Clinical trial results:
Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction or Maintenance Treatment of Anemia in Subjects with Incident Dialysis Dependent Chronic Kidney Disease (DD-CKD) (INNO2VATE – Correction/Conversion)

Summary

EudraCT number	2016-000838-21
Trial protocol	DE PT IT
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	15 April 2021
First version publication date	15 April 2021

Trial information

Trial identification

Sponsor protocol code	AKB-6548-CI-0016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02865850
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
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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 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 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 after the correction of hemoglobin (Hb) or conversion from current erythropoiesis-stimulating agent (ESA) therapy, in subjects who have recently initiated dialysis treatment for dialysis-dependent chronic kidney disease (DD-CKD).

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	18 July 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Brazil: 38
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Ukraine: 62
Country: Number of subjects enrolled	United States: 199
Worldwide total number of subjects	369
EEA total number of subjects	42

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)	259
From 65 to 84 years	106
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 652 subjects were screened for entry into the study. Of these, 369 subjects were enrolled and randomized in the study.

Period 1

Period 1 title	Overall Study (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 on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Arm type	Active comparator
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

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 bolus use

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

Number of subjects in period 1	Vadadustat	Darbepoetin Alfa
Started	181	188
Completed	160	165
Not completed	21	23
Consent withdrawn by subject	3	2
Death	15	19
Lost to follow-up	3	2

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 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	181	188	369
Age categorical Units:			
Age continuous Units: years			
arithmetic mean	56.5	55.6	
standard deviation	± 14.80	± 14.60	-
Gender categorical Units: subjects			
Female	74	75	149
Male	107	113	220
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	12	8	20
Black or African American	38	35	73
White	129	143	272
Not Reported	0	1	1
Reported as Other	0	1	1
Multiple	1	0	1
Average hemoglobin Units: grams per deciliter (g/dL)			
arithmetic mean	9.369	9.190	
standard deviation	± 1.0701	± 1.1381	-

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 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	181[1]	188[2]		
Units: grams per deciliter (g/dL)				
least squares mean (standard error)	1.26 (± 0.109)	1.58 (± 0.108)		

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	369
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Least squares mean difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[3] - Establishment of non-inferiority was based on a margin of -0.75 g/dL applied to the difference in mean change: 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	181[4]	188[5]		
Units: g/dL				
least squares mean (standard error)	1.42 (± 0.132)	1.50 (± 0.136)		

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	369
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Least squares mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.134

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to approximately 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) on or after the first dose, are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

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 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	89 / 179 (49.72%)	105 / 186 (56.45%)	
number of deaths (all causes)	15	20	
number of deaths resulting from adverse events	15	18	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Choroid melanoma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasm			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive urgency			
subjects affected / exposed	7 / 179 (3.91%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 12	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 179 (1.12%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hypertensive crisis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			

subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 179 (1.12%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 179 (1.12%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accelerated hypertension			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachiocephalic vein thrombosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steal syndrome			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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			
Pre-eclampsia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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			
Non-cardiac chest pain			
subjects affected / exposed	3 / 179 (1.68%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Impaired healing			

subjects affected / exposed	2 / 179 (1.12%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	5 / 179 (2.79%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	4 / 179 (2.23%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	2 / 179 (1.12%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord leukoplakia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar I disorder			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Device occlusion			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 179 (0.56%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	2 / 179 (1.12%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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			
Arteriovenous fistula thrombosis			
subjects affected / exposed	3 / 179 (1.68%)	6 / 186 (3.23%)	
occurrences causally related to treatment / all	0 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis			

subjects affected / exposed	1 / 179 (0.56%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	2 / 179 (1.12%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 179 (1.12%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft thrombosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Traumatic intracranial haematoma			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis			

subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	4 / 179 (2.23%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 179 (1.68%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrial fibrillation			
subjects affected / exposed	3 / 179 (1.68%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 179 (1.68%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 179 (1.12%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Myocardial infarction			
subjects affected / exposed	2 / 179 (1.12%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	2 / 179 (1.12%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	2 / 179 (1.12%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 179 (1.12%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac valve disease			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic left ventricular failure			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 179 (1.12%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem syndrome			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral hypoperfusion			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postresuscitation encephalopathy			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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	2 / 179 (1.12%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood disorder			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery thrombosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 179 (0.00%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
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	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal migraine			

subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dolichocolon acquired			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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 / 179 (0.00%)	1 / 186 (0.54%)	
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 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic congestion			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Porcelain gallbladder			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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			

Skin ulcer			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hidradenitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Chronic kidney disease			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLE arthritis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 179 (4.47%)	7 / 186 (3.76%)	
occurrences causally related to treatment / all	0 / 15	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	3 / 179 (1.68%)	6 / 186 (3.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Osteomyelitis			
subjects affected / exposed	4 / 179 (2.23%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 179 (2.23%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	3 / 179 (1.68%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	3 / 179 (1.68%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	4 / 179 (2.23%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	3 / 179 (1.68%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 179 (0.56%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 179 (0.56%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Arteriovenous fistula site infection			
subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 179 (0.00%)	3 / 186 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 179 (1.12%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site infection			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal graft infection			
subjects affected / exposed	0 / 179 (0.00%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 179 (0.56%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site abscess			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus syndrome			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (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 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subacute endocarditis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site infection			

subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
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	10 / 179 (5.59%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 16	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	5 / 179 (2.79%)	4 / 186 (2.15%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 179 (1.12%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 179 (1.12%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 179 (0.56%)	2 / 186 (1.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			

subjects affected / exposed	0 / 179 (0.00%)	1 / 186 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 186 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Vadadustat	Darbepoetin Alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 179 (44.13%)	83 / 186 (44.62%)	
Injury, poisoning and procedural complications			
Procedural hypotension			
subjects affected / exposed	11 / 179 (6.15%)	12 / 186 (6.45%)	
occurrences (all)	14	21	
Dialysis related complication			
subjects affected / exposed	8 / 179 (4.47%)	11 / 186 (5.91%)	
occurrences (all)	10	19	
Fall			
subjects affected / exposed	10 / 179 (5.59%)	8 / 186 (4.30%)	
occurrences (all)	13	11	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 179 (15.08%)	24 / 186 (12.90%)	
occurrences (all)	48	31	
Hypotension			
subjects affected / exposed	5 / 179 (2.79%)	16 / 186 (8.60%)	
occurrences (all)	7	17	
Nervous system disorders			

Headache			
subjects affected / exposed	8 / 179 (4.47%)	11 / 186 (5.91%)	
occurrences (all)	11	11	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	18 / 179 (10.06%)	17 / 186 (9.14%)	
occurrences (all)	25	21	
Nausea			
subjects affected / exposed	14 / 179 (7.82%)	13 / 186 (6.99%)	
occurrences (all)	17	14	
Vomiting			
subjects affected / exposed	13 / 179 (7.26%)	9 / 186 (4.84%)	
occurrences (all)	16	10	
Constipation			
subjects affected / exposed	3 / 179 (1.68%)	13 / 186 (6.99%)	
occurrences (all)	4	17	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	13 / 179 (7.26%)	10 / 186 (5.38%)	
occurrences (all)	13	11	
Cough			
subjects affected / exposed	11 / 179 (6.15%)	5 / 186 (2.69%)	
occurrences (all)	12	5	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 179 (1.12%)	10 / 186 (5.38%)	
occurrences (all)	2	11	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	9 / 179 (5.03%)	16 / 186 (8.60%)	
occurrences (all)	10	19	
Nasopharyngitis			
subjects affected / exposed	10 / 179 (5.59%)	8 / 186 (4.30%)	
occurrences (all)	11	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 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. o Screening Period changed from up to 4 weeks to up to 8 weeks. o One retest was allowed for each laboratory parameter, within the Screening Period. o Subjects who received iron replacement therapy may have had a retest screening hemoglobin (Hb) a minimum of 3 weeks after completion of iron replacement therapy. • Updated Exclusion Criteria. • Vadadustat dosing and dose adjustment guidelines were updated to clarify that subjects who received 1 tablet of dosing prior to interruption resumed treatment with 1 tablet after interruption. • Updated to reflect information from recently completed studies. • Section 6.4.1 (Executive Steering Committee) details were added. • 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. • Section 9.2.2 (Laboratory Evaluations) was revised to reflect the following: o Modification to the frequency of protocol specified biomarker sample collection. o Additional exploratory sample collection. • Section 11.2 (Study Analysis Populations) clarified the study analysis populations.
28 August 2017	• Aligned with standard of care for incident dialysis-dependent chronic kidney disease (DD-CKD) subjects, restriction on erythropoiesis-stimulating agent (ESA) use in the 4 weeks prior to and during the initial Screening Period was removed. • ESA was allowed during screening per standard of care. However, for all subjects, it was recommended that no additional ESA doses be administered after Screening Visit -2 and prior to the Randomization Visit.

18 January 2018	• Updated to reflect that subjects may enter the study on prior ESA therapy. • Updated to reflect information from recently completed studies and for alignment with vadadustat Investigator's Brochure. • Updated to reflect addition of several key secondary, other secondary efficacy, and safety endpoints in alignment with the Statistical Analysis Plan (SAP). • Modified inclusion criteria to allow subjects who had a mean screening Hb between 8.0 and 11.0 grams per deciliter (g/dL) (inclusive) as determined by the average of 2 Hb values measured by the central laboratory during Screening. • Exclusion Criterion added to define and exclude subjects who were hyporesponsive to ESAs within 8 weeks prior to or during Screening. • Section 7.4.1 retesting was updated for simplification. • Updated to add Lack of Efficacy as a reason for discontinuation for accurate data capture. • Revised to guide investigators to follow printed dose adjustment algorithms. • Updated to align with published guidelines to prescribe iron supplementation and for initiation of ESA rescue. • Updated to specify a dosing compliance range of 80% to 120%. • Updated to clarify that if 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. • Updated to require monthly monitoring of Hb drawn as part of local standard of care or via an unscheduled visit. • Updated to require that all new and recurrent malignancies (with a few exceptions) be reported as serious adverse events (SAEs) to standardize reporting. • Updated to define overdose of study drugs. • Updated to reflect a change in the non-inferiority margin from -0.5 to -1.0 g/dL. • Updated with enrollment projections and median study drug exposure times. • Updated definition of missing data to align with the SAP. • Updated to pre-specify key subgroups for subsequent analysis. • Updated to provide adverse event (AE) summaries for specific subgroups.

13 September 2018	• Updated with revised subject numbering. • Updated to clarify that red blood cell (RBC) transfusion were not allowed within 8 weeks prior to randomization. • Clarified that all enrolled subjects were to be allowed to complete the primary efficacy period prior to global study completion. • Clarified procedures at time of global study completion (GSC) and the importance of continuing to follow subjects through GSC. • Stated that if study drug was temporarily interrupted for more than 60 days, the Medical Monitor had to be contacted before resuming study drug. • End of Trial/Follow-up Visits to be performed at time of permanent discontinuation of study drug. • Added information for investigator regarding subject withdrawal and follow up (FU) and detailed steps to support sites to identify subjects lost to FU. • Updated target enrollment. • Updated with information for which the study teams will remain blinded. • Clarified when study drug to be restarted after ESA rescue and RBC transfusion. • Clarified study drug dosing following ESA administration. • Aligned with change in Exclusion Criteria to clarify RBC transfusions. • Provided guidance on management of concomitant statin use. • Included details on AE collection and managing subjects that permanently stopped study drug. • Defined the EOS assessments that documented subject status at the global study completion/time of subject withdrawal/when subject was deemed lost to FU or upon death. • Added guidance on managing subjects who developed malignancy while on study drug. • Indicated that the sponsor had defined events that classified as serious regardless of their assessment. • Clarified the AE reporting period. • Updated to reflect how Baseline was calculated for Hb. • Updated non-inferiority margin details. • Updated definitions of the primary safety endpoint and how non inferiority was established. • Added Full Analysis Set Population definition. • Added use of analysis of covariance with multiple imputation.
18 December 2018	• Updated to include reference to the Pharmacy Manual which provided further details on storage and managing temperature excursions. • Updated to provide further guidance regarding concomitant use of simvastatin drug interactions with vadadustat. • Provided guidance regarding concomitant use of breast cancer resistance protein substrates with vadadustat. • Updated to reflect recent results of investigative toxicology studies. • Liver function tests (LFTs) were increased in Year 2, 3, and 4 to include Week 64, 88, 116, 140, 168, and 192.
26 February 2019	• Updated to include a reference to Study Drug Stopping Rules for management of subjects with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) abnormalities. • Included the table of LFT 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 is now a condition for permanent discontinuation. • Updated to include information defining designated medical events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: