:

Total follow-up duration of 6 months from administration of study vaccine.

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3058	3054		
Units: events				
COVID-19	129	115		
No COVID-19	2929	2939		

Statistical analyses

Statistical analysis title	Cumulative incidence

Statistical analysis description:

Reported as the cumulative incidence by treatment arm. Competing risk analysis using Fine and Gray regression with mortality as potential competing event and adjusted for site of enrolment, age (categorized as 60-69, 70-79 and ≥ 80 years), chronic cardiovascular disease (including hypertension), diabetes mellitus (type 1 and 2), and chronic pulmonary disease. The effect was reported as a sub-distribution hazard ratio (SDHR) with 95% CI.

Comparison groups	Active v Placebo
Number of subjects included in analysis	6112
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.44

Notes:

[2] - Fine & Gray regression

Secondary: Asymptomatic SARS-CoV-2 infection

End point title	Asymptomatic SARS-CoV-2 infection

End point description:

microbiological evidence of COVID-19 without self-reported or medically documented symptoms realted to the episode - as determined by the adjudication committee.

End point type	Secondary

End point timeframe:

6 month follow-up duration

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3058	3054		
Units: events				
Asymptomatic SARS-CoV-2 infection	16	11		
No asymptomatic SARS-CoV-2 infection	3042	3043		

Statistical analyses

Statistical analysis title	Cumulative incidence

Statistical analysis description:

Reported as the cumulative incidence by treatment arm. Competing risk analysis using Fine and Gray regression with mortality as potential competing event and adjusted for site of enrolment, age (categorized as 60-69, 70-79 and ≥ 80 years), chronic cardiovascular disease (including hypertension), diabetes mellitus (type 1 and 2), and chronic pulmonary disease. The effect was reported as a sub-distribution hazard ratio (SDHR) with 95% CI.

Comparison groups	Active v Placebo
Number of subjects included in analysis	6112
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	3.14

Notes:

[3] - Fine & Gray regression

Secondary: Mild-moderate SARS-CoV-2 infection

End point title	Mild-moderate SARS-CoV-2 infection

End point description:

Microbiologically confirmed SARS-CoV-2 infection with self-reported or medically documented symptoms compatible with COVID-19 as determined by the adjudication committee.

End point type	Secondary

End point timeframe:

6-month follow-up period

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3058	3054		
Units: events				
Mild-moderate SARS-CoV-2 infection	111	94		
No mild-moderate SARS-CoV-2 infection	2947	2960		

Statistical analyses

Statistical analysis title	Cumulative incidence

Statistical analysis description:

Reported as the cumulative incidence by treatment arm. Competing risk analysis using Fine and Gray regression with mortality as potential competing event and adjusted for site of enrolment, age (categorized as 60-69, 70-79 and ≥ 80 years), chronic cardiovascular disease (including hypertension), diabetes mellitus (type 1 and 2), and chronic pulmonary disease. The effect was reported as a sub-distribution hazard ratio (SDHR) with 95% CI.

Comparison groups	Active v Placebo
Number of subjects included in analysis	6112
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.55

Notes:

[4] - Fine & Gray regression

Secondary: COVID-19 related admissions

End point title	COVID-19 related admissions

End point description:

Documented symptomatic SARS-CoV-2 infection as determined by the adjudication committee and associated with hospitalization.

End point type	Secondary

End point timeframe:

6-month follow-up period

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3058	3054		
Units: events				
COVID-19 related admissions	18	21		
No COVID-19 related admissions	3040	3033		

Statistical analyses

Statistical analysis title	Cumulative incidence

Statistical analysis description:

Reported as the cumulative incidence by treatment arm. Competing risk analysis using Fine and Gray regression with mortality as potential competing event and adjusted for site of enrolment, age (categorized as 60-69, 70-79 and ≥ 80 years), chronic cardiovascular disease (including hypertension), diabetes mellitus (type 1 and 2), and chronic pulmonary disease. The effect was reported as a sub-distribution hazard ratio (SDHR) with 95% CI.

Comparison groups	Active v Placebo
Number of subjects included in analysis	6112
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.61

Notes:

[5] - Fine & Gray regression

Secondary: Clinically relevant RTI

End point title	Clinically relevant RTI

End point description:

An episode meeting all of the following criteria:
• Respiratory tract infection (RTI), defined as new onset or sudden aggravation of:
- At least one respiratory symptom (cough, sore throat, runny or congested nose, dyspnea, loss of smell or taste, signs at auscultation or percussions of the lungs)
- At least one systemic symptom (fever, headache, muscle ache, sweats or chills, tiredness, confusion)
• Requirement of a medical intervention. A medical intervention was defined as the initiation of antibiotic, antiviral or corticosteroid treatment in primary or secondary care, adaptation in pulmonary maintenance medication, or hospitalization.

End point type	Secondary

End point timeframe:

6-month follow-up period

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3058	3054		
Units: events				
Clinically relevant RTI	66	72		
No clinically relevant RTI	2992	2982		

Statistical analyses

Statistical analysis title	Cumulative incidence

Statistical analysis description:

Reported as the cumulative incidence by treatment arm. Competing risk analysis using Fine and Gray regression with mortality as potential competing event and adjusted for site of enrolment, age (categorized as 60-69, 70-79 and ≥ 80 years), chronic cardiovascular disease (including hypertension), diabetes mellitus (type 1 and 2), and chronic pulmonary disease. The effect was reported as a sub-distribution hazard ratio (SDHR) with 95% CI.

Comparison groups	Active v Placebo
Number of subjects included in analysis	6112
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.28

Notes:

[6] - Fine & Gray regression

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4 weeks after administration of study vaccine for injection site reactions. Up to 6 months after administration of study vaccine for adverse events that required medical consultation.

Adverse event reporting additional description:

Injection site reaction events were solicited for up to 4 weeks after administration of study vaccine by means of a weekly questionnaire. Medical consultations were reported by means of a bi-weekly questionnaire up to 6-month after administration of study vaccine and medical records of these consultations were screened for (serious) adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Active

Reporting group description:

0.1 mL of BCG (Danish strain 1331, SSI, Denmark) via intradermal injection preferrably in the left upper arm

Reporting group title	Placebo

Reporting group description:

0.1 mL saline placebo via intradermal injection preferrably in the left upper arm

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	256 / 3058 (8.37%)	217 / 3054 (7.11%)	
number of deaths (all causes)	15	19	
number of deaths resulting from adverse events	15	19	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 3058 (0.00%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 3058 (0.03%)	3 / 3054 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phaeochromocytoma			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal cell carcinoma			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Aneurysm			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic intramural haematoma			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 3058 (0.00%)	3 / 3054 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	3 / 3058 (0.10%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm rupture			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominal wall operation			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm repair			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stent insertion			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula operation			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder polypectomy			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast conserving surgery			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ablation			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 3058 (0.00%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker replacement			

subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac resynchronisation therapy			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardioversion			
subjects affected / exposed	2 / 3058 (0.07%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary angioplasty			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve operation			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve replacement			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			

subjects affected / exposed	2 / 3058 (0.07%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip surgery			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia repair			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian operation			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palliative care			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Percutaneous coronary intervention			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery bypass			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tumour excision			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal laminectomy			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toe amputation			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
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			
Cardiac death			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest discomfort			
subjects affected / exposed	2 / 3058 (0.07%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 3058 (0.07%)	3 / 3054 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 3058 (0.03%)	4 / 3054 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 4	
Drug withdrawal syndrome			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent stenosis			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
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			
Ovarian enlargement			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital prolapse			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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			
Bronchospasm			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	5 / 3058 (0.16%)	6 / 3054 (0.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 3058 (0.13%)	4 / 3054 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 3058 (0.03%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 3058 (0.16%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 3058 (0.13%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device operational issue			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood potassium decreased			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac normal			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonoscopy			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Heart rate decreased			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal scratch			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Foot fracture			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic complication			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	3 / 3058 (0.10%)	3 / 3054 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb fracture			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract procedural complication			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 3058 (0.00%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Ehlers-Danlos syndrome			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inherited cardiac conduction disorder			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	5 / 3058 (0.16%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	18 / 3058 (0.59%)	12 / 3054 (0.39%)	
occurrences causally related to treatment / all	0 / 19	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 3058 (0.03%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	21 / 3058 (0.69%)	17 / 3054 (0.56%)	
occurrences causally related to treatment / all	0 / 22	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	4 / 3058 (0.13%)	3 / 3054 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac asthma			

subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac discomfort			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	6 / 3058 (0.20%)	5 / 3054 (0.16%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac hypertrophy			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular symptom			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	9 / 3058 (0.29%)	4 / 3054 (0.13%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	7 / 3058 (0.23%)	3 / 3054 (0.10%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Palpitations			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paroxysmal arrhythmia			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
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	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	4 / 3058 (0.13%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	4 / 3058 (0.13%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 3058 (0.00%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 3058 (0.03%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post polio syndrome			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			

subjects affected / exposed	5 / 3058 (0.16%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 3058 (0.07%)	5 / 3054 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typical aura without headache			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3058 (0.07%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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 pain			
subjects affected / exposed	0 / 3058 (0.00%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 3058 (0.03%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ischaemia			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	3 / 3058 (0.10%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 3058 (0.00%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	3 / 3058 (0.10%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 3058 (0.03%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract discomfort			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
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	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
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 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 3058 (0.03%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacroiliac joint dysfunction			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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			
Abscess limb			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	21 / 3058 (0.69%)	22 / 3054 (0.72%)	
occurrences causally related to treatment / all	0 / 21	0 / 22	
deaths causally related to treatment / all	0 / 5	0 / 6	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 3058 (0.00%)	2 / 3054 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 3058 (0.16%)	7 / 3054 (0.23%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia viral			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelitis			
subjects affected / exposed	1 / 3058 (0.03%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 3058 (0.07%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord abscess			
subjects affected / exposed	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 3058 (0.07%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 3058 (0.00%)	3 / 3054 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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			
Electrolyte imbalance			
subjects affected / exposed	1 / 3058 (0.03%)	0 / 3054 (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	0 / 3058 (0.00%)	1 / 3054 (0.03%)	
occurrences causally related to treatment / all	0 / 0	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	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1440 / 3058 (47.09%)	140 / 3054 (4.58%)	
General disorders and administration site conditions			
Injection site reaction			

subjects affected / exposed	1440 / 3058 (47.09%)	140 / 3054 (4.58%)	
occurrences (all)	1443	141	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2020	The research population will include older adults, both females and males, who are vulnerable according to the below definition. Recruitment of patients is planned from August till December 1th. b. Inclusion criteria In order to be eligible to participate in this study, a participant must meet the following criteria: Age ≥60 years Meeting at least one of the following criteria: a) Having a chronic somatic disease* b) Having undergone major surgery** c) Planned to be discharged from the hospital or discharged from the hospital less than 6 weeks ago; a hospital admission is defined as an overnight stay. Departments of interest are those that in the opinion of the principle investigator admit mostly vulnerable elderly and include but are not limited to: cardiology, pulmonology, internal medicine, neurology. d) Attending the thrombosis care service * Chronic somatic diseases do not include risk factors such as hypertension or obesity unless the participant receives medication targeted against the risk factor. ** Major surgery is any invasive operative procedure in which a more extensive resection is performed, e.g. a body cavity is entered, organs are removed, or normal anatomy is altered. In general, if a mesenchymal barrier is opened (pleural cavity, peritoneum, meninges), the surgery is considered major. c. Exclusion criteria A potential participant who meets any of the following criteria will be excluded from participation in this study: Fever (>38 ºC) within the past 24 hours Suspicion of current active viral or bacterial infection; the requirement to finish an antibiotic course upon discharge is not an exclusion criterion when the infection is controlled in the opinion of the attending physician Vaccination with live vaccine in the past four weeks or planned vaccination with live vaccine during the next four weeks Severely immunocompromised participants. This exclusion category comprises: a) known infection by the human ion 2.0,

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Non-serious adverse events other than injection site reactions occurring in the first 4 weeks after study vaccine administration were only systematically inquired if a medical consultation was required.

Notes: