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

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 ± 30 min after discontinuation of CPB. In case of non-CPB surgery (subjects < 45 years old), study drug will be administered approximately 4 h ± 30 min after the last coronary bypass and completion of anastomosis and achievement of hemostasis.

Arm title	Placebo

Arm description:

Placebo (sterile isotonic saline for injection)

Arm type	Placebo

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 ± 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 ± 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
Physician decision	1	1
Consent withdrawn by subject	14	10
Death	18	27
Lost to follow-up	3	1

Baseline characteristics

Reporting groups

Reporting group title	QPI-1002

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

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
Subject analysis set type	Intention-to-treat

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

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

Reporting group description:

Placebo (sterile isotonic saline for injection)

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

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

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 ≥ 25% reduction in eGFR at the Day 90 visit. For the primary analysis, eGFR was to be based on serum cystatin C (eGFRcys). Estimated GFR based on serum creatinine (eGFRcreat) was to be used in a sensitivity analysis.

End point type	Primary

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

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 >=25% reduction in eGFRScysC 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	QPI-1002

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

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

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

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

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

subjects affected / exposed	17 / 513 (3.31%)	20 / 510 (3.92%)	
occurrences (all)	17	20	
Transaminases increased			
subjects affected / exposed	10 / 513 (1.95%)	7 / 510 (1.37%)	
occurrences (all)	10	7	
Urine output decreased			
subjects affected / exposed	8 / 513 (1.56%)	10 / 510 (1.96%)	
occurrences (all)	8	10	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	11 / 513 (2.14%)	7 / 510 (1.37%)	
occurrences (all)	11	7	
Fall			
subjects affected / exposed	0 / 513 (0.00%)	6 / 510 (1.18%)	
occurrences (all)	0	6	
Incision site pain			
subjects affected / exposed	44 / 513 (8.58%)	53 / 510 (10.39%)	
occurrences (all)	44	53	
Post procedural haemorrhage			
subjects affected / exposed	8 / 513 (1.56%)	2 / 510 (0.39%)	
occurrences (all)	8	2	
Postoperative delirium			
subjects affected / exposed	16 / 513 (3.12%)	8 / 510 (1.57%)	
occurrences (all)	16	8	
Procedural nausea			
subjects affected / exposed	11 / 513 (2.14%)	7 / 510 (1.37%)	
occurrences (all)	11	7	
Procedural pain			
subjects affected / exposed	79 / 513 (15.40%)	78 / 510 (15.29%)	
occurrences (all)	79	78	
Wound complication			
subjects affected / exposed	5 / 513 (0.97%)	8 / 510 (1.57%)	
occurrences (all)	5	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	15 / 513 (2.92%)	21 / 510 (4.12%)	
occurrences (all)	15	21	
Ileus			
subjects affected / exposed	7 / 513 (1.36%)	3 / 510 (0.59%)	
occurrences (all)	7	3	
Nausea			
subjects affected / exposed	108 / 513 (21.05%)	110 / 510 (21.57%)	
occurrences (all)	108	110	
Vomiting			
subjects affected / exposed	29 / 513 (5.65%)	38 / 510 (7.45%)	
occurrences (all)	29	38	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	8 / 513 (1.56%)	8 / 510 (1.57%)	
occurrences (all)	8	8	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	96 / 513 (18.71%)	63 / 510 (12.35%)	
occurrences (all)	96	63	
Haematuria			
subjects affected / exposed	5 / 513 (0.97%)	8 / 510 (1.57%)	
occurrences (all)	5	8	
Oliguria			
subjects affected / exposed	14 / 513 (2.73%)	17 / 510 (3.33%)	
occurrences (all)	14	17	
Renal failure			
subjects affected / exposed	18 / 513 (3.51%)	6 / 510 (1.18%)	
occurrences (all)	18	6	
Urinary incontinence			
subjects affected / exposed	6 / 513 (1.17%)	9 / 510 (1.76%)	
occurrences (all)	6	9	
Urinary retention			
subjects affected / exposed	22 / 513 (4.29%)	18 / 510 (3.53%)	
occurrences (all)	22	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	78 / 513 (15.20%)	71 / 510 (13.92%)	
occurrences (all)	78	71	
Fluid retention			
subjects affected / exposed	7 / 513 (1.36%)	4 / 510 (0.78%)	
occurrences (all)	7	4	
Hyperglycaemia			
subjects affected / exposed	31 / 513 (6.04%)	36 / 510 (7.06%)	
occurrences (all)	31	36	
Hyperkalaemia			
subjects affected / exposed	41 / 513 (7.99%)	31 / 510 (6.08%)	
occurrences (all)	41	31	
Hypernatraemia			
subjects affected / exposed	7 / 513 (1.36%)	8 / 510 (1.57%)	
occurrences (all)	7	8	
Hypervolaemia			
subjects affected / exposed	4 / 513 (0.78%)	10 / 510 (1.96%)	
occurrences (all)	4	10	
Hypocalcaemia			
subjects affected / exposed	19 / 513 (3.70%)	14 / 510 (2.75%)	
occurrences (all)	19	14	
Hypoglycaemia			
subjects affected / exposed	30 / 513 (5.85%)	15 / 510 (2.94%)	
occurrences (all)	30	15	
Hypokalaemia			
subjects affected / exposed	34 / 513 (6.63%)	32 / 510 (6.27%)	
occurrences (all)	34	32	
Hypomagnesaemia			
subjects affected / exposed	6 / 513 (1.17%)	7 / 510 (1.37%)	
occurrences (all)	6	7	
Hyponatraemia			
subjects affected / exposed	22 / 513 (4.29%)	17 / 510 (3.33%)	
occurrences (all)	22	17	
Hypophosphataemia			
subjects affected / exposed	15 / 513 (2.92%)	8 / 510 (1.57%)	
occurrences (all)	15	8	
Hypovolaemia			

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2018	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. 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. 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). Exploratory analysis: Previous Secondary Endpoints based on serum cystatin C will now be evaluated. New renal function assessment added. 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. Surgical parameters: Additional information on pump priming fluid will be collected. Clarification for the local laboratory assessments for eligibility that should be reviewed at the Baseline/Day -1 visit. Measurement of Renal Function: Clarified the planned assessment for creatinine and urea clearance. Added new renal function assessment – measured GFR by iohexol/iothalamate, to be done at Day 90 for a subset of subjects AEs: Added text to reflect safety assessments to be done at the new Post Study Day 365 visit Clarification on when and how to record Renal Replacement Therapy Added new timepoint (Screening Visit) where creatinine and urea clearance evaluation will be done. Added new measurement of renal function (mGFR by iohexol/iothalamate to be done at the Day 90 Visit.
17 August 2018	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. 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. Hypothermic circulatory arrest is no longer an exclusion, for the rationale as stated for Inclusion Criterion #5. 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.

25 September 2019	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. Clarify the timing for study drug administration for subjects 18 to <45 years old who may be undergoing non-cardiopulmonary bypass surgery. 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. 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. Clarify non-emergent vs emergent surgery in Inclusion Criterion #5 and Exclusion Criterion #4. 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. Restrict administration of methylene blue until 48 h after study drug administration to minimize potential unknown drug-drug interactions that may impact patient outcomes. 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. Clarify that study drug administration errors are only recorded as an AE if an AE occurs as a result of study drug administration. Add clarification on the definition of AEs to support reporting. MACE will not be collected after Day 30 visit, to be consistent with the collection of AEs and SAEs. Subject consent for Day 365 Study Visit will be obtained during the overall study consent process at the Screening Visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported