Clinical trial results:
Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation – In Atrial Fibrillation. ENVISAGE-TAVI AF

Summary

EudraCT number	2016-003930-26
Trial protocol	BE AT GB DE ES NL IT
Global end of trial date	28 February 2021

Results information

Result version number	v1 (current)
This version publication date	17 March 2022
First version publication date	17 March 2022

Trial information

Trial identification

Sponsor protocol code	DU176B-C-U4001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02943785
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mount Airy Rd, Basking Ridge, United States, 07920
Public contact	Clinical Director, Daiichi Sankyo Inc., +1 908 992 6400, CTRinfo@dsi.com
Scientific contact	Clinical Director, Daiichi Sankyo Inc., +1 908 992 6400, CTRinfo@dsi.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	28 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Co-Primary Objectives
•To assess the effect of Edoxaban versus vitamin K antagonist (VKA) on net adverse clinical events (NACE), i.e., the composite of all-cause death, myocardial infarction (MI), ischemic stroke, systemic thromboembolism (SEE), valve thrombosis, and major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition).
•To assess the effect of Edoxaban versus VKA on major bleeding (ISTH definition).

Protection of trial subjects:

The study protocol, amendments (if any), the informed consent form(s), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). In addition, this study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 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	Netherlands: 55
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Spain: 344
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Austria: 62
Country: Number of subjects enrolled	Belgium: 34
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 336
Country: Number of subjects enrolled	Italy: 132
Country: Number of subjects enrolled	Japan: 159
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Switzerland: 34
Country: Number of subjects enrolled	United States: 154

Worldwide total number of subjects	1426
EEA total number of subjects	1029

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)	10
From 65 to 84 years	948
85 years and over	468

Subject disposition

Recruitment

Recruitment details:

A total of 1426 participants who met all inclusion criteria and no exclusion criteria were randomized to treatment
at 173 clinic sites in Europe, Asia, and North America.

Pre-assignment

Screening details:

Participants in the study underwent successful transcatheter aortic valve implantation (TAVI) and had a preexisting
atrial fibrillation (AF) or new onset AF.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open-label

Arms

Are arms mutually exclusive?	Yes
Arm title	Edoxaban

Arm description:

Patients randomized to receive the Edoxaban-based regimen which included 60 mg and 30 mg film coated tablets for once-daily oral use, and 15 mg film coated tablet in case of transitioning at the end of treatment. Dosing followed the locally approved label.

Arm type	Experimental
Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	Savaysa, Lixiana
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

15 mg, 30 mg and 60 mg film coated tablet for oral use (with anti-platelet therapy pre-declared at randomization if prescribed)

Arm title	Vitamin K Antagonist (VKA)

Arm description:

Patients randomized to receive the VKA-based regimen which included oral VKA tablets as selected and provided by the site and used in accordance with the local label. The Investigator monitored the patient and adjusted the VKA dose to maintain the dose within target.

Arm type	Active comparator
Investigational medicinal product name	Vitamin K Antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosed at International Normalized Ratio (INR) levels, which is a test of how long it takes for blood to clot. Standard of Care treatment in the country location (with anti-platelet therapy pre-declared at randomization if prescribed).

Number of subjects in period 1	Edoxaban	Vitamin K Antagonist (VKA)
Started	713	713
Completed	431	350
Not completed	282	363
Consent withdrawn by subject	63	126
Physician decision	23	47
Did not receive any study medication	21	28
Adverse event, non-fatal	112	97
Death	46	46
Not specified	16	19
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Edoxaban
Reporting group description:	
Patients randomized to receive the Edoxaban-based regimen which included 60 mg and 30 mg film coated tablets for once-daily oral use, and 15 mg film coated tablet in case of transitioning at the end of treatment. Dosing followed the locally approved label.	
Reporting group title	Vitamin K Antagonist (VKA)
Reporting group description:	
Patients randomized to receive the VKA-based regimen which included oral VKA tablets as selected and provided by the site and used in accordance with the local label. The Investigator monitored the patient and adjusted the VKA dose to maintain the dose within target.	

Reporting group values	Edoxaban	Vitamin K Antagonist (VKA)	Total
Number of subjects	713	713	1426
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)	5	5	10
From 65-84 years	473	475	948
85 years and over	235	233	468
Age continuous Units: years			
arithmetic mean	82.1	82.1	
standard deviation	± 5.4	± 5.5	-
Gender categorical Units: Subjects			
Female	347	331	678
Male	366	382	748
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	92	89	181
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	4	5
White	593	594	1187
More than one race	0	0	0
Unknown or Not Reported	27	26	53
Hypertension Units: Subjects			
Yes	647	657	1304
No	66	56	122

Diabetes mellitus Units: Subjects			
Yes	270	257	527
No	443	456	899
Congestive heart failure Units: Subjects			
Yes	591	619	1210
No	122	94	216
Mitral valve disease Units: Subjects			
Yes	57	60	117
No	656	653	1309
History of stroke or transient ischemic attack Units: Subjects			
Yes	123	116	239
No	590	597	1187
Coronary artery disease Units: Subjects			
Yes	293	297	590
No	420	416	836
Congestive heart failure, NYHA Class III or IV status Units: Subjects			
Yes	314	328	642
No	399	385	784
Prior coronary bypass surgery Units: Subjects			
Yes	67	60	127
No	646	653	1299
Prior percutaneous coronary intervention Units: Subjects			
Yes	176	192	368
No	537	521	1058
Prior myocardial infarction Units: Subjects			
Yes	97	101	198
No	616	612	1228
Weight Units: kg			
arithmetic mean	74.6	76.0	
standard deviation	± 17.9	± 17.3	-
Body mass index Units: kg/m^2			
arithmetic mean	27.5	27.9	
standard deviation	± 5.7	± 5.4	-
Creatinine clearance (Cockcroft-Gault formula) Units: mL/min			
arithmetic mean	57.9	58.6	
standard deviation	± 24.0	± 24.3	-

End points

End points reporting groups

Reporting group title	Edoxaban
Reporting group description:	
Patients randomized to receive the Edoxaban-based regimen which included 60 mg and 30 mg film coated tablets for once-daily oral use, and 15 mg film coated tablet in case of transitioning at the end of treatment. Dosing followed the locally approved label.	
Reporting group title	Vitamin K Antagonist (VKA)
Reporting group description:	
Patients randomized to receive the VKA-based regimen which included oral VKA tablets as selected and provided by the site and used in accordance with the local label. The Investigator monitored the patient and adjusted the VKA dose to maintain the dose within target.	

Primary: Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on ISTH Criteria in Patients Taking Edoxaban vs VKA

End point title	Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on ISTH Criteria in Patients Taking Edoxaban vs VKA
End point description:	
The composite endpoint net adverse clinical events (NACE) included all-cause death, myocardial infarction (MI), ischemic stroke, systemic embolic events (SEE), valve thrombosis, and major bleeding per definition of the International Society on Thrombosis and Haemostasis (ISTH].	
End point type	Primary
End point timeframe:	
Baseline up to 36 months post-dose	

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with net adverse clinical events	170	157		

Statistical analyses

Statistical analysis title	Noninferiority test of Edoxaban vs VKA
Comparison groups	Edoxaban v Vitamin K Antagonist (VKA)

Number of subjects included in analysis	1426
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0141 [1]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.31

Notes:

[1] - The two-sided p-value (Noninferiority) was based on the noninferiority margin of 1.38.

Primary: Number of Patients Who Experienced Major Bleeding (Adjudicated Data) Based on ISTH Criteria in Patients Taking Edoxaban vs VKA

End point title	Number of Patients Who Experienced Major Bleeding (Adjudicated Data) Based on ISTH Criteria in Patients Taking Edoxaban vs VKA

End point description:

ISTH Bleeding Criteria for Major Bleeding are defined as clinically overt bleeding that is associated with: a fall in
hemoglobin of 2 g/dL (1.24 mmol/L) or more, or a transfusion of 2 or more units of whole blood or packed red blood
cells, or symptomatic bleeding into a critical site or organ such as intracranial, intraspinal, intraocular, retroperitoneal,
pericardial, intra-articular, or intramuscular with compartment syndrome, or a fatal outcome.

End point type	Primary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with major bleeding	98	68		

Statistical analyses

Statistical analysis title	Noninferiority test of Edoxaban vs VKA
Comparison groups	Edoxaban v Vitamin K Antagonist (VKA)

Number of subjects included in analysis	1426
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9267 [2]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.91

Notes:

[2] - The two-sided p-value (Noninferiority) was based on the noninferiority margin of 1.38.

Secondary: Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on TIMI Criteria in Patients Taking Edoxaban vs VKA

End point title	Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on TIMI Criteria in Patients Taking Edoxaban vs VKA

End point description:

The composite endpoint of net adverse event clinical events (NACE) included all-cause death, myocardial infarction
(MI), ischemic stroke, systemic embolic events (SEE), valve thrombosis, and major bleeding based on Thrombolysis in
Myocardial Infarction (TIMI) criteria. Bleeding by TIMI criteria was defined as the following: (1) Major, any intracranial
hemorrhage or any clinically overt bleeding, (including bleeding evident in imaging studies) associated with a fall of
hemoglobin (Hb) of ≥ 5g/dL or fatal bleeding and (2) Minor, any clinically overt bleeding associated with a fall in Hb ≥
3g/dL but < 5 g/dL.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Composite endpoint NACE (TIMI)	154	141		
Composite of major and minor bleeding (TIMI)	72	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on BARC Type 3 or 5 Criteria in Patients Taking Edoxaban vs VKA

End point title	Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on BARC Type 3 or 5 Criteria in Patients Taking Edoxaban vs VKA

End point description:

The composite endpoint of net adverse event clinical events (NACE) included all-cause death, MI, ischemic stroke,
SEE, valve thrombosis, and major bleeding based on Bleeding Academic Research Consortium (BARC) Type 3 or
5 criteria. Major bleeding by BARC criteria was defined as Type 3: clinical, laboratory, and/or imaging evidence of
bleeding with provider responses; Type 3a: any transfusion with overt bleeding; overt bleeding plus Hb drop of 3 to <
5 g/dL; Type 3b: overt bleeding plus Hb drop ≥ 5 g/dL; cardiac tamponade; bleeding requiring surgical intervention;
bleeding requiring intravenous vasoactive drugs; Type 3c: intracranial hemorrhage; subcategories confirmed by
autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision; Type 5: fatal bleeding; Type 5a: probable
fatal bleeding; no autopsy or imaging confirmation but clinically suspicious; Type 5b: definite fatal bleeding; overt
bleeding or autopsy or imaging confirmation.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Composite endpoint NACE (BARC Type 3 or 5)	164	151		
Major bleeding (BARC Type 3 or 5)	89	57		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on GUSTO Criteria in Patients Taking Edoxaban vs VKA

End point title	Number of Patients Who Experienced Net Adverse Clinical Events (Adjudicated Data) Based on GUSTO Criteria in Patients Taking Edoxaban vs VKA

End point description:

The composite endpoint of net adverse event clinical events (NACE) included all-cause death, MI, ischemic stroke,

SEE, valve thrombosis, and major bleeding based on Global Utilization of Streptokinase and Tissue Plasminogen
Activator for Occluded Coronary Arteries (GUSTO). GUSTO criteria was defined as the following: severe or life
threatening: intracerebral hemorrhage or resulting in substantial hemodynamic compromise requiring treatment and
moderate: requiring blood transfusion but not resulting in hemodynamic compromise.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Composite endpoint NACE (GUSTO)	160	146		
Severe/life threatening, moderate bleeding (GUSTO)	82	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Major Adverse Cardiac Events (MACE) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point title	Number of Patients Who Experienced Major Adverse Cardiac Events (MACE) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point description:

Major adverse cardiac events (MACE) is defined as the composite of all-cause death (excluding adjudicated noncardiac
death), MI, or repeat coronary revascularization of the target lesion.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with MACE	61	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Major Adverse Cardiac and Cerebrovascular Events (MACCE) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point title	Number of Patients Who Experienced Major Adverse Cardiac and Cerebrovascular Events (MACCE) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point description:

Major adverse cardiac and cerebrovascular events (MACCE) is defined as the composite of all-cause death
(excluding adjudicated non-cardiac death), MI, stroke (ischemic, hemorrhagic, or undetermined), or repeat coronary
revascularization of the target lesion.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with MACCE	86	80		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced a Composite of Adverse Events in Patients Taking Edoxaban vs VKA

End point title	Number of Patients Who Experienced a Composite of Adverse Events in Patients Taking Edoxaban vs VKA

End point description:

A composite of clinical adverse events included cardiovascular death, MI ischemic stroke, SEE, valve thrombosis, and
major bleeding as defined by ISTH criteria.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with a composite of adverse events	151	123		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Stroke Events (Ischemic, Hemorrhagic, Undetermined) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point title	Number of Patients Who Experienced Stroke Events (Ischemic, Hemorrhagic, Undetermined) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point description:

Stroke events are categorized as any stroke, fatal stroke, and non-fatal stroke.

End point type	Secondary

End point timeframe:

Baseline to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Any stroke - ischemic/hemorrhagic/undetermined	29	35		
Fatal stroke - ischemic/hemorrhagic/undetermined	4	3		
Non-fatal stroke- ischemic/hemorrhagic/undetermined	25	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Systemic Embolic Events in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point title	Number of Patients Who Experienced Systemic Embolic Events in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point description:

Systemic thromboembolism [non-central nervous system] is defined as abrupt vascular insufficiency of an extremity or
organ associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms,
(e.g., trauma, atherosclerosis, instrumentation).

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with systemic embolic events	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Myocardial Infarctions (MI) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point title	Number of Patients Who Experienced Myocardial Infarctions (MI) in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point description:

Peri-procedural MI was defined as new ischemic symptoms or signs and elevated cardiac biomarkers within 72 hours
after index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x as the upper
reference limit (URL) for troponin or 5x for CK-MB. Spontaneous MI is defined as any one of the following: Detection
of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile URL, together with the
evidence of myocardial ischemia with at least one of the following: Symptoms of ischemia; ECG changes indicative of
new ischemia; New pathological Q-waves in at least two contiguous leads; Imaging evidence of a new loss of viable
myocardium or new wall motion abnormality; Sudden, unexpected cardiac death, involving cardiac arrest, often with
symptoms suggestive of myocardial ischemia, and accompanied by new ST elevation or new left bundle branch block,
and/or evidence of fresh thrombus; Pathological findings of an acute MI.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with myocardial infarctions	12	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Experienced Valve Thrombosis in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point title	Number of Patients Who Experienced Valve Thrombosis in Patients Taking Edoxaban vs VKA (Adjudicated Data)

End point description:

Valve thrombosis was defined as any thrombus attached to or near an implanted valve that occludes part of the blood
flow path, interferes with valve function, or is sufficiently large to warrant treatment.

End point type	Secondary

End point timeframe:

Baseline up to 36 months post-dose

End point values	Edoxaban	Vitamin K Antagonist (VKA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	713		
Units: participants				
number (not applicable)				
Patients with valve thrombosis	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from the Safety Analysis Set from baseline up 4 weeks post-discontinuation of study treatment, up to 36 months post-dose.

Adverse event reporting additional description:

Treatment-emergent adverse events are defined as events which start on or after any first dose of the assigned study medication regimen or started prior to but then worsened after any first dose of the assigned study medication regimen.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Edoxaban

Reporting group description:

Patients randomized to receive the Edoxaban-based regimen which included 60 mg and 30 mg film coated tablets for once-daily oral use, and 15 mg film coated tablet in case of transitioning at the end of treatment. Dosing followed the locally approved label.

Reporting group title	Vitamin K Antagonist (VKA)

Reporting group description:

Patients randomized to receive the VKA-based regimen which included oral VKA tablets as selected and provided by the site and used in accordance with the local label. The Investigator monitored the patient and adjusted the VKA dose to maintain the dose within target.

Serious adverse events	Edoxaban	Vitamin K Antagonist (VKA)	
Total subjects affected by serious adverse events			
subjects affected / exposed	388 / 693 (55.99%)	372 / 684 (54.39%)	
number of deaths (all causes)	83	78	
number of deaths resulting from adverse events	83	78	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anogenital warts			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myelomonocytic leukaemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lymphoma			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm malignant			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm prostate			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm skin			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory cytopenia with unilineage dysplasia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Aortic occlusion			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic perforation			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic thrombosis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blue toe syndrome			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery embolism			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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 / 693 (0.29%)	9 / 684 (1.32%)	
occurrences causally related to treatment / all	0 / 2	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	8 / 693 (1.15%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery stenosis			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	3 / 693 (0.43%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	7 / 693 (1.01%)	5 / 684 (0.73%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 693 (0.58%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	8 / 693 (1.15%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	2 / 8	0 / 3	
deaths causally related to treatment / all	2 / 8	0 / 3	
Fatigue			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General physical health deterioration			
subjects affected / exposed	3 / 693 (0.43%)	6 / 684 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Impaired healing			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site haematoma			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	5 / 693 (0.72%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Non-cardiac chest pain			
subjects affected / exposed	4 / 693 (0.58%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pacemaker generated arrhythmia			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent-graft endoleak			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	4 / 693 (0.58%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 shock			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic haematoma			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectocele			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	5 / 693 (0.72%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory failure			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchial hyperreactivity			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.72%)	7 / 684 (1.02%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea			
subjects affected / exposed	11 / 693 (1.59%)	8 / 684 (1.17%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea exertional			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	7 / 693 (1.01%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	6 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemothorax			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			

subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haematoma			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pickwickian syndrome			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 693 (0.72%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 693 (0.29%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 693 (0.29%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	7 / 693 (1.01%)	8 / 684 (1.17%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	4 / 693 (0.58%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Stress			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device leakage			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device power source issue			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Blood lactic acid increased			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus test positive			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition normal			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate irregular			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory marker increased			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			

subjects affected / exposed	1 / 693 (0.14%)	5 / 684 (0.73%)	
occurrences causally related to treatment / all	0 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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			
Acetabulum fracture			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia postoperative			
subjects affected / exposed	0 / 693 (0.00%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bone contusion			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon injury			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.14%)	0 / 684 (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	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Extradural haematoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Face injury			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	9 / 693 (1.30%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 11	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	4 / 693 (0.58%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	5 / 693 (0.72%)	6 / 684 (0.88%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	3 / 693 (0.43%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Heat illness			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 693 (0.29%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 693 (0.29%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open globe injury			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	0 / 693 (0.00%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	2 / 693 (0.29%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural fever			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	0 / 693 (0.00%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative delirium			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (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	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 693 (0.29%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			

subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	3 / 693 (0.43%)	5 / 684 (0.73%)	
occurrences causally related to treatment / all	1 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tendon rupture			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	2 / 693 (0.29%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular access site haematoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site pseudoaneurysm			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			

subjects affected / exposed	6 / 693 (0.87%)	8 / 684 (1.17%)	
occurrences causally related to treatment / all	4 / 8	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 693 (0.58%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	2 / 693 (0.29%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	17 / 693 (2.45%)	18 / 684 (2.63%)	
occurrences causally related to treatment / all	0 / 17	1 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	6 / 693 (0.87%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	3 / 693 (0.43%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	9 / 693 (1.30%)	6 / 684 (0.88%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bifascicular block			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	6 / 693 (0.87%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			

subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 693 (0.29%)	7 / 684 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 6	
Cardiac asthma			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
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	57 / 693 (8.23%)	64 / 684 (9.36%)	
occurrences causally related to treatment / all	1 / 76	1 / 81	
deaths causally related to treatment / all	0 / 10	0 / 5	
Cardiac failure acute			
subjects affected / exposed	8 / 693 (1.15%)	11 / 684 (1.61%)	
occurrences causally related to treatment / all	0 / 11	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac failure congestive			
subjects affected / exposed	23 / 693 (3.32%)	12 / 684 (1.75%)	
occurrences causally related to treatment / all	0 / 27	0 / 13	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardiac tamponade			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic left ventricular failure			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conduction disorder			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mitral valve disease			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	6 / 693 (0.87%)	8 / 684 (1.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pericardial effusion			
subjects affected / exposed	4 / 693 (0.58%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prosthetic cardiac valve thrombosis			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	4 / 693 (0.58%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	2 / 693 (0.29%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dysfunction			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 693 (0.29%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Metastases to pelvis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Altered state of consciousness			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.00%)	1 / 684 (0.15%)	
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	5 / 693 (0.72%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	2 / 2	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 693 (0.29%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral microangiopathy			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chorea			
subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choreoathetosis			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	3 / 693 (0.43%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cubital tunnel syndrome			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	6 / 693 (0.87%)	5 / 684 (0.73%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysaesthesia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			

subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	4 / 693 (0.58%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 693 (0.14%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	2 / 3	
Haemorrhagic stroke			
subjects affected / exposed	1 / 693 (0.14%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
Headache			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	9 / 693 (1.30%)	10 / 684 (1.46%)	
occurrences causally related to treatment / all	6 / 11	6 / 12	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lacunar infarction			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Partial seizures			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Syncope			
subjects affected / exposed	13 / 693 (1.88%)	12 / 684 (1.75%)	
occurrences causally related to treatment / all	0 / 14	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	7 / 693 (1.01%)	8 / 684 (1.17%)	
occurrences causally related to treatment / all	2 / 7	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 693 (0.00%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 693 (4.47%)	11 / 684 (1.61%)	
occurrences causally related to treatment / all	17 / 36	6 / 12	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anaemia folate deficiency			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	5 / 693 (0.72%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochromic anaemia			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	3 / 693 (0.43%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic anaemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normocytic anaemia			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Splenic infarction			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous haematoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 693 (0.00%)	6 / 684 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular paroxysmia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			

subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroidal detachment			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous detachment			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			

subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 693 (1.01%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocele			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal ulcer			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	5 / 693 (0.72%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Inguinal hernia			
subjects affected / exposed	2 / 693 (0.29%)	6 / 684 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Intestinal obstruction			

subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Intestinal polyp			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	16 / 693 (2.31%)	7 / 684 (1.02%)	
occurrences causally related to treatment / all	13 / 17	6 / 7	
deaths causally related to treatment / all	1 / 1	1 / 1	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic failure			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal haemorrhage			
subjects affected / exposed	4 / 693 (0.58%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subileus			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative duodenitis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	8 / 693 (1.15%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	7 / 8	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			

subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	4 / 693 (0.58%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 693 (0.29%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermal cyst			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	1 / 693 (0.14%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin ulcer haemorrhage			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	18 / 693 (2.60%)	17 / 684 (2.49%)	
occurrences causally related to treatment / all	0 / 19	1 / 19	
deaths causally related to treatment / all	0 / 3	1 / 3	
Calculus bladder			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 693 (0.14%)	5 / 684 (0.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
End stage renal disease			

subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			
subjects affected / exposed	11 / 693 (1.59%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	5 / 12	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 693 (0.58%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal haematoma			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral haemorrhage			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	4 / 693 (0.58%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bursitis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall haematoma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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 / 693 (0.00%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	5 / 693 (0.72%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 693 (0.00%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.00%)	1 / 684 (0.15%)	
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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue disorder			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.14%)	0 / 684 (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 soft tissue			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter bacteraemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolar osteitis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 693 (0.00%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergilloma			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 693 (0.29%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacterial sepsis			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	4 / 693 (0.58%)	5 / 684 (0.73%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 693 (0.29%)	6 / 684 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 3	
COVID-19 pneumonia			
subjects affected / exposed	1 / 693 (0.14%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	3 / 693 (0.43%)	4 / 684 (0.58%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Citrobacter sepsis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis			

subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis klebsiella			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	14 / 693 (2.02%)	7 / 684 (1.02%)	
occurrences causally related to treatment / all	0 / 15	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 1	
Endocarditis enterococcal			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			

subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	2 / 693 (0.29%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epididymitis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal tracheitis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric infection			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 693 (0.43%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin infection			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	2 / 693 (0.29%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster oticus			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective aneurysm			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	4 / 693 (0.58%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			

subjects affected / exposed	3 / 693 (0.43%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Medical device site infection			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycotic corneal ulcer			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	39 / 693 (5.63%)	37 / 684 (5.41%)	
occurrences causally related to treatment / all	0 / 43	0 / 41	
deaths causally related to treatment / all	0 / 6	0 / 5	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	7 / 693 (1.01%)	13 / 684 (1.90%)	
occurrences causally related to treatment / all	0 / 7	0 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 693 (0.87%)	7 / 684 (1.02%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 3	
Septic shock			
subjects affected / exposed	5 / 693 (0.72%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Sinusitis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
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	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Streptococcal endocarditis			
subjects affected / exposed	3 / 693 (0.43%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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	0 / 693 (0.00%)	1 / 684 (0.15%)	
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	21 / 693 (3.03%)	17 / 684 (2.49%)	
occurrences causally related to treatment / all	0 / 27	0 / 22	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	6 / 693 (0.87%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Viral infection			

subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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			
Acidosis			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased appetite			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 693 (0.43%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

subjects affected / exposed	2 / 693 (0.29%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fructose intolerance			
subjects affected / exposed	1 / 693 (0.14%)	0 / 684 (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 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 693 (0.00%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 693 (0.14%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 693 (0.14%)	3 / 684 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 693 (0.00%)	2 / 684 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 693 (0.14%)	1 / 684 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Edoxaban	Vitamin K Antagonist (VKA)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	522 / 693 (75.32%)	429 / 684 (62.72%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	35 / 693 (5.05%)	23 / 684 (3.36%)	
occurrences (all)	35	23	
Vascular disorders			
Haematoma			
subjects affected / exposed	26 / 693 (3.75%)	41 / 684 (5.99%)	
occurrences (all)	26	41	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	23 / 693 (3.32%)	36 / 684 (5.26%)	
occurrences (all)	23	36	
Cardiac failure			
subjects affected / exposed	78 / 693 (11.26%)	85 / 684 (12.43%)	
occurrences (all)	78	85	
Nervous system disorders			
Dizziness			

subjects affected / exposed	47 / 693 (6.78%)	33 / 684 (4.82%)	
occurrences (all)	47	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	62 / 693 (8.95%)	40 / 684 (5.85%)	
occurrences (all)	62	40	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	39 / 693 (5.63%)	35 / 684 (5.12%)	
occurrences (all)	39	35	
Epistaxis			
subjects affected / exposed	64 / 693 (9.24%)	30 / 684 (4.39%)	
occurrences (all)	64	30	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	40 / 693 (5.77%)	18 / 684 (2.63%)	
occurrences (all)	40	18	
Infections and infestations			
Pneumonia			
subjects affected / exposed	45 / 693 (6.49%)	43 / 684 (6.29%)	
occurrences (all)	45	43	
Urinary tract infection			
subjects affected / exposed	63 / 693 (9.09%)	45 / 684 (6.58%)	
occurrences (all)	63	45	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2017	Editorial changes were incorporated to improve clarity and consistency; Japan was added as a potential participating country; and additional criteria were included to cover the potential transfer of patients during the study
05 July 2018	Minor editorial changes were incorporated to improve clarity and to reflect the changing medical practice
29 July 2019	Minor editorial changes were incorporated to improve clarity throughout the protocol, including safety/AE definitions
17 April 2020	Incorporated temporary measures while COVID-19 restrictions were in effect

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported