



Clinical trial results:

A Randomized, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of QPI-1002 for the Prevention of Major Adverse Kidney Events (MAKE) in Subjects at High Risk for Acute Kidney Injury (AKI) Following Cardiac Surgery

Summary

EudraCT number	2018-000757-49
Trial protocol	DE ES GB BE CZ AT
Global end of trial date	30 March 2021

Results information

Result version number	v1 (current)
This version publication date	23 July 2021
First version publication date	23 July 2021

Trial information

Trial identification

Sponsor protocol code	QRK309
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03510897
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Quark Pharmaceuticals, Inc.
Sponsor organisation address	7999 Gateway Boulevard, Suite 310, Newark, United States, 94560
Public contact	Clinical Operations, Quark Pharmaceuticals, Inc., dcafaro@quarkpharma.com
Scientific contact	Clinical Operations, Quark Pharmaceuticals, Inc., dcafaro@quarkpharma.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	23 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2021
Global end of trial reached?	Yes
Global end of trial date	30 March 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- Primary objective: To assess the efficacy of a single intravenous (IV) infusion of QPI-1002 in preventing Major Adverse Kidney Events (MAKE) in subjects at high risk for acute kidney injury (AKI) following cardiac surgery.
- Secondary objectives: To assess the safety and tolerability of an IV infusion of QPI-1002 in comparison to placebo when administered to subjects at high risk for AKI following cardiac surgery.

Protection of trial subjects:

The trial was completed according to the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Background therapy:

Post surgical care

Evidence for comparator: -

Actual start date of recruitment	25 May 2018
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	Australia: 49
Country: Number of subjects enrolled	Canada: 254
Country: Number of subjects enrolled	New Zealand: 36
Country: Number of subjects enrolled	United States: 311
Country: Number of subjects enrolled	Spain: 86
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czechia: 43
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 233
Worldwide total number of subjects	1043
EEA total number of subjects	393

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)	173
From 65 to 84 years	852
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 02-July-2018

Countries: Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, New Zealand, Spain, USA

96 study centres in total

Pre-assignment

Screening details:

Subjects undergoing non emergent open chest cavity cardiovascular surgeries, with use of cardiopulmonary bypass pump, with or without hypothermic circulatory arrest at high risk of AKI. 1,354 subjects were screened, of which 1,043 (1,039 subjects ≥ 45 years old) were randomized and 1,023 (1,019 subjects ≥ 45 years old) received test treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QPI-1002

Arm description:

QPI-1002 is a synthetic small interfering ribonucleic acid (siRNA). QPI-1002 injection is supplied at 25 mg/mL in a preservative-free, sterile solution compounded in phosphate-buffered-saline. The injection is administered via IV bolus over approximately 1–2 minutes, at a dose of 10 mg/kg. Single administration after surgery at a single dose level.

Arm type	Experimental
Investigational medicinal product name	QPI-1002
Investigational medicinal product code	
Other name	Teprasiran
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

QPI-1002 injection is supplied at 25 mg/mL in a preservative-free, sterile solution compounded in phosphate-buffered-saline. Each 10 mL vial contains 250 mg of QPI-1002. There is no reconstitution or dilution of QPI-1002 injection. The calculated dose of investigational product to be administered is determined using the subject's weight (kg) obtained at the Baseline visit. The injection is administered directly into the most proximal port of an available central venous line or through an available peripheral line (if no central line can be accessed), using standard IV push technique, including flushing the line prior to and after administration. The solution will be administered via IV bolus, at a dose of 10 mg/kg, approximately 4 h \pm 30 min after discontinuation of CPB. In case of non-CPB surgery (subjects < 45 years old), study drug will be administered approximately 4 h \pm 30 min after the last coronary bypass and completion of anastomosis and achievement of hemostasis.

Arm title	Placebo
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Arm description:

Placebo (sterile isotonic saline for injection)

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Placebo is commercially available isotonic saline for injection matched for volume. The injection is administered directly into the most proximal port of an available central venous line or through an available peripheral line (if no central line can be accessed), using standard IV push technique, including flushing the line prior to and after administration. The solution will be administered via IV bolus, at a dose of 10 mg/kg, approximately 4 hours \pm 30 minutes after discontinuation of CPB. In case of non-CPB surgery (subjects 18 to < 45 years old), study drug will be administered approximately 4 hours \pm 30 minutes after the last coronary bypass and completion of anastomosis and achievement of hemostasis.

Number of subjects in period 1	QPI-1002	Placebo
Started	524	519
Completed	488	480
Not completed	36	39
Consent withdrawn by subject	14	10
Physician decision	1	1
Death	18	27
Lost to follow-up	3	1

Baseline characteristics

Reporting groups

Reporting group title	QPI-1002
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Reporting group description:

QPI-1002 is a synthetic small interfering ribonucleic acid (siRNA). QPI-1002 injection is supplied at 25 mg/mL in a preservative-free, sterile solution compounded in phosphate-buffered-saline. The injection is administered via IV bolus over approximately 1–2 minutes, at a dose of 10 mg/kg. Single administration after surgery at a single dose level.

Reporting group title	Placebo
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Reporting group description:

Placebo (sterile isotonic saline for injection)

Reporting group values	QPI-1002	Placebo	Total
Number of subjects	524	519	1043
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)	93	80	173
From 65-84 years	424	428	852
85 years and over	7	11	18
Age continuous			
Units: years			
arithmetic mean	70.2	71.2	
full range (min-max)	43 to 89	42 to 89	-
Gender categorical			
Units: Subjects			
Female	142	160	302
Male	382	359	741

Subject analysis sets

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT population is defined as all subjects who are randomized, regardless of the treatment the subject actually received.

The ITT population was used for the assessment of the primary endpoint in subjects aged 45 years and above.

Reporting group values	ITT		
Number of subjects	1039		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	169		
From 65-84 years	852		
85 years and over	18		
Age continuous Units: years			
arithmetic mean	70.8		
full range (min-max)	45 to 89		
Gender categorical Units: Subjects			
Female	299		
Male	740		

End points

End points reporting groups

Reporting group title	QPI-1002
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Reporting group description:

QPI-1002 is a synthetic small interfering ribonucleic acid (siRNA). QPI-1002 injection is supplied at 25 mg/mL in a preservative-free, sterile solution compounded in phosphate-buffered-saline. The injection is administered via IV bolus over approximately 1–2 minutes, at a dose of 10 mg/kg. Single administration after surgery at a single dose level.

Reporting group title	Placebo
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Reporting group description:

Placebo (sterile isotonic saline for injection)

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT population is defined as all subjects who are randomized, regardless of the treatment the subject actually received.

The ITT population was used for the assessment of the primary endpoint in subjects aged 45 years and above.

Primary: Subjects 45 years old and above developing MAKE90

End point title	Subjects 45 years old and above developing MAKE90
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End point description:

The primary efficacy endpoint was defined as the proportion of subjects 45 years old and above who develop any of the components of MAKE90, defined as either death through day 90, initiation of renal replacement therapy (RRT) through day 90, or a $\geq 25\%$ reduction in eGFR at the Day 90 visit. For the primary analysis, eGFR was to be based on serum cystatin C (eGFR_{cys}). Estimated GFR based on serum creatinine (eGFR_{creat}) was to be used in a sensitivity analysis.

End point type	Primary
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End point timeframe:

Day 90

End point values	QPI-1002	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	517		
Units: events				
number (not applicable)	161.7	168.5		

Statistical analyses

Statistical analysis title	Primary endpoint MAKE90
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Statistical analysis description:

The analysis of the primary endpoint was conducted on the intention-to-treat (ITT) population in subjects aged 45 years and above. The ITT population was analyzed as randomized, regardless of the treatment the subject actually received. MAKE90 is defined as experiencing any one of these components: Death through Study Day 90, Initiation of Renal Replacement Therapy (RRT) through Day Study 90, or a $\geq 25\%$ reduction in eGFR_{ScysC} at the Day 90 Visit from Baseline.

Comparison groups	QPI-1002 v Placebo
Number of subjects included in analysis	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5726 ^[1]
Method	Wald's chi-square test
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.21

Notes:

[1] - Odds ratio (QPI-1002/Placebo) multivariable logit model with stratification factors using Wald's chi-square test

Event n. Placebo 168.5; QPI-1002 161.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected through Day 30. Serious adverse events (SAEs) were collected through 90 days post study drug administration. Renal function, subject survival and malignancy status were assessed at Day 365.

Adverse event reporting additional description:

Safety assessments (AEs and SAEs) were reported with their severity and relationship to study drug. Vital signs and routine labs (haematology and chemistry panel) were also collected. Safety analyses were conducted in the as-treated population, defined as all subjects randomized and dosed (QPI-1002 or placebo) regardless of age.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	QPI-1002
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Reporting group description:

QPI-1002 is a synthetic small interfering ribonucleic acid (siRNA). QPI-1002 injection is supplied at 25 mg/mL in a preservative-free, sterile solution compounded in phosphate-buffered-saline. The injection is administered via IV bolus over approximately 1–2 minutes, at a dose of 10 mg/kg. Single administration after surgery at a single dose level.

Reporting group title	Placebo
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Reporting group description:

Placebo (isotonic saline for injection)

Serious adverse events	QPI-1002	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	215 / 513 (41.91%)	222 / 510 (43.53%)	
number of deaths (all causes)	26	36	
number of deaths resulting from adverse events	18	25	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	5 / 513 (0.97%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hypovolaemic shock		
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Labile blood pressure		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Orthostatic hypotension		
subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pelvic venous thrombosis		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral arterial occlusive disease		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery occlusion		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral ischaemia		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Shock		

subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
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 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haematoma			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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			
Death			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Extravasation			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			

subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal haemorrhage			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	5 / 513 (0.97%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 513 (0.00%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical deconditioning			
subjects affected / exposed	3 / 513 (0.58%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute pulmonary oedema			
subjects affected / exposed	1 / 513 (0.19%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 513 (0.39%)	6 / 510 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	3 / 513 (0.58%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atelectasis			
subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 513 (0.19%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			

subjects affected / exposed	1 / 513 (0.19%)	3 / 510 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperventilation		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxia		
subjects affected / exposed	4 / 513 (0.78%)	4 / 510 (0.78%)
occurrences causally related to treatment / all	2 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Mediastinal haematoma		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mediastinal haemorrhage		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Organising pneumonia		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural effusion		
subjects affected / exposed	19 / 513 (3.70%)	22 / 510 (4.31%)
occurrences causally related to treatment / all	0 / 19	0 / 22
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia aspiration		
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumothorax		

subjects affected / exposed	3 / 513 (0.58%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary air leakage			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	3 / 513 (0.58%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	14 / 513 (2.73%)	11 / 510 (2.16%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract oedema			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Brief psychotic disorder with marked stressors			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 513 (0.39%)	4 / 510 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device leakage			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lead dislodgement			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Accidental poisoning			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
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	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion postoperative			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drain site complication			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site impaired healing			
subjects affected / exposed	6 / 513 (1.17%)	5 / 510 (0.98%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
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	1 / 513 (0.19%)	0 / 510 (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	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 513 (0.39%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative delirium			
subjects affected / exposed	1 / 513 (0.19%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative thoracic procedure complication			
subjects affected / exposed	5 / 513 (0.97%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpericardiotomy syndrome			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular bypass dysfunction			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm ruptured			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weaning failure			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	3 / 513 (0.58%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrioventricular septal defect			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal arteriovenous malformation			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 513 (0.58%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute right ventricular failure			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Angina pectoris			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
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	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	15 / 513 (2.92%)	18 / 510 (3.53%)	
occurrences causally related to treatment / all	0 / 15	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 513 (0.19%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			

subjects affected / exposed	1 / 513 (0.19%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	8 / 513 (1.56%)	5 / 510 (0.98%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	3 / 513 (0.58%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bifascicular block			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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	2 / 513 (0.39%)	4 / 510 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	8 / 513 (1.56%)	9 / 510 (1.76%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiac failure			
subjects affected / exposed	5 / 513 (0.97%)	11 / 510 (2.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			

subjects affected / exposed	4 / 513 (0.78%)	4 / 510 (0.78%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 513 (0.78%)	6 / 510 (1.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	5 / 513 (0.97%)	16 / 510 (3.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	7 / 513 (1.36%)	7 / 510 (1.37%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiomyopathy			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic left ventricular failure			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular hypertrophy			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			
subjects affected / exposed	2 / 513 (0.39%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal rhythm			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	11 / 513 (2.14%)	14 / 510 (2.75%)	
occurrences causally related to treatment / all	0 / 11	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 513 (0.19%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus arrest			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
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	2 / 513 (0.39%)	4 / 510 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic anterior motion of mitral valve			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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 / 513 (0.39%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asterixis			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carotid artery occlusion			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery embolism			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral artery stenosis		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral infarction		
subjects affected / exposed	1 / 513 (0.19%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral ischaemia		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebrovascular accident		
subjects affected / exposed	3 / 513 (0.58%)	12 / 510 (2.35%)
occurrences causally related to treatment / all	0 / 3	0 / 12
deaths causally related to treatment / all	0 / 1	0 / 0
Cognitive disorder		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dementia		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic ketoacidotic hyperglycaemic coma		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Embolic stroke		

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalopathy		
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiparesis		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic encephalopathy		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy		
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1
Intensive care unit acquired weakness		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic stroke		
subjects affected / exposed	2 / 513 (0.39%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Nervous system disorder		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Neuropathy peripheral		

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 513 (0.39%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible ischaemic neurological deficit			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 513 (0.39%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal epidural haematoma			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 513 (0.58%)	4 / 510 (0.78%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 513 (1.36%)	5 / 510 (0.98%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	1 / 513 (0.19%)	5 / 510 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	3 / 513 (0.58%)	4 / 510 (0.78%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiplonic appendagitis			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Faecaloma		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Functional gastrointestinal disorder		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer haemorrhage		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis erosive		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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 / 513 (0.97%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemoperitoneum		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus		

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatitis acute			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 513 (0.19%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haematoma			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 513 (0.19%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	25 / 513 (4.87%)	29 / 510 (5.69%)	
occurrences causally related to treatment / all	0 / 25	1 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 513 (0.19%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			

subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	5 / 513 (0.97%)	7 / 510 (1.37%)	
occurrences causally related to treatment / all	1 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subacute kidney injury			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcapsular renal haematoma			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
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	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall haematoma			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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			
Arteriovenous graft site infection			

subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 513 (0.19%)	6 / 510 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterobacter infection			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enterococcal sepsis		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Gastroenteritis		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis clostridial		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Herpes zoster		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infection		
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Infection susceptibility increased		
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza		

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Localised infection		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mediastinitis		
subjects affected / exposed	3 / 513 (0.58%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis		
subjects affected / exposed	2 / 513 (0.39%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis acute		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
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 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		

subjects affected / exposed	11 / 513 (2.14%)	18 / 510 (3.53%)
occurrences causally related to treatment / all	0 / 11	0 / 18
deaths causally related to treatment / all	0 / 1	0 / 0
Pneumonia bacterial		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia haemophilus		
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia pseudomonal		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia serratia		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
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	9 / 513 (1.75%)	9 / 510 (1.76%)
occurrences causally related to treatment / all	0 / 9	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary sepsis		
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis		
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection		

subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 513 (1.17%)	14 / 510 (2.75%)	
occurrences causally related to treatment / all	0 / 6	0 / 14	
deaths causally related to treatment / all	0 / 1	1 / 3	
Septic embolus			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 513 (0.58%)	4 / 510 (0.78%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 4	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	4 / 513 (0.78%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (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 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 513 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 513 (0.39%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	3 / 513 (0.58%)	9 / 510 (1.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			

subjects affected / exposed	1 / 513 (0.19%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 513 (0.58%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 513 (0.39%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 513 (0.19%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipasaemia			
subjects affected / exposed	0 / 513 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	QPI-1002	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	279 / 513 (54.39%)	268 / 510 (52.55%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	7 / 513 (1.36%)	8 / 510 (1.57%)	
occurrences (all)	7	8	
Hypertension			

subjects affected / exposed occurrences (all)	28 / 513 (5.46%) 28	26 / 510 (5.10%) 26	
Hypotension subjects affected / exposed occurrences (all)	49 / 513 (9.55%) 49	48 / 510 (9.41%) 48	
Orthostatic hypotension subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	6 / 510 (1.18%) 6	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	15 / 513 (2.92%) 15	13 / 510 (2.55%) 13	
Chest pain subjects affected / exposed occurrences (all)	10 / 513 (1.95%) 10	9 / 510 (1.76%) 9	
Fatigue subjects affected / exposed occurrences (all)	9 / 513 (1.75%) 9	7 / 510 (1.37%) 7	
Generalised oedema subjects affected / exposed occurrences (all)	12 / 513 (2.34%) 12	19 / 510 (3.73%) 19	
Non-cardiac chest pain subjects affected / exposed occurrences (all)	12 / 513 (2.34%) 12	3 / 510 (0.59%) 3	
Oedema subjects affected / exposed occurrences (all)	19 / 513 (3.70%) 19	27 / 510 (5.29%) 27	
Oedema peripheral subjects affected / exposed occurrences (all)	58 / 513 (11.31%) 58	69 / 510 (13.53%) 69	
Pain subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	4 / 510 (0.78%) 4	
Physical deconditioning			

subjects affected / exposed occurrences (all)	2 / 513 (0.39%) 2	6 / 510 (1.18%) 6	
Pyrexia subjects affected / exposed occurrences (all)	32 / 513 (6.24%) 32	28 / 510 (5.49%) 28	
Respiratory, thoracic and mediastinal disorders			
Atelectasis subjects affected / exposed occurrences (all)	51 / 513 (9.94%) 51	49 / 510 (9.61%) 49	
Bronchospasm subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	13 / 510 (2.55%) 13	
Cough subjects affected / exposed occurrences (all)	25 / 513 (4.87%) 25	19 / 510 (3.73%) 19	
Dyspnoea subjects affected / exposed occurrences (all)	27 / 513 (5.26%) 27	25 / 510 (4.90%) 25	
Dyspnoea exertional subjects affected / exposed occurrences (all)	12 / 513 (2.34%) 12	19 / 510 (3.73%) 19	
Epistaxis subjects affected / exposed occurrences (all)	8 / 513 (1.56%) 8	4 / 510 (0.78%) 4	
Hypoxia subjects affected / exposed occurrences (all)	11 / 513 (2.14%) 11	16 / 510 (3.14%) 16	
Lung hypoinflation subjects affected / exposed occurrences (all)	8 / 513 (1.56%) 8	5 / 510 (0.98%) 5	
Pleural effusion subjects affected / exposed occurrences (all)	145 / 513 (28.27%) 145	132 / 510 (25.88%) 132	
Pneumothorax			

subjects affected / exposed occurrences (all)	28 / 513 (5.46%) 28	26 / 510 (5.10%) 26	
Productive cough subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	6 / 510 (1.18%) 6	
Pulmonary congestion subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	9 / 510 (1.76%) 9	
Pulmonary oedema subjects affected / exposed occurrences (all)	24 / 513 (4.68%) 24	14 / 510 (2.75%) 14	
Respiratory acidosis subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	4 / 510 (0.78%) 4	
Respiratory failure subjects affected / exposed occurrences (all)	15 / 513 (2.92%) 15	19 / 510 (3.73%) 19	
Tachypnoea subjects affected / exposed occurrences (all)	9 / 513 (1.75%) 9	4 / 510 (0.78%) 4	
Wheezing subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	3 / 510 (0.59%) 3	
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	4 / 510 (0.78%) 4	
Anxiety subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	12 / 510 (2.35%) 12	
Confusional state subjects affected / exposed occurrences (all)	26 / 513 (5.07%) 26	28 / 510 (5.49%) 28	
Delirium subjects affected / exposed occurrences (all)	42 / 513 (8.19%) 42	52 / 510 (10.20%) 52	

Disorientation subjects affected / exposed occurrences (all)	9 / 513 (1.75%) 9	4 / 510 (0.78%) 4	
Hallucination subjects affected / exposed occurrences (all)	12 / 513 (2.34%) 12	1 / 510 (0.20%) 1	
Insomnia subjects affected / exposed occurrences (all)	31 / 513 (6.04%) 31	28 / 510 (5.49%) 28	
Sleep disorder subjects affected / exposed occurrences (all)	12 / 513 (2.34%) 12	12 / 510 (2.35%) 12	
Investigations			
Amylase increased subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	2 / 510 (0.39%) 2	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	8 / 513 (1.56%) 8	9 / 510 (1.76%) 9	
Blood creatine increased subjects affected / exposed occurrences (all)	19 / 513 (3.70%) 19	11 / 510 (2.16%) 11	
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	5 / 510 (0.98%) 5	
Blood lactic acid increased subjects affected / exposed occurrences (all)	3 / 513 (0.58%) 3	6 / 510 (1.18%) 6	
Blood magnesium decreased subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	4 / 510 (0.78%) 4	
Blood potassium decreased subjects affected / exposed occurrences (all)	1 / 513 (0.19%) 1	7 / 510 (1.37%) 7	
Haemoglobin decreased			

subjects affected / exposed occurrences (all)	17 / 513 (3.31%) 17	20 / 510 (3.92%) 20	
Transaminases increased subjects affected / exposed occurrences (all)	10 / 513 (1.95%) 10	7 / 510 (1.37%) 7	
Urine output decreased subjects affected / exposed occurrences (all)	8 / 513 (1.56%) 8	10 / 510 (1.96%) 10	
Injury, poisoning and procedural complications			
Anaemia postoperative subjects affected / exposed occurrences (all)	11 / 513 (2.14%) 11	7 / 510 (1.37%) 7	
Fall subjects affected / exposed occurrences (all)	0 / 513 (0.00%) 0	6 / 510 (1.18%) 6	
Incision site pain subjects affected / exposed occurrences (all)	44 / 513 (8.58%) 44	53 / 510 (10.39%) 53	
Post procedural haemorrhage subjects affected / exposed occurrences (all)	8 / 513 (1.56%) 8	2 / 510 (0.39%) 2	
Postoperative delirium subjects affected / exposed occurrences (all)	16 / 513 (3.12%) 16	8 / 510 (1.57%) 8	
Procedural nausea subjects affected / exposed occurrences (all)	11 / 513 (2.14%) 11	7 / 510 (1.37%) 7	
Procedural pain subjects affected / exposed occurrences (all)	79 / 513 (15.40%) 79	78 / 510 (15.29%) 78	
Wound complication subjects affected / exposed occurrences (all)	5 / 513 (0.97%) 5	8 / 510 (1.57%) 8	
Cardiac disorders			

Atrial fibrillation		
subjects affected / exposed	154 / 513 (30.02%)	148 / 510 (29.02%)
occurrences (all)	154	148
Atrial flutter		
subjects affected / exposed	20 / 513 (3.90%)	5 / 510 (0.98%)
occurrences (all)	20	5
Atrioventricular block first degree		
subjects affected / exposed	5 / 513 (0.97%)	10 / 510 (1.96%)
occurrences (all)	5	10
Bradycardia		
subjects affected / exposed	21 / 513 (4.09%)	21 / 510 (4.12%)
occurrences (all)	21	21
Cardiomegaly		
subjects affected / exposed	10 / 513 (1.95%)	4 / 510 (0.78%)
occurrences (all)	10	4
Nodal rhythm		
subjects affected / exposed	11 / 513 (2.14%)	8 / 510 (1.57%)
occurrences (all)	11	8
Pericardial effusion		
subjects affected / exposed	9 / 513 (1.75%)	16 / 510 (3.14%)
occurrences (all)	9	16
Pericarditis		
subjects affected / exposed	4 / 513 (0.78%)	8 / 510 (1.57%)
occurrences (all)	4	8
Sinus tachycardia		
subjects affected / exposed	12 / 513 (2.34%)	11 / 510 (2.16%)
occurrences (all)	12	11
Tachycardia		
subjects affected / exposed	16 / 513 (3.12%)	8 / 510 (1.57%)
occurrences (all)	16	8
Ventricular extrasystoles		
subjects affected / exposed	8 / 513 (1.56%)	13 / 510 (2.55%)
occurrences (all)	8	13
Ventricular tachycardia		
subjects affected / exposed	11 / 513 (2.14%)	9 / 510 (1.76%)
occurrences (all)	11	9

Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 513 (2.53%)	18 / 510 (3.53%)	
occurrences (all)	13	18	
Headache			
subjects affected / exposed	8 / 513 (1.56%)	8 / 510 (1.57%)	
occurrences (all)	8	8	
Syncope			
subjects affected / exposed	3 / 513 (0.58%)	7 / 510 (1.37%)	
occurrences (all)	3	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	97 / 513 (18.91%)	92 / 510 (18.04%)	
occurrences (all)	97	92	
Blood loss anaemia			
subjects affected / exposed	13 / 513 (2.53%)	7 / 510 (1.37%)	
occurrences (all)	13	7	
Coagulopathy			
subjects affected / exposed	6 / 513 (1.17%)	1 / 510 (0.20%)	
occurrences (all)	6	1	
Leukocytosis			
subjects affected / exposed	34 / 513 (6.63%)	38 / 510 (7.45%)	
occurrences (all)	34	38	
Thrombocytopenia			
subjects affected / exposed	35 / 513 (6.82%)	31 / 510 (6.08%)	
occurrences (all)	35	31	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 513 (1.56%)	8 / 510 (1.57%)	
occurrences (all)	8	8	
Constipation			
subjects affected / exposed	79 / 513 (15.40%)	74 / 510 (14.51%)	
occurrences (all)	79	74	
Diarrhoea			
subjects affected / exposed	17 / 513 (3.31%)	16 / 510 (3.14%)	
occurrences (all)	17	16	
Dysphagia			

subjects affected / exposed occurrences (all)	15 / 513 (2.92%) 15	21 / 510 (4.12%) 21	
Ileus subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	3 / 510 (0.59%) 3	
Nausea subjects affected / exposed occurrences (all)	108 / 513 (21.05%) 108	110 / 510 (21.57%) 110	
Vomiting subjects affected / exposed occurrences (all)	29 / 513 (5.65%) 29	38 / 510 (7.45%) 38	
Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all)	8 / 513 (1.56%) 8	8 / 510 (1.57%) 8	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	96 / 513 (18.71%) 96	63 / 510 (12.35%) 63	
Haematuria subjects affected / exposed occurrences (all)	5 / 513 (0.97%) 5	8 / 510 (1.57%) 8	
Oliguria subjects affected / exposed occurrences (all)	14 / 513 (2.73%) 14	17 / 510 (3.33%) 17	
Renal failure subjects affected / exposed occurrences (all)	18 / 513 (3.51%) 18	6 / 510 (1.18%) 6	
Urinary incontinence subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	9 / 510 (1.76%) 9	
Urinary retention subjects affected / exposed occurrences (all)	22 / 513 (4.29%) 22	18 / 510 (3.53%) 18	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 513 (0.39%)	6 / 510 (1.18%)	
occurrences (all)	2	6	
Back pain			
subjects affected / exposed	16 / 513 (3.12%)	11 / 510 (2.16%)	
occurrences (all)	16	11	
Musculoskeletal chest pain			
subjects affected / exposed	6 / 513 (1.17%)	8 / 510 (1.57%)	
occurrences (all)	6	8	
Musculoskeletal pain			
subjects affected / exposed	10 / 513 (1.95%)	8 / 510 (1.57%)	
occurrences (all)	10	8	
Pain in extremity			
subjects affected / exposed	7 / 513 (1.36%)	8 / 510 (1.57%)	
occurrences (all)	7	8	
Infections and infestations			
Infection susceptibility increased			
subjects affected / exposed	7 / 513 (1.36%)	5 / 510 (0.98%)	
occurrences (all)	7	5	
Pneumonia			
subjects affected / exposed	11 / 513 (2.14%)	11 / 510 (2.16%)	
occurrences (all)	11	11	
Postoperative wound infection			
subjects affected / exposed	9 / 513 (1.75%)	7 / 510 (1.37%)	
occurrences (all)	9	7	
Urinary tract infection			
subjects affected / exposed	22 / 513 (4.29%)	25 / 510 (4.90%)	
occurrences (all)	22	25	
Wound infection			
subjects affected / exposed	3 / 513 (0.58%)	6 / 510 (1.18%)	
occurrences (all)	3	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 513 (0.78%)	10 / 510 (1.96%)	
occurrences (all)	4	10	
Fluid overload			

subjects affected / exposed occurrences (all)	78 / 513 (15.20%) 78	71 / 510 (13.92%) 71
Fluid retention subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	4 / 510 (0.78%) 4
Hyperglycaemia subjects affected / exposed occurrences (all)	31 / 513 (6.04%) 31	36 / 510 (7.06%) 36
Hyperkalaemia subjects affected / exposed occurrences (all)	41 / 513 (7.99%) 41	31 / 510 (6.08%) 31
Hypernatraemia subjects affected / exposed occurrences (all)	7 / 513 (1.36%) 7	8 / 510 (1.57%) 8
Hypervolaemia subjects affected / exposed occurrences (all)	4 / 513 (0.78%) 4	10 / 510 (1.96%) 10
Hypocalcaemia subjects affected / exposed occurrences (all)	19 / 513 (3.70%) 19	14 / 510 (2.75%) 14
Hypoglycaemia subjects affected / exposed occurrences (all)	30 / 513 (5.85%) 30	15 / 510 (2.94%) 15
Hypokalaemia subjects affected / exposed occurrences (all)	34 / 513 (6.63%) 34	32 / 510 (6.27%) 32
Hypomagnesaemia subjects affected / exposed occurrences (all)	6 / 513 (1.17%) 6	7 / 510 (1.37%) 7
Hyponatraemia subjects affected / exposed occurrences (all)	22 / 513 (4.29%) 22	17 / 510 (3.33%) 17
Hypophosphataemia subjects affected / exposed occurrences (all)	15 / 513 (2.92%) 15	8 / 510 (1.57%) 8
Hypovolaemia		

subjects affected / exposed occurrences (all)	4 / 513 (0.78%) 4	7 / 510 (1.37%) 7	
Malnutrition subjects affected / exposed occurrences (all)	3 / 513 (0.58%) 3	6 / 510 (1.18%) 6	
Metabolic acidosis subjects affected / exposed occurrences (all)	17 / 513 (3.31%) 17	9 / 510 (1.76%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2018	<p>QRK309.1 (Amendment 1). Day 365 visit (one year post dose) added to the study as a solicited post-study follow-up visit in response to regulatory agency feedback. Safety Assessments updated to include the new post-study follow-up visit, including additional evaluation of renal function.</p> <p>Inclusion Criterion #5 expanded to include history of prior open-heart surgery as category of surgical risk as it is comparable in risk to other listed complicated surgeries. In addition, corrected an oversight that had not included non-insulin diabetes as a secondary risk factor.</p> <p>Primary Endpoint, Key- and other- Secondary Endpoints revised in response to regulatory agency feedback. Primary- and Key-secondary endpoints to be conducted in subjects 45 years old and above (except when noted otherwise).</p> <p>Exploratory analysis: Previous Secondary Endpoints based on serum cystatin C will now be evaluated. New renal function assessment added.</p> <p>Demographics and medical history: eGFR measurements will be automatically derived in the database based on the single serum creatinine value so clinical sites will not need to record eGFR separately.</p> <p>Surgical parameters: Additional information on pump priming fluid will be collected.</p> <p>Clarification for the local laboratory assessments for eligibility that should be reviewed at the Baseline/Day -1 visit.</p> <p>Measurement of Renal Function: Clarified the planned assessment for creatinine and urea clearance. Added new renal function assessment – measured GFR by iohexol/iotalamate, to be done at Day 90 for a subset of subjects</p> <p>AEs: Added text to reflect safety assessments to be done at the new Post Study Day 365 visit</p> <p>Clarification on when and how to record Renal Replacement Therapy</p> <p>Added new timepoint (Screening Visit) where creatinine and urea clearance evaluation will be done.</p> <p>Added new measurement of renal function (mGFR by iohexol/iotalamate to be done at the Day 90 Visit.</p>
17 August 2018	<p>QRK309.2 (Amendment 2). Inclusion Criterion #5 expanded to include surgeries performed with or without hypothermic arrest. Patients undergoing full hypothermic cardiac arrest for aortic arch surgery/dissection are very much at increased risk for AKI. These procedures are longer and more complicated than the typical open-heart surgery.</p> <p>Exclusion Criteria #5: the rationale to include patients younger than 45 years old off CPB is to gain experience in such lower risk population. They will be handled in the same manner as the overall enrollment of <45 years old from an analysis perspective.</p> <p>Hypothermic circulatory arrest is no longer an exclusion, for the rationale as stated for Inclusion Criterion #5.</p> <p>Local Laboratory Assessments to Evaluate Eligibility: Given the potential for variability of urine dipstick values, confirmation is required when this risk factor (albuminuria) is the sole risk factor for eligibility.</p>

25 September 2019	<p>QRK309.3 (Amendment 3). Allow for a potential enrollment cap to be implemented based on the proportion of randomized subjects per AKI risk factor, to approximate the proportions seen in the high-risk responder subpopulation of the Phase 2 study QRK209.</p> <p>Clarify the timing for study drug administration for subjects 18 to <45 years old who may be undergoing non-cardiopulmonary bypass surgery.</p> <p>SAE reporting requirements clarified. The collection of SAEs are based on the number of days post study drug administration (90 days) and not on the actual Day 90 Visit.</p> <p>Inclusion Criterion #4c clarified and made obvious the instruction to confirm albuminuria via dipstick or urine albumin creatinine ratio, as applicable, if albuminuria is the only possible risk factor for eligibility.</p> <p>Clarify non-emergent vs emergent surgery in Inclusion Criterion #5 and Exclusion Criterion #4.</p> <p>New exclusion criterion added. As methylene blue binds to nucleic acids, and as the effects of this binding on PK and PD QPI-1002 are unknown, exclude subjects treated with methylene blue from eligibility to minimize unknown factors that may affect the data analysis.</p> <p>Restrict administration of methylene blue until 48 h after study drug administration to minimize potential unknown drug-drug interactions that may impact patient outcomes.</p> <p>Removed language regarding collection of surgical output volumes, and the discordance between cystatin C and serum creatinine to determine eligibility for the mGFR by iohexol/iothalamate clearance substudy.</p> <p>Clarify that study drug administration errors are only recorded as an AE if an AE occurs as a result of study drug administration.</p> <p>Add clarification on the definition of AEs to support reporting.</p> <p>MACE will not be collected after Day 30 visit, to be consistent with the collection of AEs and SAEs.</p> <p>Subject consent for Day 365 Study Visit will be obtained during the overall study consent process at the Screening Visit.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported