Clinical trial results:
Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD) (PRO2TECT - CONVERSION)

Summary

EudraCT number	2015-004774-14
Trial protocol	HU DE AT CZ ES BG SK GB IT
Global end of trial date	18 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	AKB-6548-CI-0015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02680574
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Akebia Therapeutics, Inc.
Sponsor organisation address	245 First Street, Suite 1400, Cambridge, Massachusetts, United States, 02142
Public contact	Clinical Trial Information Desk, Akebia Therapeutics, Inc., +1 617-844-6128, trials@akebia.com
Scientific contact	Steven Burke, Chief Medical Officer, Akebia Therapeutics, Inc., +1 617-844-6128, trials@akebia.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	31 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with non-dialysis-dependent chronic kidney disease (NDD-CKD) after conversion from current erythropoiesis-stimulating agents (ESA) therapy.

Protection of trial subjects:

The study was conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), International Council for Harmonisation (ICH) guidelines, and all of the applicable United States Code of Federal Regulations 21 (US CFR 21 CFR Part 50 and 312).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 February 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 97
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Brazil: 86
Country: Number of subjects enrolled	Bulgaria: 96
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Hungary: 64
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	Malaysia: 26
Country: Number of subjects enrolled	Mexico: 119

Country: Number of subjects enrolled	Romania: 62
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Serbia: 58
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	South Africa: 34
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	Ukraine: 112
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	United States: 665
Worldwide total number of subjects	1725
EEA total number of subjects	347

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)	651
From 65 to 84 years	952
85 years and over	122

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2961 subjects were screened for entry into the study. Of these, 1725 subjects were enrolled and randomized into the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vadadustat

Arm description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Arm type	Experimental
Investigational medicinal product name	Vadadustat
Investigational medicinal product code	AKB-6548
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg white to off-white, round, bi-convex film-coated tablets for oral administration with a starting dose of 300 mg/day

Arm title	Darbepoetin Alfa

Arm description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Arm type	Experimental
Investigational medicinal product name	Darbepoetin Alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

pre-filled syringes as an injectable solution for intravenous (IV) administration

Investigational medicinal product name	Darbepoetin Alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:
pre-filled syringes as an injectable solution for subcutaneous (SC) administration

Number of subjects in period 1	Vadadustat	Darbepoetin Alfa
Started	862	863
Completed	704	711
Not completed	158	152
Consent withdrawn by subject	17	9
Death	137	137
Lost to follow-up	4	6

Baseline characteristics

Reporting groups	
Reporting group title	Vadadustat

Reporting group description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Reporting group title	Darbepoetin Alfa

Reporting group description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Reporting group values	Vadadustat	Darbepoetin Alfa	Total
Number of subjects	862	863	1725
Age categorical Units:			
Age continuous Units: years			
arithmetic mean	67.3	66.5	
standard deviation	± 13.14	± 13.52	-
Gender categorical Units: subjects			
Female	468	488	956
Male	394	375	769
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	32	26	58
Asian	62	55	117
Black or African American	93	131	224
Native Hawaiian or Other Pacific Islander	3	0	3
White	631	603	1234
Not Reported	15	13	28
Reported as Other	25	32	57
Multiple	1	3	4
Average hemoglobin Units: milligrams per deciliter (mg/dL)			
arithmetic mean	10.423	10.390	
standard deviation	± 0.8871	± 0.9430	-

End points

End points reporting groups

Reporting group title	Vadadustat

Reporting group description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Reporting group title	Darbepoetin Alfa

Reporting group description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Primary: Change in Average Hemoglobin (Hb) between Baseline and the Primary Efficacy Period (Weeks 24 to 36)

End point title	Change in Average Hemoglobin (Hb) between Baseline and the Primary Efficacy Period (Weeks 24 to 36)

End point description:

Change from Baseline was calculated as the Primary Efficacy Period value minus the Baseline value. The Primary Efficacy Period was comprised of Weeks 24 to 36. Analysis was conducted in members of the Randomized Population, comprised of all subjects randomized. Analyses of this population were based on the randomized treatment. Analysis was conducted using an analysis of covariance (ANCOVA) model with multiple imputation for missing data with Baseline hemoglobin concentration, region, and New York Heart Association congestive heart failure (NYHA CHF) class as covariates.

End point type	Primary

End point timeframe:

Baseline; Weeks 24 to 36

End point values	Vadadustat	Darbepoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	862[1]	863[2]		
Units: grams per deciliter (g/dL)				
least squares mean (standard error)	0.41 (± 0.036)	0.42 (± 0.037)		

Notes:

[1] - Randomized Population

[2] - Randomized Population

Statistical analyses

Statistical analysis title	ANCOVA with Multiple Imputation

Statistical analysis description:

Treatment Comparison: Vadadustat minus Darbepoetin Alfa

Comparison groups	Vadadustat v Darbepoetin Alfa

Number of subjects included in analysis	1725
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Least squares mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.042

Notes:

[3] - Establishment of non-inferiority was based on a margin of -0.75 g/dL applied to the difference in mean change of hemoglobin: vadadustat minus darbepoetin alfa

Secondary: Change in Average Hb Value between Baseline and the Secondary Efficacy Period (Weeks 40 to 52)

End point title	Change in Average Hb Value between Baseline and the Secondary Efficacy Period (Weeks 40 to 52)

End point description:

Change from Baseline was calculated as the Secondary Efficacy Period value minus the Baseline value. The Secondary Efficacy Period was comprised of Weeks 40 to 52. Analysis was conducted using an ANCOVA model with multiple imputation for missing data with Baseline hemoglobin concentration, region, and NYHA CHF class as covariates.

End point type	Secondary

End point timeframe:

Baseline; Weeks 40 to 52

End point values	Vadadustat	Darbepoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	862[4]	863[5]		
Units: g/dL				
least squares mean (standard error)	0.43 (± 0.044)	0.44 (± 0.044)		

Notes:

[4] - Randomized Population

[5] - Randomized Population

Statistical analyses

Statistical analysis title	ANCOVA with Multiple Imputation

Statistical analysis description:

Treatment Comparison: Vadadustat minus Darbepoetin Alfa

Comparison groups	Vadadustat v Darbepoetin Alfa

Number of subjects included in analysis	1725
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Least squares mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[6] - Establishment of non-inferiority was based on a margin of -0.75 g/dL applied to the difference in mean change of hemoglobin: vadadustat minus darbepoetin alfa

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 168 weeks

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs), defined as adverse events (AEs) that began (or pre-existing AEs that worsened) or or after the first dose, are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Vadadustat

Reporting group description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Reporting group title	Darbepoetin Alfa

Reporting group description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Serious adverse events	Vadadustat	Darbepoetin Alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	504 / 861 (58.54%)	488 / 862 (56.61%)	
number of deaths (all causes)	139	139	
number of deaths resulting from adverse events	135	137	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	3 / 861 (0.35%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Basal cell carcinoma			
subjects affected / exposed	4 / 861 (0.46%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 861 (0.12%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer recurrent			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm malignant			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder cancer			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bladder cancer recurrent			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer metastatic			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cancer pain			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar tumour			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cervix carcinoma			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
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	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gallbladder cancer			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer stage IV			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hairy cell leukaemia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung cancer metastatic			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic bronchial carcinoma			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm malignant			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-small cell lung cancer stage I			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian adenoma			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer stage II			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seborrhoeic keratosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of pharynx			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (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	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 861 (0.93%)	9 / 862 (1.04%)	
occurrences causally related to treatment / all	1 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	5 / 861 (0.58%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	1 / 6	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	4 / 861 (0.46%)	8 / 862 (0.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			

subjects affected / exposed	4 / 861 (0.46%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	6 / 861 (0.70%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 861 (0.00%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 861 (0.35%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic stenosis			
subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	4 / 861 (0.46%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	4 / 861 (0.46%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			

subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Steal syndrome			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accelerated hypertension			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Axillary vein thrombosis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein stenosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular rupture			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stenosis			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (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	20 / 861 (2.32%)	13 / 862 (1.51%)	
occurrences causally related to treatment / all	0 / 20	0 / 13	
deaths causally related to treatment / all	0 / 20	0 / 13	
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 861 (0.46%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	5 / 861 (0.58%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 861 (0.12%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 861 (0.12%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter site haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	3 / 861 (0.35%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 861 (0.35%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chest discomfort			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Treatment noncompliance			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			

subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polyp			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure			
subjects affected / exposed	14 / 861 (1.63%)	9 / 862 (1.04%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 2	0 / 2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	10 / 861 (1.16%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	0 / 13	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	5 / 861 (0.58%)	11 / 862 (1.28%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	5 / 861 (0.58%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	0 / 5	1 / 7	
deaths causally related to treatment / all	0 / 0	1 / 3	
Respiratory failure			
subjects affected / exposed	4 / 861 (0.46%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	2 / 861 (0.23%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 861 (0.12%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	4 / 861 (0.46%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	2 / 861 (0.23%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	3 / 861 (0.35%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchiectasis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	2 / 861 (0.23%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 861 (0.12%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Delirium			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anger			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
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 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			

subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 861 (0.81%)	8 / 862 (0.93%)	
occurrences causally related to treatment / all	1 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 861 (0.46%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	1 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 861 (0.12%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 861 (0.12%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticoagulation drug level below therapeutic			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose fluctuation			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prothrombin time prolonged			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	8 / 861 (0.93%)	12 / 862 (1.39%)	
occurrences causally related to treatment / all	0 / 10	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	12 / 861 (1.39%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 12	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 861 (0.12%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	4 / 861 (0.46%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	2 / 861 (0.23%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tibia fracture			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula maturation failure			

subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haematoma			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula aneurysm			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device placement issue			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye contusion			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
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	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haematoma			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysis complication			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt occlusion			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site haematoma			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	29 / 861 (3.37%)	31 / 862 (3.60%)	
occurrences causally related to treatment / all	0 / 39	1 / 43	
deaths causally related to treatment / all	0 / 3	0 / 2	
Acute myocardial infarction			
subjects affected / exposed	34 / 861 (3.95%)	24 / 862 (2.78%)	
occurrences causally related to treatment / all	1 / 36	1 / 26	
deaths causally related to treatment / all	0 / 3	0 / 9	
Cardiac failure acute			
subjects affected / exposed	15 / 861 (1.74%)	16 / 862 (1.86%)	
occurrences causally related to treatment / all	0 / 17	0 / 16	
deaths causally related to treatment / all	0 / 2	0 / 3	
Atrial fibrillation			

subjects affected / exposed	16 / 861 (1.86%)	13 / 862 (1.51%)	
occurrences causally related to treatment / all	0 / 20	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	10 / 861 (1.16%)	19 / 862 (2.20%)	
occurrences causally related to treatment / all	0 / 12	0 / 21	
deaths causally related to treatment / all	0 / 4	0 / 6	
Cardiac arrest			
subjects affected / exposed	9 / 861 (1.05%)	16 / 862 (1.86%)	
occurrences causally related to treatment / all	0 / 9	1 / 16	
deaths causally related to treatment / all	0 / 7	1 / 13	
Coronary artery disease			
subjects affected / exposed	7 / 861 (0.81%)	9 / 862 (1.04%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	7 / 861 (0.81%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	1 / 12	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Acute left ventricular failure			
subjects affected / exposed	5 / 861 (0.58%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	7 / 861 (0.81%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 6	0 / 3	
Left ventricular failure			
subjects affected / exposed	3 / 861 (0.35%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	3 / 861 (0.35%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial flutter			
subjects affected / exposed	2 / 861 (0.23%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	3 / 861 (0.35%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 4	
Bradycardia			
subjects affected / exposed	4 / 861 (0.46%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	2 / 861 (0.23%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiorenal syndrome			
subjects affected / exposed	4 / 861 (0.46%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Angina pectoris			
subjects affected / exposed	1 / 861 (0.12%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrioventricular block			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
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	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			

subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arrhythmia			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
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	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve incompetence			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mitral valve calcification			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis uraemic			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia induced cardiomyopathy			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve incompetence			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypokinesia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	6 / 861 (0.70%)	9 / 862 (1.04%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	5 / 861 (0.58%)	9 / 862 (1.04%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	7 / 861 (0.81%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	8 / 861 (0.93%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 8	1 / 2	
deaths causally related to treatment / all	0 / 4	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	6 / 861 (0.70%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 6	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	3 / 861 (0.35%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Seizure			
subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dementia			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Migraine			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Toxic encephalopathy			

subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem stroke			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral artery thrombosis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic coma			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic encephalopathy			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic encephalopathy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
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 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental impairment			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic stroke			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
VIth nerve disorder			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 861 (1.86%)	18 / 862 (2.09%)	
occurrences causally related to treatment / all	1 / 19	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	2 / 861 (0.23%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	1 / 861 (0.12%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			

subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Iron deficiency anaemia			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract diabetic			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tractional retinal detachment			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	7 / 861 (0.81%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	6 / 861 (0.70%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	3 / 861 (0.35%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 861 (0.46%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	3 / 861 (0.35%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	3 / 861 (0.35%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
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 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peptic ulcer			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyschezia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia incarcerated			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiectasia			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic mass			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertensive gastropathy			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	3 / 861 (0.35%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystitis			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatic failure			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gallbladder rupture			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatous liver disease			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis alcoholic			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steatohepatitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	5 / 861 (0.58%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			

subjects affected / exposed	4 / 861 (0.46%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic ulcer			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillaritis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hidradenitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash scarlatiniform			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
End stage renal disease			
subjects affected / exposed	232 / 861 (26.95%)	238 / 862 (27.61%)	
occurrences causally related to treatment / all	0 / 241	0 / 247	
deaths causally related to treatment / all	0 / 11	0 / 10	
Acute kidney injury			
subjects affected / exposed	34 / 861 (3.95%)	32 / 862 (3.71%)	
occurrences causally related to treatment / all	0 / 40	0 / 35	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	6 / 861 (0.70%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Azotaemia			
subjects affected / exposed	4 / 861 (0.46%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 2	
Renal impairment			
subjects affected / exposed	3 / 861 (0.35%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	3 / 861 (0.35%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			

subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic kidney disease			
subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute phosphate nephropathy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis membranoproliferative			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulosclerosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive nephropathy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurogenic bladder			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux nephropathy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal mass			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal papillary necrosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal vascular thrombosis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	5 / 861 (0.58%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	3 / 861 (0.35%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	3 / 861 (0.35%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankylosing spondylitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (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	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall haematoma			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic amyotrophy			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy endocrine			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (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			
Pneumonia			
subjects affected / exposed	56 / 861 (6.50%)	49 / 862 (5.68%)	
occurrences causally related to treatment / all	0 / 63	0 / 50	
deaths causally related to treatment / all	0 / 2	0 / 5	
Urinary tract infection			
subjects affected / exposed	20 / 861 (2.32%)	20 / 862 (2.32%)	
occurrences causally related to treatment / all	0 / 20	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	17 / 861 (1.97%)	16 / 862 (1.86%)	
occurrences causally related to treatment / all	0 / 20	0 / 16	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cellulitis			
subjects affected / exposed	6 / 861 (0.70%)	17 / 862 (1.97%)	
occurrences causally related to treatment / all	0 / 9	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	10 / 861 (1.16%)	7 / 862 (0.81%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 5	0 / 2	
Osteomyelitis			
subjects affected / exposed	5 / 861 (0.58%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	8 / 861 (0.93%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 12	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	6 / 861 (0.70%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	3 / 861 (0.35%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	3 / 861 (0.35%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 861 (0.35%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	4 / 861 (0.46%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis chronic			

subjects affected / exposed	4 / 861 (0.46%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 861 (0.35%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	4 / 861 (0.46%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 861 (0.23%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 861 (0.35%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 861 (0.12%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bronchitis			
subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			

subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 861 (0.23%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 861 (0.00%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site infection			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 861 (0.00%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			

subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 861 (0.00%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			

subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal wall abscess			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis C			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve vegetation			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter bacteraemia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site cellulitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptosporidiosis infection			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis bacterial			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis klebsiella			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal peritonitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis viral			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (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	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (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	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal sepsis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (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 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis bacterial			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid abscess			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyonephrosis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal graft infection			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Salmonella bacteraemia			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scarlet fever			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia bacteraemia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt infection			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinea pedis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection pseudomonas			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	17 / 861 (1.97%)	12 / 862 (1.39%)	
occurrences causally related to treatment / all	0 / 18	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	16 / 861 (1.86%)	10 / 862 (1.16%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	13 / 861 (1.51%)	9 / 862 (1.04%)	
occurrences causally related to treatment / all	0 / 15	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	13 / 861 (1.51%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 14	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	4 / 861 (0.46%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	3 / 861 (0.35%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 861 (0.23%)	6 / 862 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	3 / 861 (0.35%)	5 / 862 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 861 (0.35%)	4 / 862 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	4 / 861 (0.46%)	3 / 862 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	3 / 861 (0.35%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	3 / 861 (0.35%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 861 (0.12%)	2 / 862 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 861 (0.23%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 861 (0.12%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	2 / 861 (0.23%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acidosis			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cachexia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased appetite			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercalcaemia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 861 (0.12%)	0 / 862 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 861 (0.00%)	1 / 862 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vadadustat	Darbepoetin Alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	482 / 861 (55.98%)	436 / 862 (50.58%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	64 / 861 (7.43%)	53 / 862 (6.15%)	
occurrences (all)	78	68	
Vascular disorders			
Hypertension			
subjects affected / exposed	120 / 861 (13.94%)	123 / 862 (14.27%)	
occurrences (all)	157	165	
Nervous system disorders			

Headache			
subjects affected / exposed	22 / 861 (2.56%)	45 / 862 (5.22%)	
occurrences (all)	24	50	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	84 / 861 (9.76%)	85 / 862 (9.86%)	
occurrences (all)	107	102	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	117 / 861 (13.59%)	76 / 862 (8.82%)	
occurrences (all)	147	93	
Nausea			
subjects affected / exposed	73 / 861 (8.48%)	57 / 862 (6.61%)	
occurrences (all)	82	68	
Constipation			
subjects affected / exposed	44 / 861 (5.11%)	38 / 862 (4.41%)	
occurrences (all)	50	40	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	42 / 861 (4.88%)	48 / 862 (5.57%)	
occurrences (all)	44	57	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	93 / 861 (10.80%)	113 / 862 (13.11%)	
occurrences (all)	120	186	
Nasopharyngitis			
subjects affected / exposed	53 / 861 (6.16%)	61 / 862 (7.08%)	
occurrences (all)	68	79	
Upper respiratory tract infection			
subjects affected / exposed	55 / 861 (6.39%)	44 / 862 (5.10%)	
occurrences (all)	64	49	
Bronchitis			
subjects affected / exposed	44 / 861 (5.11%)	32 / 862 (3.71%)	
occurrences (all)	52	36	
Metabolism and nutrition disorders			

Hyperkalaemia subjects affected / exposed occurrences (all)	71 / 861 (8.25%) 84	78 / 862 (9.05%) 94	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2016	• Added Exclusion Criteria. • Clarified that the adrenal function assessment (adrenocorticotropic hormone [ACTH] stimulation test) was to be conducted in a subset of 200 subjects in the European Union (100 subjects from the vadadustat treatment arm and 100 subjects from the darbepoetin alfa treatment arm) across the 2 non-dialysis-dependent chronic kidney disease (NDD-CKD) studies: AKB 6548-CI-0014 and AKB-6548-CI-0015. • Defined that the study completion date (end of trial) was to take place when 631 major adverse cardiovascular events (MACE) events had accrued over the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015). • Clarified that the double-barrier method should be practiced starting at Screening Visit 1, throughout the study, and for 30 days after the last dose of study drug. • Added that "In case of substantial protocol amendment, the sponsor will obtain approval from responsible Regulatory Authorities before implementation."
18 April 2016	• Update Exclusion Criteria. • Added hospitalization for heart failure (HF) as an adjudicated safety endpoint in addition to MACE and thromboembolic events. • Clarified that the darbepoetin alfa dosing adjustment guidelines were based on the approved local product label for adult subjects with CKD not on dialysis. • Allowed subjects who transitioned to hemodialysis or peritoneal dialysis during the study to continue to receive study drug (vadadustat or darbepoetin alfa). This was supported by acceptable safety data from a recently-completed Phase 2 trial of vadadustat in subjects with DD-CKD. • Introduced a binary causality system (i.e., "related" or "unrelated") for clinical trial investigators to assign causality of adverse events to study drugs in accordance with recommendations from the Council for International Organizations of Medical Sciences (CIOMS) VI Working Group. • Described and justified the sparse pharmacokinetic (PK) sampling scheme. The results of PK simulations indicated that collection of a sample between 0.25 to 1 hour after administration of the first dose along with sparse samples collected during Weeks 4, 12, 28 and 52 provided additional information to help characterize the population PK and PK/pharmacodynamic (PD) relationships. • Aligned adverse event reporting related to critically increased liver function test results with the United States Food and Drug Administration (FDA) Drug-Induced Liver Injury (DILI) guidelines to provide instructions to study sites regarding reporting for improved consistency and case quality. • Added visit windows to provide flexibility to the subjects and the study sites during scheduling of study visits. • Clarified definitions for renal events to improve understanding and site compliance.

08 June 2017	• Updated the study design from the current screening period of up to 4 weeks to up to 8 weeks and allowed iron, vitamin B12, and folate supplementation as needed during the screening period. • Screening period changed from up to 4 weeks to up to 8 weeks. • Allowed one retest for each laboratory parameter, within the screening period. • Clarified that subjects who received iron replacement may have retested screening hemoglobin (Hb) a minimum of 3 weeks after completion of iron replacement therapy. • Updated Inclusion and Exclusion Criteria. • Increased the number of total sites in efforts to increase enrollment. • Updated vadadustat dosing and dose adjustment guidelines to clarify that subjects receiving 1 tablet of dosing prior to interruption were to resume treatment with 1 tablet after interruption. • Updated to reflect information from recently completed trials. • Added information regarding Executive Steering Committee. • To clarify darbepoetin alfa administration and accountability, the following details were added: o Darbepoetin alfa was changed to be administered per the label. o Darbepoetin alfa was changed to allow doses to be self-administered or administered by health care professional at the clinics, site facility, or at subject's home according to the investigator's determination and local practice. o Added additional information on return of darbepoetin alfa for drug accountability and compliance assessment. • Modified laboratory evaluations schedule. • Clarified study analysis populations.
18 January 2018	• Updated with information from recently completed trials and aligned with vadadustat Investigator's Brochure. • Updated to reflect addition of several key secondary, other secondary efficacy endpoints and Safety Endpoints to align with the Statistical Analysis Plan (SAP). • Section 7.4.1 Retesting was updated for simplification. • Updated to clarify that all enrolled subjects in this study were to have had the opportunity to complete (at least) the Week 36 visit. • Updated to add Lack of Efficacy as a reason for discontinuation for accurate data capture. • Updated dosing guidelines and instructions. • Updated to align with published guidelines to prescribe iron supplementation and for initiation of erythropoiesis-stimulating agent (ESA) rescue. • Updated to specify a dosing compliance range of 80% to 120% which is commonly used in clinical trials with oral products. • Updated to include text clarifying that if the duration of the screening period was less than 30 days, all medications taken within 30 days prior to first dose of study drug were to be recorded. • Added the requirement for monthly monitoring of Hb drawn as part of local standard of care labs or via an unscheduled visit. • Added text defining overdose of study drugs. • Updated to require all new and recurrent malignancies (with a few exceptions) to be reported as a serious adverse events (SAEs) to standardize reporting. • Updated to reflect a change in the noninferiority margin from -0.5 to -1.0 grams per deciliter (g/dL). • Updated with enrollment projections as well as median study drug exposure times. • Updated missing data information to align with the Statistical Analysis Plan (SAP). • Updated to pre-specify key subgroups for subsequent analysis. • Clarified that adverse event (AE) summaries were to be provided for specific subgroups.

13 September 2018	• Revised subject number. • Clarified that all enrolled subjects were to be allowed to complete the primary efficacy period prior to global study completion (GSC). • Clarified procedures at time of GSC. • Emphasized the importance of continuing to follow subjects through GSC. • Stated that if study drug was temporarily interrupted for more than 60 days, Medical Monitor should be contacted before resuming study drug. • Updated timing of End of Trial (EOT) visit and Follow-up visit following permanent discontinuation of study medication. • Updated with all options to be considered by the Investigator before a subject withdrew consent. • Included all options available to the Investigator to follow subjects that permanently discontinued study drug. • Detailed steps to support sites in efforts to identify subjects lost to follow-up. • Updated to reflect information for which the Sponsor and Contract Research Organization (CRO) study teams were to remain blinded. • Clarified restarting of study drug after erythropoiesis-stimulating agent (ESA) rescue and red blood cell (RBC) transfusion. • Clarified study drug dosing following ESA administration. • Provided guidance on how to manage concomitant use of statins with vadadustat. • Included timing of collection of AEs. • Detailed managing subjects that permanently stopped study drug and subjects on study drug at GSC. • Defined the end of study assessments that documented subject status. • Added guidance on managing subjects who developed malignancy while on study drug. • Indicated that Sponsor had defined events that were to be classified as serious regardless of their assessment. • Clarified AE reporting period. • Updated how Baseline was calculated for Hb. • Updated with a change in the non-inferiority margin. • Updated definition for primary safety endpoint and how non-inferiority was established between treatment groups. • Defined full analysis population. • Updated with use of analysis of covariance (ANCOVA).
18 December 2018	• Updated to include reference to the Pharmacy Manual which provides further details on storage and managing temperature excursions. •Provided further guidance regarding concomitant use of simvastatin drug interactions with vadadustat. • Provide guidance regarding concomitant use of breast cancer resistance protein (BCRP) substrates with vadadustat. • Updated to reflect recent results of investigative toxicology studies. • Liver function tests were increased in Year 2, 3, and 4 to include Week 64, 88, 116, 140, 168, and 192.
26 February 2019	• Include a reference to Study Drug Stopping Rules for management of subjects with alanine aminotransferase (ALT) and asparate aminotransferase (AST) abnormalities. • Include the table of liver function test results that would require permanent discontinuation of vadadustat. • Updated to exclude subjects with elevations in ALT or AST >3 times the upper limit of normal (ULN) with an elevation of total serum bilirubin >2 times ULN from conditions of temporary discontinuation, as this was a condition for permanent discontinuation. • Section 10.1.2 Serious adverse events was updated to include information defining designated medical events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported