Clinical trial results:
A phase 3 randomized, open-label (sponsor-blind), active controlled, parallel-group, multi-center, event driven study in dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoietin-stimulating agents

Summary

EudraCT number	2016-000541-31
Trial protocol	HU BE GB DK CZ DE SE PT ES NL AT GR FR IT
Global end of trial date	09 November 2020

Results information

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

Trial information

Trial identification

Sponsor protocol code	200807

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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	15 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To compare daprodustat to recombinant human erthropoetin (rhEPO) for cardiovascular (CV) safety (non-inferiority)
- To compare daprodustat to rhEPO for hemoglobin (Hgb) efficacy (non-inferiority)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 70
Country: Number of subjects enrolled	Malaysia: 31
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Korea, Republic of: 129
Country: Number of subjects enrolled	Taiwan: 43
Country: Number of subjects enrolled	Bulgaria: 80
Country: Number of subjects enrolled	Czechia: 50
Country: Number of subjects enrolled	Estonia: 11
Country: Number of subjects enrolled	Hungary: 143
Country: Number of subjects enrolled	Poland: 73
Country: Number of subjects enrolled	Romania: 37
Country: Number of subjects enrolled	Russian Federation: 207
Country: Number of subjects enrolled	South Africa: 47
Country: Number of subjects enrolled	Turkey: 24
Country: Number of subjects enrolled	Ukraine: 163
Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Belgium: 39
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	France: 27

Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Greece: 96
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	New Zealand: 44
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Portugal: 64
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Argentina: 182
Country: Number of subjects enrolled	Brazil: 156
Country: Number of subjects enrolled	Mexico: 88
Country: Number of subjects enrolled	United States: 846
Worldwide total number of subjects	2964
EEA total number of subjects	829

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)	1985
From 65 to 84 years	931
85 years and over	48

Subject disposition

Recruitment

Recruitment details:

This was a randomized, open-label (sponsor blind), active-controlled, parallel-group, event-driven study conducted at 431 centers in 35 countries. Participants were randomized to receive daprodustat and recombinant human erythropoietin (rhEPO) (epoetin alfa or darbepoetin alfa).

Pre-assignment

Screening details:

A total of 2964 participants were 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	Daprodustat

Arm description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received daprodustat tablets at dose levels of 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily until the required number of major adverse cardiovascular event (MACE) occurred, at approximately 45.1 months of randomized treatment. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]).

Arm type	Experimental
Investigational medicinal product name	Daprodustat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daprodustat was given orally once daily at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered orally, one tablet daily.

Arm title	rhEPO

Arm description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received treatment with rhEPO. Participants on hemodialysis received epoetin alfa as intravenous (IV) injection once weekly or three-times weekly with total weekly dose levels ranging from 1500 to 60,000 Units. Participants on peritoneal dialysis received subcutaneous (SC) injection of darbepoetin alfa every 1, 2, or 4 weeks with 4-weekly total dose levels ranging from 20 to 400 microgram (mcg). Darbepoetin could be given by IV injection for peritoneal dialysis participants switching to hemodialysis. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL) and administered until the required number of MACE events occurred, at approximately 45.1 months of randomized treatment.

Arm type	Active comparator

Investigational medicinal product name	Epoetin alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Epoetin alfa was administered as once weekly or three-times weekly intravenous (IV) injection at total weekly dose levels ranging from 1500 to 60,000 Units .

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered orally, one tablet daily.

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

Dosage and administration details:

Darbepoetin alfa was administered subcutaneously (SC) or as IV injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg).

Number of subjects in period 1	Daprodustat	rhEPO
Started	1487	1477
Completed	1370	1366
Not completed	117	111
Consent withdrawn by subject	44	42
Investigator Site Closed	55	57
Unknown	1	-
Lost to follow-up	17	12

Baseline characteristics

Reporting groups	
Reporting group title	Daprodustat

Reporting group description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received daprodustat tablets at dose levels of 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily until the required number of major adverse cardiovascular event (MACE) occurred, at approximately 45.1 months of randomized treatment. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]).

Reporting group title	rhEPO

Reporting group description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received treatment with rhEPO. Participants on hemodialysis received epoetin alfa as intravenous (IV) injection once weekly or three-times weekly with total weekly dose levels ranging from 1500 to 60,000 Units. Participants on peritoneal dialysis received subcutaneous (SC) injection of darbepoetin alfa every 1, 2, or 4 weeks with 4-weekly total dose levels ranging from 20 to 400 microgram (mcg). Darbepoetin could be given by IV injection for peritoneal dialysis participants switching to hemodialysis. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL) and administered until the required number of MACE events occurred, at approximately 45.1 months of randomized treatment.

Reporting group values	Daprodustat	rhEPO	Total
Number of subjects	1487	1477	2964
Age categorical			
All Randomized (Intent-to-treat [ITT]) Population comprised of all randomized participants. Participants were analyzed according to the treatment to which they were randomized.			
Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1007	978	1985
From 65-84 years	458	473	931
85 years and over	22	26	48
Age Continuous			
All Randomized (Intent-to-treat [ITT]) Population comprised of all randomized participants. Participants were analyzed according to the treatment to which they were randomized.			
Units: years			
arithmetic mean	57.2	57.3	
standard deviation	± 14.29	± 14.65	-
Sex: Female, Male			
All Randomized (Intent-to-treat [ITT]) Population comprised of all randomized participants. Participants were analyzed according to the treatment to which they were randomized.			
Units: Participants			
Female	636	630	1266
Male	851	847	1698
Race/Ethnicity, Customized			
All Randomized (Intent-to-treat [ITT]) Population comprised of all randomized participants. Participants were analyzed according to the treatment to which they were randomized.			

Units: Subjects			
American Indian or Alaskan Native	19	32	51
Asian - Central/South Asian Heritage	36	46	82
Asian - East Asian Heritage	97	86	183
Asian - Japanese Heritage	3	3	6
Asian - South East Asian Heritage	40	45	85
Black or African American	228	233	461
Native Hawaiian or Other Pacific Islander	26	25	51
White - Arabic/North African Heritage	8	14	22
White - White/Caucasian/European Heritage	987	968	1955
Mixed Asian Race	0	1	1
Mixed Race	43	24	67

End points

End points reporting groups

Reporting group title	Daprodustat

Reporting group description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received daprodustat tablets at dose levels of 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily until the required number of major adverse cardiovascular event (MACE) occurred, at approximately 45.1 months of randomized treatment. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]).

Reporting group title	rhEPO

Reporting group description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received treatment with rhEPO. Participants on hemodialysis received epoetin alfa as intravenous (IV) injection once weekly or three-times weekly with total weekly dose levels ranging from 1500 to 60,000 Units. Participants on peritoneal dialysis received subcutaneous (SC) injection of darbepoetin alfa every 1, 2, or 4 weeks with 4-weekly total dose levels ranging from 20 to 400 microgram (mcg). Darbepoetin could be given by IV injection for peritoneal dialysis participants switching to hemodialysis. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL) and administered until the required number of MACE events occurred, at approximately 45.1 months of randomized treatment.

Primary: Time to first occurrence of adjudicated major adverse cardiovascular event (MACE) during cardiovascular (CV) events follow-up time period: Non-inferiority analysis

End point title	Time to first occurrence of adjudicated major adverse cardiovascular event (MACE) during cardiovascular (CV) events follow-up time period: Non-inferiority analysis

End point description:

Time to MACE defined as time to first occurrence of Clinical Events Committee (CEC) adjudicated MACE (composite of all-cause mortality, non-fatal myocardial infarction [MI] and non-fatal stroke) was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to first occurrence was computed as (event date minus randomization date)+1. Incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95 percent (%) confidence interval (CI). First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. All Randomized (Intent-to-treat [ITT]) Population comprised of all randomized participants. Participants were analyzed according to the treatment to which they were randomized.

End point type	Primary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[1]	1477[2]		
Units: Events per 100 person years				
number (confidence interval 95%)	11.07 (9.98 to 12.26)	11.86 (10.72 to 13.09)		

Notes:

[1] - All Randomized (ITT) Population

[2] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.07

Notes:

[3] - Non-inferiority was achieved if the upper limit of the two-sided 95% CI for the hazard ratio was below the pre-specified non-inferiority margin of 1.25.

Primary: Mean Change from Baseline in Hemoglobin (Hgb) levels During Evaluation Period (Week 28 to Week 52)

End point title	Mean Change from Baseline in Hemoglobin (Hgb) levels During Evaluation Period (Week 28 to Week 52)

End point description:

Blood samples were collected from participants for hemoglobin measurements. Hemoglobin during the evaluation period was defined as the mean of all available post-randomization hemoglobin values (on and off-treatment) during the evaluation period (Week 28 to Week 52). For the primary analysis, missing post-Baseline hemoglobin values were imputed using pre-specified multiple imputation methods. Change from Baseline was defined as post-Baseline value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date.

End point type	Primary

End point timeframe:

Baseline (Pre-dose on Day 1) and evaluation period (Week 28 to Week 52)

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[4]	1477[5]		
Units: Grams per deciliter				
least squares mean (standard error)	0.28 (± 0.022)	0.10 (± 0.022)		

Notes:

[4] - All Randomized (ITT) Population

[5] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Analysis of covariance (ANCOVA) model adjusted for treatment, Baseline Hgb, dialysis type and region along with 95% CI for treatment difference (daprodustat-rhEPO).

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Least square (LS) mean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.24

Notes:

[6] - Non-inferiority was to be established if the lower limit of the two-sided 95% CI for the treatment difference was greater than -0.75 g/dL.

Secondary: Time to first occurrence of adjudicated MACE during CV events follow-up time period: Superiority analysis

End point title	Time to first occurrence of adjudicated MACE during CV events follow-up time period: Superiority analysis

End point description:

Time to MACE defined as the time to first occurrence of CEC adjudicated MACE was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariate. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. This endpoint was adjusted for multiplicity using the Holm-Bonferonni method.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[7]	1477[8]		
Units: Events per 100 person years				
number (confidence interval 95%)	11.07 (9.98 to 12.26)	11.86 (10.72 to 13.09)		

Notes:

[7] - All Randomized (ITT) Population

[8] - All Randomized (ITT) Population

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group,

dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156123 [9]
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.07

Notes:

[9] - The p-value was compared against 0.0125 based on the Holm-Bonferonni adjustment.

Secondary: Time to first occurrence of adjudicated MACE or thromboembolic event during CV events follow-up time period

End point title	Time to first occurrence of adjudicated MACE or thromboembolic event during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated MACE or thromboembolic event (vascular access thrombosis, symptomatic deep vein thrombosis or symptomatic pulmonary embolism) was analyzed using a Cox proportional hazards regression model with with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. This endpoint was adjusted for multiplicity using the Holm-Bonferonni method.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[10]	1477[11]		
Units: Events per 100 person years				
number (confidence interval 95%)	15.84 (14.48 to 17.30)	17.85 (16.38 to 19.42)		

Notes:

[10] - All Randomized (ITT) Population.

[11] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023539 [12]
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1

Notes:

[12] - The p-value was compared against 0.006250 based on the Holm-Bonferonni adjustment.

Secondary: Time to first occurrence of adjudicated MACE or hospitalization for heart failure during CV events follow-up time period

End point title	Time to first occurrence of adjudicated MACE or hospitalization for heart failure during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated MACE or hospitalization for heart failure was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. This endpoint was adjusted for multiplicity using the Holm-Bonferonni method.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[13]	1477[14]		
Units: Events per 100 person years				
number (confidence interval 95%)	12.98 (11.77 to 14.27)	13.38 (12.15 to 14.70)		

Notes:

[13] - All Randomized (ITT) Population.

[14] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.325797 [15]
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.11

Notes:

[15] - The p-value was compared against 0.025000 based on the Holm-Bonferonni adjustment.

Secondary: Mean average monthly On-treatment IV iron dose per participant

End point title	Mean average monthly On-treatment IV iron dose per participant

End point description:

Average monthly IV iron dose (milligrams) per participant from Day 1 to Week 52 was determined by calculating the total IV iron dose per participant from treatment start date + 1 to the earliest of (Week 52 visit date, first blood (red blood cell [RBC] or whole blood) transfusion date, and treatment stop date + 1 day) which corresponds to the time while the participant was on randomized treatment and before receiving a blood transfusion. This total IV iron dose was divided by (the number of days from treatment start date + 1 to the earliest of (Week 52 visit date, first blood transfusion date (RBC or whole blood), and treatment stop date +1) / 30.4375 days). This endpoint was adjusted for multiplicity using the Holm-Bonferonni method. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1482[16]	1472[17]		
Units: Milligrams				
least squares mean (standard error)	90.8 (± 3.34)	99.9 (± 3.35)		

Notes:

[16] - All Randomized (ITT) Population.

[17] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Analysis was carried out by using ANCOVA model with terms for treatment, Baseline monthly IV iron dose, dialysis type and region.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2954
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026947 [18]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	0.2

Notes:

[18] - The p-value was compared against 0.008333 based on the Holm-Bonferonni adjustment.

Secondary: Time to First occurrence of Adjudicated All-Cause Mortality during vital status for follow-up time period

End point title	Time to First occurrence of Adjudicated All-Cause Mortality during vital status for follow-up time period

End point description:

Time to first occurrence of adjudicated all-cause mortality was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the vital status for follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for vital status follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[19]	1477[20]		
Units: Events per 100 person years				
number (confidence interval 95%)	8.32 (7.39 to 9.32)	8.59 (7.65 to 9.62)		

Notes:

[19] - All Randomized (ITT) Population.

[20] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3281
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.13

Secondary: Time to First occurrence of Adjudicated CV Mortality during CV events follow-up time period

End point title	Time to First occurrence of Adjudicated CV Mortality during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated CV mortality was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[21]	1477[22]		
Units: Events per 100 person years				
number (confidence interval 95%)	3.31 (2.74 to 3.97)	3.46 (2.88 to 4.14)		

Notes:

[21] - All Randomized (ITT) Population.

[22] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3553
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.23

Secondary: Time to First occurrence of Adjudicated Myocardial Infarction (MI) (Fatal and Non-Fatal) during CV events follow-up time period

End point title	Time to First occurrence of Adjudicated Myocardial Infarction (MI) (Fatal and Non-Fatal) during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated MI (fatal and non-fatal) was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[23]	1477[24]		
Units: Events per 100 person years				
number (confidence interval 95%)	3.34 (2.76 to 4.01)	4.08 (3.43 to 4.83)		

Notes:

[23] - All Randomized (ITT) Population.

[24] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0524
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.04

Secondary: Time to First occurrence of Adjudicated Stroke (Fatal and Non-Fatal) during CV events follow-up time period

End point title	Time to First occurrence of Adjudicated Stroke (Fatal and Non-Fatal) during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated stroke (fatal and non-fatal) was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[25]	1477[26]		
Units: Events per 100 person years				
number (confidence interval 95%)	1.23 (0.89 to 1.66)	1.48 (1.10 to 1.94)		

Notes:

[25] - All Randomized (ITT) Population.

[26] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1927
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.25

Secondary: Number of participants with Adjudicated MACE or Hospitalization for Heart Failure (Recurrent events analysis)

End point title	Number of participants with Adjudicated MACE or Hospitalization for Heart Failure (Recurrent events analysis)

End point description:

Number of participants with adjudicated MACE or hospitalization for heart failure (recurrent events analysis) is presented, categorized by number of occurrences of adjudicated MACE or hospitalization for heart failure per participant.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[27]	1477[28]		
Units: Participants				
Occurrences per participant: 0	1062	1044		
Occurrences per participant: 1	315	300		
Occurrences per participant: 2	72	88		
Occurrences per participant: 3	25	22		
Occurrences per participant: 4	3	11		
Occurrences per participant: 5	4	4		
Occurrences per participant: 6	4	3		
Occurrences per participant: 7	0	2		
Occurrences per participant: 8	0	1		
Occurrences per participant: 9	1	1		
Occurrences per participant: 10	1	1		

Notes:

[27] - All Randomized (ITT) Population.

[28] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Overall HR is presented using Model 1. Model 1 assumed a common treatment effect, regardless of number of events experienced. HR was estimated using a Prentice, Williams and Peterson(PWP) model, with treatment, dialysis type and region as covariates.

Comparison groups	rhEPO v Daprodustat
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0351
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.01

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

First Event Hazard ratio is presented using Model 2. Model 2 assumed treatment effect differs by number of events experienced. Hazard Ratio (HR) was estimated using a PWP model, with treatment, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3258
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.11

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Second Event Hazard ratio is presented using Model 2. Model 2 assumed treatment effect differs by number of events experienced. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0158
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.98

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Third Event Hazard ratio is presented using Model 2. Model 2 assumed treatment effect differs by number of events experienced. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0981
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.17

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

First Event Hazard ratio is presented using Model 3. Model 3 assumed treatment effect for first event differs from a common effect for subsequent events. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3258
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.11

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Subsequent Event Hazard ratio is presented using Model 3. Model 3 assumed treatment effect for first event differs from a common effect for subsequent events. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.94

Secondary: Time to First Occurrence of Adjudicated CV Mortality or Non-Fatal MI during CV events follow-up time period

End point title	Time to First Occurrence of Adjudicated CV Mortality or Non-Fatal MI during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated CV mortality or non-fatal MI was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[29]	1477[30]		
Units: Events per 100 person years				
number (confidence interval 95%)	5.98 (5.18 to 6.86)	6.79 (5.94 to 7.73)		

Notes:

[29] - All Randomized (ITT) Population.

[30] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0872
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.06

Secondary: Time to First Occurrence of All-Cause Hospitalization during CV events follow-up time period

End point title	Time to First Occurrence of All-Cause Hospitalization during CV events follow-up time period

End point description:

All-cause hospitalization events were hospital admissions recorded on the Hospitalization electronic case report form (eCRF) with a hospitalization duration >=24 hours. Time to first occurrence of all-cause hospitalization was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[31]	1477[32]		
Units: Events per 100 person years				
number (confidence interval 95%)	43.92 (41.18 to 46.81)	46.03 (43.17 to 49.04)		

Notes:

[31] - All Randomized (ITT) Population.

[32] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.154
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.04

Secondary: Time to First Occurrence of All-Cause Hospital Re-admission within 30 Days during CV events follow-up time period

End point title	Time to First Occurrence of All-Cause Hospital Re-admission within 30 Days during CV events follow-up time period

End point description:

All-cause hospital re-admissions within 30days are defined as hospital admissions recorded on hospitalization eCRF with hospitalization duration of >=24 hours and admission date within 30days following previous discharge date of all-cause hospitalization event, where previous hospitalization was >=24 hours. Time to first occurrence of all-cause hospital re-admission within 30days was analyzed using Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date)+1. Incidence rate per 100person years calculated as(100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event+cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[33]	1477[34]		
Units: Events per 100 person years				
number (confidence interval 95%)	8.86 (7.85 to 9.95)	9.67 (8.62 to 10.82)		

Notes:

[33] - All Randomized (ITT) Population.

[34] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1244
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.07

Secondary: Time to First Occurrence of Adjudicated MACE or Hospitalization for Heart Failure or Thromboembolic events during CV events follow-up time period

End point title	Time to First Occurrence of Adjudicated MACE or Hospitalization for Heart Failure or Thromboembolic events during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated MACE or hospitalization for heart failure or thromboembolic events were analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[35]	1477[36]		
Units: Events per 100 person years				
number (confidence interval 95%)	17.74 (16.28 to 19.30)	19.50 (17.94 to 21.16)		

Notes:

[35] - All Randomized (ITT) Population.

[36] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.02

Secondary: Time to First Occurrence of Adjudicated Hospitalization for Heart Failure during CV events follow-up time period

End point title	Time to First Occurrence of Adjudicated Hospitalization for Heart Failure during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated hospitalization for heart failure was analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[37]	1477[38]		
Units: Events per 100 person years				
number (confidence interval 95%)	3.30 (2.72 to 3.97)	3.01 (2.45 to 3.65)		

Notes:

[37] - All Randomized (ITT) Population.

[38] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7658
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.45

Secondary: Time to First Occurrence of Adjudicated Thromboembolic Events during CV events follow-up time period

End point title	Time to First Occurrence of Adjudicated Thromboembolic Events during CV events follow-up time period

End point description:

Time to first occurrence of adjudicated thromboembolic events were analyzed using a Cox proportional hazards regression model with treatment group, dialysis type and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

End point type	Secondary

End point timeframe:

Up to 3.9 person-years for CV follow-up time period

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[39]	1477[40]		
Units: Events per 100 person years				
number (confidence interval 95%)	5.66 (4.87 to 6.54)	6.75 (5.88 to 7.72)		

Notes:

[39] - All Randomized (ITT) Population.

[40] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0425
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.02

Secondary: Change From Baseline in Post-randomization Hemoglobin levels at Week 52

End point title	Change From Baseline in Post-randomization Hemoglobin levels at Week 52

End point description:

Blood samples were collected from participants for hemoglobin measurements. Change from Baseline was defined as post-Baseline value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using mixed model repeated measures (MMRM) model fitted from Baseline up to Week 52, excluding values collected during the stabilization period, with factors for treatment, time, dialysis type, region, Baseline hemoglobin and Baseline hemoglobin by time and treatment by time interactions. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1358[41]	1347[42]		
Units: Grams per deciliter				
least squares mean (standard error)	0.26 (± 0.032)	0.14 (± 0.032)		

Notes:

[41] - All Randomized (ITT) Population.

[42] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2705
Analysis specification	Pre-specified
Analysis type	non-inferiority[43]
Parameter estimate	LS mean difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.21

Notes:

[43] - Non-inferiority was to be established if the lower limit of the two-sided 95% CI for the treatment difference was greater than the pre-specified non-inferiority margin of -0.75 g/dL.

Secondary: Number of Hgb Responders in the Hgb Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52)

End point title	Number of Hgb Responders in the Hgb Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52)

End point description:

Mean Hgb during the evaluation period was defined as the mean of all evaluable Hgb values during the evaluation period (Week 28 to Week 52) including any evaluable unscheduled Hgb values that were taken during this time period. Hemoglobin responders were defined as participants with a mean Hgb during the evaluation period that falls within the Hgb analysis range of 10-11.5 g/dL. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 28 to Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1238[44]	1247[45]		
Units: Participants	903	866		

Notes:

[44] - All Randomized (ITT) Population.

[45] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test adjusted for dialysis type, and region was used to compare the number of responders between the treatment groups.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0367
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	7.1

Secondary: Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52): Non-inferiority analysis

End point title	Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52): Non-inferiority analysis

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the evaluation period (Week 28 to Week 52), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time in the analysis range during evaluation period is calculated as time in range during the evaluation period / [Earlier of (Date of the last evaluable Hgb value, Week 52 visit date) – Later of (Date of the first evaluable Hgb value that between Week 16 and Week 52 inclusive, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 28 to Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1202[46]	1224[47]		
Units: Percentage of days				
median (full range (min-max))	60.9 (0.0 to 100.0)	59.4 (0.0 to 100.0)		

Notes:

[46] - All Randomized (ITT) Population.

[47] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hodges-Lehmann estimate of the treatment difference (daprodustat-rhEPO) and associated two-sided asymptotic 95% CI is presented.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2426
Analysis specification	Pre-specified
Analysis type	non-inferiority[48]
Parameter estimate	Median difference (final values)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.86

Notes:

[48] - Non-inferiority was to be established if the lower limit of the two-sided 95% confidence interval for the treatment difference was greater than non-inferiority margin of -15%.

Secondary: Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52): Superiority analysis

End point title	Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52): Superiority analysis

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the evaluation period (Week 28 to Week 52), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time in the analysis range during evaluation period is calculated as time in range during the evaluation period / [Earlier of (Date of the last evaluable Hgb value, Week 52 visit date) – Later of (Date of the first evaluable Hgb value that between Week 16 and Week 52 inclusive, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 28 to Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1202[49]	1224[50]		
Units: Percentage of days				
median (full range (min-max))	60.9 (0.0 to 100.0)	59.4 (0.0 to 100.0)		

Notes:

[49] - All Randomized (ITT) Population.

[50] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Mann-Whitney estimate (Probability) of the treatment effect has been presented.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2426
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0805
Method	van Elteren test
Parameter estimate	Probability
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.54

Secondary: Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 to End of study): Non-inferiority analysis

End point title	Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 to End of study): Non-inferiority analysis

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the maintenance period (Week 28 to end of study), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time in the analysis range during maintenance period is calculated as time in range during the maintenance period / [Earlier of (Date of the last evaluable Hgb value, End of study date)– Later of (Date of the first evaluable Hgb value that is on or after week 16, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 28 to end of study (3.9 person-years for follow-up time period)

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1203[51]	1224[52]		
Units: Percentage of days				
median (full range (min-max))	60.9 (0.0 to 100.0)	57.7 (0.0 to 100.0)		

Notes:

[51] - All Randomized (ITT) Population.

[52] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hodges-Lehmann estimate of the treatment difference (daprodustat-rhEPO) and associated two-sided asymptotic 95% CI is presented.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2427
Analysis specification	Pre-specified
Analysis type	non-inferiority[53]
Parameter estimate	Median difference (final values)
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	4.05

Notes:

[53] - Non-inferiority was to be established if the lower limit of the two-sided 95% confidence interval for the treatment difference was greater than non-inferiority margin of -15%.

Secondary: Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 to End of study): Superiority analysis

End point title	Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 to End of study): Superiority analysis

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the maintenance period (Week 28 to end of study), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time in the analysis range during maintenance period is calculated as time in range during the maintenance period / [Earlier of (Date of the last evaluable Hgb value, End of study date)– Later of (Date of the first evaluable Hgb value that is on or after week 16, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 28 to end of study (3.9 person-years for follow-up time period)

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1203[54]	1224[55]		
Units: Percentage of days				
median (full range (min-max))	60.9 (0.0 to 100.0)	57.7 (0.0 to 100.0)		

Notes:

[54] - All Randomized (ITT) Population.

[55] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Mann-Whitney estimate (Probability) of the treatment effect has been presented.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2427
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0139
Method	van Elteren test
Parameter estimate	Probability
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.55

Secondary: Change from Baseline in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Blood Pressure (MAP) at Week 52

End point title	Change from Baseline in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Blood Pressure (MAP) at Week 52

End point description:

SBP, DBP and MAP were measured in a semi-supine or seated position in the dialysis chair after at least a 5-minutes of rest. MAP is the average BP in an individual's arteries during a single cardiac cycle. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using MMRM model with treatment group + time + dialysis type + region + Baseline value + Baseline value*time + treatment group*time, using an unstructured covariance matrix. Data for post-dialysis BP measurements have been presented. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week -4) and Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1455[56]	1442[57]		
Units: Millimeter of mercury				
least squares mean (standard error)				
SBP	-0.61 (± 0.582)	-0.93 (± 0.578)		
DBP	-1.04 (± 0.326)	-0.58 (± 0.324)		
MAP	-0.89 (± 0.370)	-0.71 (± 0.368)		

Notes:

[56] - All Randomized (ITT) Population.

[57] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The difference in change from Baseline in SBP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in means between arms.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2897
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6551
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	1.94

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The difference in change from Baseline in DBP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in means between arms.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2897
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1586
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	0.44

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

The difference in change from Baseline in MAP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in means between arms.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2897
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3646
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.84

Secondary: Change from Baseline in SBP, DBP, MAP at End of Treatment

End point title	Change from Baseline in SBP, DBP, MAP at End of Treatment

End point description:

SBP, DBP and MAP were measured in a semi-supine or seated position in the dialysis chair after at least a 5-minutes of rest. MAP is an average BP in an individual's arteries during a single cardiac cycle. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. This analysis was carried out by using ANCOVA model with terms for treatment group, dialysis type, region and Baseline value. Data for post-dialysis BP measurements have been presented. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week -4) and 45.1 months

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1468[58]	1454[59]		
Units: Millimeter of mercury				
least squares mean (standard error)				
SBP	-0.43 (± 0.554)	-0.43 (± 0.557)		
DBP	-0.92 (± 0.310)	-1.37 (± 0.312)		
MAP	-0.75 (± 0.350)	-1.06 (± 0.351)		

Notes:

[58] - All Randomized (ITT) Population.

[59] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

For SBP: Treatment group comparisons were based on an ANCOVA model with terms for treatment group, dialysis type, region and Baseline value.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2922
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5012
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	1.54

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

For DBP: Treatment group comparisons were based on an ANCOVA model with terms for treatment group, dialysis type, region and Baseline value.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2922
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8451
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	1.31

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

For MAP: Treatment group comparisons were based on an ANCOVA model with terms for treatment group, dialysis type, region and Baseline value.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2922
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7312
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	1.28

Secondary: Blood Pressure (BP) Exacerbation Event Rate per 100 Participant Years

End point title	Blood Pressure (BP) Exacerbation Event Rate per 100 Participant Years

End point description:

BP exacerbation was defined (based on post-dialysis) as: SBP >= 25 millimeter of mercury (mmHg) increased from Baseline or SBP >=180 mmHg; DBP >=15 mmHg increased from Baseline or DBP >=110 mmHg. The BP exacerbation events per 100 participant years was estimated using the negative binomial model with treatment, dialysis type and region as covariates and the logarithm of time on-treatment as an offset variable. Data for post-dialysis BP measurements have been presented. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Day 1 to end of study (3.9 person-years for follow-up time period)

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1470[60]	1458[61]		
Units: Events per 100 participant years				
number (confidence interval 95%)	207.13 (188.83 to 227.21)	206.38 (187.88 to 226.71)		

Notes:

[60] - All Randomized (ITT) Population.

[61] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Ratio of model estimated exacerbation rates and CIs were estimated using a negative binomial model for the treatment group comparison.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2928
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.529
Method	Negative binomial model
Parameter estimate	Ratio of exacerbation rate
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.11

Secondary: Number of Participants with at Least one BP Exacerbation Event During Study

End point title	Number of Participants with at Least one BP Exacerbation Event During Study

End point description:

BP exacerbation was defined as: SBP >= 25 mmHg increased from Baseline or SBP >=180 mmHg; DBP >=15 mmHg increased from Baseline or DBP >=110 mmHg. Number of participants with at least one BP exacerbation event is presented. Only those participants with data available at the indicated time points

were analyzed.

End point type	Secondary

End point timeframe:

Day 1 to end of study (3.9 person-years for follow-up time period)

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1480[62]	1470[63]		
Units: Participants	1191	1186		

Notes:

[62] - All Randomized (ITT) Population.

[63] - All Randomized (ITT) Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria

End point title	Percentage of Participants Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria

End point description:

Percentage of participants permanently stopping randomized treatment due to meeting rescue criteria has been presented.

End point type	Secondary

End point timeframe:

Day 1 to 45.1 months

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1487[64]	1477[65]		
Units: Percentage of participants				
number (not applicable)	3.6	3.6		

Notes:

[64] - All Randomized (ITT) Population.

[65] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model adjusted for treatment group, dialysis type and region.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	2964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5772
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.52

Secondary: Change from Baseline in On-Treatment Physical Component Score (PCS) using Short Form (SF)-36 Health-related Quality of Life (HRQoL) Questionnaire at Weeks 8, 12, 28, 52

End point title	Change from Baseline in On-Treatment Physical Component Score (PCS) using Short Form (SF)-36 Health-related Quality of Life (HRQoL) Questionnaire at Weeks 8, 12, 28, 52

End point description:

SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in following 8 health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality and general health. Each domain is scored from 0 (poorer health) to 100 (better health). The PCS is an average score derived from 4 domains (physical functioning, role-physical, bodily pain and general health) representing overall physical health. PCS ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	990[66]	943[67]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=982,936	0.30 (± 0.205)	0.01 (± 0.210)		
Week 12, n=990,943	0.33 (± 0.203)	-0.27 (± 0.207)		
Week 28, n=836,819	-0.23 (± 0.229)	-0.57 (± 0.232)		
Week 52, n=729,707	-0.52 (± 0.248)	-1.05 (± 0.252)		

Notes:

[66] - All Randomized (ITT) Population.

[67] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 8: Model was fitted from Baseline up to Week 52 and the model adjusted Week 8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.86

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12: Model was fitted from Baseline up to Week 52 and the model adjusted Week 12 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	1.18

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week 52 and the model adjusted Week 28 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.153
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.97

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week 52 and the model adjusted Week 52 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0686
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	1.22

Secondary: Change from Baseline in On-Treatment Mental Component Score (MCS) using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point title	Change from Baseline in On-Treatment Mental Component Score (MCS) using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following 8 health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality and general health. Each domain is scored from 0 (poorer health) to 100 (better health). MCS is an average score derived from 4 domains (vitality, social functioning, role-emotional and mental health) representing overall mental health. MCS ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	990[68]	943[69]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=982,936	-0.38 (± 0.254)	-0.21 (± 0.260)		
Week 12, n=990,943	-0.55 (± 0.262)	-0.72 (± 0.268)		
Week 28, n=836,819	-1.25 (± 0.286)	-1.23 (± 0.290)		
Week 52, n=729,707	-1.63 (± 0.311)	-1.03 (± 0.316)		

Notes:

[68] - All Randomized (ITT) Population.

[69] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 8: Model was fitted from Baseline up to Week 52 and the model adjusted Week 8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6807
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.54

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12: Model was fitted from Baseline up to Week 52 and the model adjusted Week 12 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3256
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.91

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week 52 and the model adjusted Week 28 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5144
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.78

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week 52 and the model adjusted Week 52 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.912
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	0.27

Secondary: Change from Baseline in On-Treatment SF-36 HRQoL Scores for Bodily Pain, General Health, Mental Health, Role-Emotional, Role-Physical, Social Functioning at Weeks 8, 12, 28, 52

End point title	Change from Baseline in On-Treatment SF-36 HRQoL Scores for Bodily Pain, General Health, Mental Health, Role-Emotional, Role-Physical, Social Functioning at Weeks 8, 12, 28, 52

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following 8 health domains: bodily pain, general health, mental health, role-emotional (role limitations caused by emotional problems), role-physical (role limitations caused by physical problems), social functioning (Social fun), physical functioning (Phy. fun) and vitality. Each domain is scored from 0 (poorer health) to 100 (better health). Each domain score ranges from 0 to 100, higher score indicates a better health state and better functioning. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	990[70]	943[71]		
Units: Scores on a scale				
least squares mean (standard error)				
Bodily pain: Week 8, n=982,936	-0.13 (± 0.265)	0.12 (± 0.272)		
Bodily pain: Week 12, n=990,943	0.20 (± 0.267)	-0.39 (± 0.274)		
Bodily pain: Week 28, n=836,819	-0.70 (± 0.297)	-0.74 (± 0.301)		
Bodily pain: Week 52, n=729,707	-1.12 (± 0.313)	-1.39 (± 0.318)		
General health: Week 8, n=982,936	-0.39 (± 0.208)	-0.65 (± 0.213)		
General health: Week 12, n=990,943	-0.59 (± 0.210)	-1.04 (± 0.215)		
General health: Week 28, n=836,819	-1.32 (± 0.232)	-0.99 (± 0.235)		
General health: Week 52, n=729,707	-1.51 (± 0.251)	-1.22 (± 0.255)		
Mental health: Week 8, n=982,936	-0.43 (± 0.238)	-0.47 (± 0.244)		
Mental health: Week 12, n=990,943	-0.86 (± 0.247)	-0.81 (± 0.253)		
Mental health: Week 28, n=836,819	-1.30 (± 0.267)	-1.43 (± 0.270)		

Mental health: Week 52, n=729,707	-1.97 (± 0.296)	-1.16 (± 0.301)		
Role-emotional: Week 8, n=982,936	-0.10 (± 0.310)	-0.02 (± 0.317)		
Role-emotional: Week 12, n=990,943	-0.17 (± 0.311)	-0.53 (± 0.318)		
Role-emotional: Week 28, n=836,819	-0.95 (± 0.335)	-0.90 (± 0.339)		
Role-emotional: Week 52, n=729,707	-0.83 (± 0.358)	-0.92 (± 0.363)		
Role-physical: Week 8, n=982,936	0.40 (± 0.241)	0.32 (± 0.246)		
Role-physical: Week 12, n=990,943	0.48 (± 0.239)	0.08 (± 0.245)		
Role-physical: Week 28, n=836,819	-0.10 (± 0.257)	-0.39 (± 0.260)		
Role-physical: Week 52, n=729,707	-0.21 (± 0.285)	-0.60 (± 0.289)		
Social functioning: Week 8, n=982,936	0.24 (± 0.241)	0.38 (± 0.247)		
Social functioning: Week 12, n=990,943	0.25 (± 0.255)	-0.44 (± 0.261)		
Social functioning: Week 28, n=836,819	-0.61 (± 0.280)	-0.94 (± 0.283)		
Social functioning: Week 52, n=729,707	-1.12 (± 0.315)	-1.14 (± 0.320)		

Notes:

[70] - All Randomized (ITT) Population.

[71] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Bodily pain,Week8: Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7432
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.5

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Bodily pain,Week12: Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0631
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	1.33

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Bodily pain,Week28: Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4604
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.87

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Bodily pain,Week52: Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2688
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.15

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

General health,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1918
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.84

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

General health,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0677
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	1.04

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

General health,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8386
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.32

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

General health,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7928
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.41

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

Mental health,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4537
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.71

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Mental health,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5548
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.65

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

Mental health,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3626
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.88

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

Mental health,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9721
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	0.02

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

Role-emotional,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5789
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	0.78

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

Role-emotional,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2054
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	1.24

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

Role-emotional,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5389
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.89

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

Role-emotional,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4289
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	1.09

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

Role-physical,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4096
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.75

Statistical analysis title	Statistical analysis 18

Statistical analysis description:

Role-physical,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1196
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	1.07

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

Role-physical,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2093
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	1.01

Statistical analysis title	Statistical analysis 20

Statistical analysis description:

Role-physical,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, dialysis type, region,Baseline value and Baseline value by time and treatment by time interactions

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1674
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.19

Statistical analysis title	Statistical analysis 21

Statistical analysis description:

Social fun, Week 8: Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6585
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.54

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

Social fun, Week 12: Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0293
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	1.4

Statistical analysis title	Statistical analysis 23

Statistical analysis description:

Social fun, Week 28: Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2057
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	1.11

Statistical analysis title	Statistical analysis 24

Statistical analysis description:

Social fun, Week 52: Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4849
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	0.9

Secondary: Change from Baseline in On-Treatment Vitality scores using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point title	Change from Baseline in On-Treatment Vitality scores using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant’s level of performance in the following 8 health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality and general health. Each domain is scored from 0 (poorer health) to 100 (better health). Vitality score ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	990[72]	943[73]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=982,936	-0.23 (± 0.219)	-0.26 (± 0.224)		
Week 12, n=990,943	-0.17 (± 0.227)	-0.51 (± 0.232)		
Week 28, n=836,819	-0.79 (± 0.242)	-1.03 (± 0.245)		
Week 52, n=729,707	-1.19 (± 0.268)	-1.04 (± 0.272)		

Notes:

[72] - All Randomized (ITT) Population.

[73] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 8: Model was fitted from Baseline up to Week 52 and model adjusted Week 8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4621
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.64

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12: Model was fitted from Baseline up to Week 52 and model adjusted Week 12 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1439
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.98

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week 52 and model adjusted Week 28 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2392
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.92

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week 52 and model adjusted Week 52 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6545
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.6

Secondary: Change from Baseline in On-Treatment Physical Functioning domain scores using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point title	Change from Baseline in On-Treatment Physical Functioning domain scores using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following 8 health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality and general health. Each domain is scored from 0 (poorer health) to 100 (better health). Physical functioning score ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as on-treatment visit value minus (-) Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	990[74]	943[75]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=982,936	0.48 (± 0.237)	-0.16 (± 0.243)		
Week 12, n=990,943	0.11 (± 0.240)	-0.45 (± 0.246)		
Week 28, n=836,819	-0.20 (± 0.273)	-0.97 (± 0.277)		
Week 52, n=729,707	-0.61 (± 0.291)	-1.19 (± 0.296)		

Notes:

[74] - All Randomized (ITT) Population.

[75] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 8: Model was fitted from Baseline up to Week 52 and model adjusted Week 8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO

Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	1.31

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12: Model was fitted from Baseline up to Week 52 and model adjusted Week 12 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0509
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	1.24

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week 52 and model adjusted Week 28 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0237
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	1.53

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week 52 and model adjusted Week 52 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	1933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0828
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	1.39

Secondary: Change from Baseline in On-Treatment Health Utility EuroQol 5 Dimensions 5 Level (EQ-5D-5L) Questionnaire Score at Week 52

End point title	Change from Baseline in On-Treatment Health Utility EuroQol 5 Dimensions 5 Level (EQ-5D-5L) Questionnaire Score at Week 52

End point description:

EQ-5D-5L is self-assessment questionnaire,consisting of 5 items covering 5 dimensions (mobility,self care,usual activities,pain/discomfort and anxiety/depression). Each dimension is measured by 5-point Likert scale (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=extreme problems). Responses for 5 dimensions together formed a 5-figure description of health state (e.g.11111 indicates no problems in all 5 dimensions). Each of these 5 figure health states were converted to a single index score by applying country-specific value set formula that attaches weights to dimensions and levels. Range for EQ-5D-5L index score is -0.594 (worst health) to 1 (full health state). Change from Baseline was calculated as on-treatment visit value-Baseline value. Baseline was latest non-missing pre-dose assessment on or before randomization date. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	333[76]	329[77]		
Units: Scores on a scale				
least squares mean (standard error)	-0.0198 (± 0.01179)	-0.0201 (± 0.01187)		

Notes:

[76] - All Randomized (ITT) Population.

[77] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4939
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.0003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0326
upper limit	0.0331

Secondary: Change from Baseline in On-Treatment EuroQol Visual Analogue Scale (EQ-VAS) at Week 52

End point title	Change from Baseline in On-Treatment EuroQol Visual Analogue Scale (EQ-VAS) at Week 52

End point description:

The EQ VAS records the respondent’s self-rated health on a vertical VAS, ranging from 0 to 100, where 0 represents the worst health one can imagine and 100 represents the best health one can imagine. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	333[78]	329[79]		
Units: Scores on a scale				
least squares mean (standard error)	-1.0 (± 0.86)	0.8 (± 0.87)		

Notes:

[78] - All Randomized (ITT) Population.

[79] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9292
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	0.6

Secondary: Change from Baseline in On-Treatment Patient Global Impression of Severity (PGI-S) at Weeks 8, 12, 28, 52

End point title	Change from Baseline in On-Treatment Patient Global Impression of Severity (PGI-S) at Weeks 8, 12, 28, 52

End point description:

The PGI-S is a 1-item questionnaire designed to assess participant’s impression of disease severity on a 5-point disease severity scale (0=absent, 1=mild, 2=moderate, 3=severe, or 4=very severe). A higher score indicated worse outcome. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1), Weeks 8, 12, 28 and 52

End point values	Daprodustat	rhEPO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1102[80]	1073[81]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=1102,1064	-0.03 (± 0.024)	0.02 (± 0.025)		
Week 12, n=1102,1073	0.02 (± 0.025)	0.06 (± 0.025)		
Week 28, n=934,933	0.04 (± 0.027)	0.08 (± 0.027)		
Week 52, n=826,814	0.06 (± 0.029)	0.11 (± 0.030)		

Notes:

[80] - All Randomized (ITT) Population.

[81] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 8: Model was fitted from Baseline up to Week 52 and model adjusted Week 8 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0428
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.01

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12: Model was fitted from Baseline up to Week 52 and model adjusted Week 12 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1155
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.03

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week 52 and model adjusted Week 28 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1426
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.03

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week 52 and model adjusted Week 52 data has been presented, with factors for treatment, time, dialysis type, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v rhEPO
Number of subjects included in analysis	2175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1152
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.03

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, treatment emergent serious adverse events (TESAEs) and non-serious treatment emergent adverse events (TEAEs) were collected up to 3.9 person-years for CV follow-up time period

Adverse event reporting additional description:

All-cause mortality used All Randomized (ITT) Population, which comprised of all randomized participants and treatment to which the participant was randomized. TESAEs and non-serious TEAEs used the Safety Population, which included all randomized participants who received at least 1 dose of randomized treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	rhEPO

Reporting group description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received treatment with rhEPO. Participants on hemodialysis received epoetin alfa as intravenous (IV) injection once weekly or three-times weekly with total weekly dose levels ranging from 1500 to 60,000 Units. Participants on peritoneal dialysis received subcutaneous (SC) injection of darbepoetin alfa every 1, 2, or 4 weeks with 4-weekly total dose levels ranging from 20 to 400 microgram (mcg). Darbepoetin could be given by IV injection for peritoneal dialysis participants switching to hemodialysis. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL) and administered until the required number of MACE events occurred, at approximately 45.1 months of randomized treatment.

Reporting group title	Daprodustat

Reporting group description:

Participants received placebo tablets orally once daily in run-in period from Week -4 up to randomization (Day 1) and subsequently received daprodustat tablets at dose levels of 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily until the required number of major adverse cardiovascular event (MACE) occurred, at approximately 45.1 months of randomized treatment. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]).

Serious adverse events	rhEPO	Daprodustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	748 / 1474 (50.75%)	773 / 1482 (52.16%)	
number of deaths (all causes)	300	294	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic cancer			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	0 / 1474 (0.00%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Papillary renal cell carcinoma			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thyroid adenoma			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal adenoma			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell type acute leukaemia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Benign neoplasm of ampulla of Vater			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct cancer			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder cancer stage 0, with cancer in situ			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder papilloma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone neoplasm			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage II			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour pulmonary			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ of eye			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve fibroelastoma			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear neoplasm malignant			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory pseudotumour			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory cytopenia with unilineage dysplasia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma stage I			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland cancer			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract neoplasm			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer regional			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	11 / 1474 (0.75%)	16 / 1482 (1.08%)	
occurrences causally related to treatment / all	0 / 14	1 / 18	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypotension			
subjects affected / exposed	19 / 1474 (1.29%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 19	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	7 / 1474 (0.47%)	12 / 1482 (0.81%)	
occurrences causally related to treatment / all	0 / 7	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive urgency			
subjects affected / exposed	8 / 1474 (0.54%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	2 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	6 / 1474 (0.41%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis hypotension			
subjects affected / exposed	5 / 1474 (0.34%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	8 / 1474 (0.54%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			

subjects affected / exposed	7 / 1474 (0.47%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematoma			
subjects affected / exposed	5 / 1474 (0.34%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	7 / 1474 (0.47%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hypertensive crisis			
subjects affected / exposed	4 / 1474 (0.27%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	3 / 1474 (0.20%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accelerated hypertension			
subjects affected / exposed	5 / 1474 (0.34%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachiocephalic vein stenosis			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 1474 (0.07%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein stenosis			

subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 1474 (0.00%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Steal syndrome			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			

subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous stenosis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial disorder			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic microangiopathy			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatosis with polyangiitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic limb pain			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vein occlusion			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	16 / 1474 (1.09%)	10 / 1482 (0.67%)	
occurrences causally related to treatment / all	0 / 23	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 1474 (0.54%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthenia			
subjects affected / exposed	6 / 1474 (0.41%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	2 / 1474 (0.14%)	9 / 1482 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 9	
Chest pain			
subjects affected / exposed	5 / 1474 (0.34%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	4 / 1474 (0.27%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Sudden cardiac death			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Fatigue			

subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Impaired healing			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Peripheral swelling			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vascular stent stenosis				
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)		
occurrences causally related to treatment / all	0 / 0	1 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Catheter site oedema				
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Catheter site thrombosis				
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Chest discomfort				
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cyst				
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Drug withdrawal syndrome				
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gait disturbance				

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serositis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyloidosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Loss of personal independence in daily activities			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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			
Prostatitis			
subjects affected / exposed	2 / 1474 (0.14%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Menorrhagia			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acquired hydrocele			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenomyosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian disorder			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal oedema			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular infarction			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	13 / 1474 (0.88%)	14 / 1482 (0.94%)	
occurrences causally related to treatment / all	0 / 14	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	15 / 1474 (1.02%)	11 / 1482 (0.74%)	
occurrences causally related to treatment / all	0 / 17	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	15 / 1474 (1.02%)	10 / 1482 (0.67%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	12 / 1474 (0.81%)	13 / 1482 (0.88%)	
occurrences causally related to treatment / all	0 / 12	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	11 / 1474 (0.75%)	13 / 1482 (0.88%)	
occurrences causally related to treatment / all	0 / 11	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	9 / 1474 (0.61%)	11 / 1482 (0.74%)	
occurrences causally related to treatment / all	0 / 10	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	10 / 1474 (0.68%)	10 / 1482 (0.67%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 6	0 / 3	
Pulmonary embolism			
subjects affected / exposed	9 / 1474 (0.61%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	3 / 9	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	4 / 1474 (0.27%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 1474 (0.14%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	4 / 1474 (0.27%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			

subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory arrest			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 1474 (0.07%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	3 / 1474 (0.20%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjustment disorder with mixed disturbance of emotion and conduct			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia nervosa			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	11 / 1474 (0.75%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	4 / 1474 (0.27%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	3 / 1474 (0.20%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device expulsion			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device kink			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	7 / 1474 (0.47%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	3 / 1474 (0.20%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 1474 (0.07%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct stone			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			

subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic ischaemia			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dyskinesia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder polyp			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder rupture			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic mass			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	4 / 1474 (0.27%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			

subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urine present			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus test positive			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus test positive			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I increased			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	57 / 1474 (3.87%)	36 / 1482 (2.43%)	
occurrences causally related to treatment / all	11 / 74	4 / 43	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	12 / 1474 (0.81%)	12 / 1482 (0.81%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft thrombosis			
subjects affected / exposed	15 / 1474 (1.02%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 25	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	7 / 1474 (0.47%)	14 / 1482 (0.94%)	
occurrences causally related to treatment / all	0 / 7	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	8 / 1474 (0.54%)	9 / 1482 (0.61%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	5 / 1474 (0.34%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular access site thrombosis			
subjects affected / exposed	5 / 1474 (0.34%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 7	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula aneurysm			
subjects affected / exposed	5 / 1474 (0.34%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	5 / 1474 (0.34%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula occlusion			
subjects affected / exposed	5 / 1474 (0.34%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	5 / 1474 (0.34%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	4 / 1474 (0.27%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	5 / 1474 (0.34%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 1474 (0.14%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site pseudoaneurysm			
subjects affected / exposed	5 / 1474 (0.34%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 1474 (0.07%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	4 / 1474 (0.27%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriovenous graft site stenosis			
subjects affected / exposed	2 / 1474 (0.14%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	6 / 1474 (0.41%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	1 / 1474 (0.07%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	4 / 1474 (0.27%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 1474 (0.07%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriovenous graft site haemorrhage			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysis complication			
subjects affected / exposed	3 / 1474 (0.20%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	3 / 1474 (0.20%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			

subjects affected / exposed	3 / 1474 (0.20%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis related complication			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt blood flow excessive			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access steal syndrome			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			

subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site haemorrhage			

subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm ruptured			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia postoperative			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic pseudoaneurysm			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft aneurysm			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial injury			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed graft function			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft loss			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantation complication			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratorhexis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haematoma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural hypotension			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural swelling			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural urine leak			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative hypertension			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restenosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt aneurysm			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal injury			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal cord injury			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site swelling			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava injury			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital cystic kidney disease			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein C deficiency			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	31 / 1474 (2.10%)	30 / 1482 (2.02%)	
occurrences causally related to treatment / all	3 / 40	4 / 33	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrial fibrillation			
subjects affected / exposed	35 / 1474 (2.37%)	23 / 1482 (1.55%)	
occurrences causally related to treatment / all	0 / 44	1 / 26	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	15 / 1474 (1.02%)	20 / 1482 (1.35%)	
occurrences causally related to treatment / all	0 / 15	1 / 20	
deaths causally related to treatment / all	0 / 8	1 / 18	

Angina pectoris			
subjects affected / exposed	16 / 1474 (1.09%)	18 / 1482 (1.21%)	
occurrences causally related to treatment / all	1 / 18	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	15 / 1474 (1.02%)	18 / 1482 (1.21%)	
occurrences causally related to treatment / all	0 / 15	1 / 23	
deaths causally related to treatment / all	0 / 1	0 / 4	
Cardiac failure congestive			
subjects affected / exposed	15 / 1474 (1.02%)	18 / 1482 (1.21%)	
occurrences causally related to treatment / all	1 / 19	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	17 / 1474 (1.15%)	11 / 1482 (0.74%)	
occurrences causally related to treatment / all	1 / 17	2 / 11	
deaths causally related to treatment / all	1 / 4	0 / 2	
Angina unstable			
subjects affected / exposed	13 / 1474 (0.88%)	14 / 1482 (0.94%)	
occurrences causally related to treatment / all	1 / 15	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	16 / 1474 (1.09%)	10 / 1482 (0.67%)	
occurrences causally related to treatment / all	1 / 16	2 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	10 / 1474 (0.68%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	5 / 1474 (0.34%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 5	1 / 8	
deaths causally related to treatment / all	0 / 2	1 / 6	
Bradycardia			

subjects affected / exposed	8 / 1474 (0.54%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	5 / 1474 (0.34%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	5 / 1474 (0.34%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 1474 (0.07%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic valve stenosis			
subjects affected / exposed	5 / 1474 (0.34%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	4 / 1474 (0.27%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	4 / 1474 (0.27%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	2 / 1474 (0.14%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	2 / 1474 (0.14%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	3 / 1474 (0.20%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	3 / 1474 (0.20%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nodal arrhythmia			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis uraemic			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stress cardiomyopathy			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac discomfort			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomegaly			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic left ventricular failure			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis noninfective			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve calcification			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal rhythm			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subendocardial ischaemia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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			
Ischaemic stroke			
subjects affected / exposed	11 / 1474 (0.75%)	11 / 1482 (0.74%)	
occurrences causally related to treatment / all	1 / 11	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	11 / 1474 (0.75%)	9 / 1482 (0.61%)	
occurrences causally related to treatment / all	2 / 13	1 / 11	
deaths causally related to treatment / all	0 / 5	0 / 3	
Syncope			
subjects affected / exposed	13 / 1474 (0.88%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 13	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	10 / 1474 (0.68%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 12	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	9 / 1474 (0.61%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	5 / 1474 (0.34%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	4 / 1474 (0.27%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Carpal tunnel syndrome			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Headache			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemic seizure			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			

subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem ischaemia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar stroke			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery stenosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral circulatory failure			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Focal dyscognitive seizures			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intracranial aneurysm			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pachymeningitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postictal state			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure cluster			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
VIth nerve paralysis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	41 / 1474 (2.78%)	26 / 1482 (1.75%)	
occurrences causally related to treatment / all	3 / 52	0 / 29	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood loss anaemia			
subjects affected / exposed	3 / 1474 (0.20%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			

subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytopenia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-immune heparin associated thrombocytopenia			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normocytic anaemia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness bilateral			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness unilateral			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoacusis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inner ear disorder			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	5 / 1474 (0.34%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract nuclear			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye pain			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid ptosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular fibrosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmoplegia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery embolism			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sympathetic ophthalmia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tolosa-Hunt syndrome			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	11 / 1474 (0.75%)	12 / 1482 (0.81%)	
occurrences causally related to treatment / all	0 / 12	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 1474 (0.47%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	4 / 1474 (0.27%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	5 / 1474 (0.34%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 1474 (0.07%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	6 / 1474 (0.41%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 1474 (0.27%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	2 / 1474 (0.14%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	4 / 1474 (0.27%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	3 / 1474 (0.20%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 1474 (0.20%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	4 / 1474 (0.27%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	3 / 1474 (0.20%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 1474 (0.34%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	4 / 1474 (0.27%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 1474 (0.00%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dieulafoy's vascular malformation			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal ulcer			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiectasia			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Obstructive pancreatitis			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			

subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholic pancreatitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discoloured vomit			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epiploic appendagitis			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric dysplasia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric mucosa erythema			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal erosion			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic necrotic pancreatitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar hernia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal motility disorder			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative gastritis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	3 / 1474 (0.20%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 1474 (0.07%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	3 / 1474 (0.20%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic wound			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkeratosis			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic skin ulcer			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin weeping			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	5 / 1474 (0.34%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Azotaemia			
subjects affected / exposed	4 / 1474 (0.27%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 1474 (0.07%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Haematuria			
subjects affected / exposed	4 / 1474 (0.27%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery thrombosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stag horn calculus			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcapsular renal haematoma			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism tertiary			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	6 / 1474 (0.41%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	6 / 1474 (0.41%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	4 / 1474 (0.27%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hungry bone syndrome			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
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	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondropathy			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall haematoma			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
High turnover osteopathy			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	1 / 1474 (0.07%)	0 / 1482 (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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacroiliitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorder			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	81 / 1474 (5.50%)	86 / 1482 (5.80%)	
occurrences causally related to treatment / all	0 / 96	1 / 97	
deaths causally related to treatment / all	0 / 2	0 / 4	
Sepsis			

subjects affected / exposed	37 / 1474 (2.51%)	29 / 1482 (1.96%)	
occurrences causally related to treatment / all	0 / 37	0 / 31	
deaths causally related to treatment / all	0 / 4	0 / 11	
Peritonitis			
subjects affected / exposed	24 / 1474 (1.63%)	31 / 1482 (2.09%)	
occurrences causally related to treatment / all	0 / 34	0 / 42	
deaths causally related to treatment / all	0 / 1	0 / 2	
COVID-19			
subjects affected / exposed	22 / 1474 (1.49%)	22 / 1482 (1.48%)	
occurrences causally related to treatment / all	0 / 22	0 / 22	
deaths causally related to treatment / all	0 / 3	0 / 5	
Cellulitis			
subjects affected / exposed	21 / 1474 (1.42%)	16 / 1482 (1.08%)	
occurrences causally related to treatment / all	0 / 26	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	19 / 1474 (1.29%)	15 / 1482 (1.01%)	
occurrences causally related to treatment / all	0 / 28	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteomyelitis			
subjects affected / exposed	13 / 1474 (0.88%)	15 / 1482 (1.01%)	
occurrences causally related to treatment / all	0 / 16	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	16 / 1474 (1.09%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 17	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Urinary tract infection			
subjects affected / exposed	11 / 1474 (0.75%)	13 / 1482 (0.88%)	
occurrences causally related to treatment / all	0 / 16	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	9 / 1474 (0.61%)	13 / 1482 (0.88%)	
occurrences causally related to treatment / all	0 / 10	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	13 / 1474 (0.88%)	9 / 1482 (0.61%)	
occurrences causally related to treatment / all	0 / 15	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	11 / 1474 (0.75%)	9 / 1482 (0.61%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	10 / 1474 (0.68%)	10 / 1482 (0.67%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza			
subjects affected / exposed	11 / 1474 (0.75%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site infection			
subjects affected / exposed	6 / 1474 (0.41%)	12 / 1482 (0.81%)	
occurrences causally related to treatment / all	0 / 6	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	7 / 1474 (0.47%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	7 / 1474 (0.47%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			

subjects affected / exposed	8 / 1474 (0.54%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 14	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	6 / 1474 (0.41%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 7	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	6 / 1474 (0.41%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	8 / 1474 (0.54%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	5 / 1474 (0.34%)	7 / 1482 (0.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacteraemia			
subjects affected / exposed	7 / 1474 (0.47%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	3 / 1474 (0.20%)	8 / 1482 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	4 / 1474 (0.27%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriovenous graft site infection			

subjects affected / exposed	5 / 1474 (0.34%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	4 / 1474 (0.27%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	3 / 1474 (0.20%)	6 / 1482 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Gastroenteritis viral			
subjects affected / exposed	6 / 1474 (0.41%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	3 / 1474 (0.20%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	2 / 1474 (0.14%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	5 / 1474 (0.34%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	3 / 1474 (0.20%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			

subjects affected / exposed	5 / 1474 (0.34%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	4 / 1474 (0.27%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	4 / 1474 (0.27%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	2 / 1474 (0.14%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site infection			
subjects affected / exposed	1 / 1474 (0.07%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal peritonitis			
subjects affected / exposed	0 / 1474 (0.00%)	4 / 1482 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	4 / 1474 (0.27%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Suspected COVID-19			
subjects affected / exposed	1 / 1474 (0.07%)	3 / 1482 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			

subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Erysipelas			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			

subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 1474 (0.07%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			

subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
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	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gas gangrene			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Klebsiella bacteraemia			

subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site abscess			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone abscess			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone tuberculosis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Boutonneuse fever			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burn infection			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida pneumonia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site abscess			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Douglas' abscess			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter pneumonia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia peritonitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis staphylococcal			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin infection			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic echinococciasis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes ophthalmic			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective aneurysm			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeraemia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Measles			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric abscess			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis infective			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyuria			

subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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 viral			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic embolus			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic encephalopathy			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shigella infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal osteomyelitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal endocarditis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			

subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibulitis			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	45 / 1474 (3.05%)	42 / 1482 (2.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 53	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	36 / 1474 (2.44%)	19 / 1482 (1.28%)	
occurrences causally related to treatment / all	0 / 41	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	9 / 1474 (0.61%)	11 / 1482 (0.74%)	
occurrences causally related to treatment / all	0 / 10	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypervolaemia			
subjects affected / exposed	3 / 1474 (0.20%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	2 / 1474 (0.14%)	5 / 1482 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 1474 (0.27%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 1474 (0.27%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 1474 (0.20%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	2 / 1474 (0.14%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 1474 (0.14%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 1474 (0.20%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calciphylaxis			

subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	2 / 1474 (0.14%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 1474 (0.07%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 1474 (0.00%)	2 / 1482 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic complication			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (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 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insulin-requiring type 2 diabetes mellitus			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	1 / 1474 (0.07%)	0 / 1482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 1474 (0.00%)	1 / 1482 (0.07%)	
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	rhEPO	Daprodustat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	827 / 1474 (56.11%)	830 / 1482 (56.01%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	84 / 1474 (5.70%)	73 / 1482 (4.93%)	
occurrences (all)	119	96	
Arteriovenous fistula site complication			
subjects affected / exposed	89 / 1474 (6.04%)	61 / 1482 (4.12%)	
occurrences (all)	121	90	
Vascular disorders			
Hypertension			
subjects affected / exposed	232 / 1474 (15.74%)	235 / 1482 (15.86%)	
occurrences (all)	356	366	
Dialysis hypotension			
subjects affected / exposed	105 / 1474 (7.12%)	135 / 1482 (9.11%)	
occurrences (all)	206	254	
Hypotension			
subjects affected / exposed	92 / 1474 (6.24%)	115 / 1482 (7.76%)	
occurrences (all)	130	140	
Nervous system disorders			
Headache			
subjects affected / exposed	139 / 1474 (9.43%)	115 / 1482 (7.76%)	
occurrences (all)	216	176	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	176 / 1474 (11.94%)	161 / 1482 (10.86%)	
occurrences (all)	228	225	
Nausea			
subjects affected / exposed	84 / 1474 (5.70%)	83 / 1482 (5.60%)	
occurrences (all)	106	95	
Vomiting			
subjects affected / exposed	76 / 1474 (5.16%)	83 / 1482 (5.60%)	
occurrences (all)	98	103	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	101 / 1474 (6.85%)	101 / 1482 (6.82%)	
occurrences (all)	133	128	
Dyspnoea			
subjects affected / exposed	74 / 1474 (5.02%)	58 / 1482 (3.91%)	
occurrences (all)	88	67	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	111 / 1474 (7.53%)	101 / 1482 (6.82%)	
occurrences (all)	138	120	
Pain in extremity			
subjects affected / exposed	76 / 1474 (5.16%)	85 / 1482 (5.74%)	
occurrences (all)	99	105	
Back pain			
subjects affected / exposed	88 / 1474 (5.97%)	64 / 1482 (4.32%)	
occurrences (all)	103	87	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	104 / 1474 (7.06%)	113 / 1482 (7.62%)	
occurrences (all)	188	188	
Upper respiratory tract infection			
subjects affected / exposed	92 / 1474 (6.24%)	99 / 1482 (6.68%)	
occurrences (all)	125	144	
Bronchitis			
subjects affected / exposed	97 / 1474 (6.58%)	87 / 1482 (5.87%)	
occurrences (all)	124	116	
Urinary tract infection			
subjects affected / exposed	79 / 1474 (5.36%)	73 / 1482 (4.93%)	
occurrences (all)	97	99	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	62 / 1474 (4.21%)	76 / 1482 (5.13%)	
occurrences (all)	72	92	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2016	Amendment 1: Applies to Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Italy, Norway, Poland, Portugal, Romania, Spain, Sweden and UK. Clarified end of the study; removal of requirement to reduce ESA dose if W-8 Hgb is >11.5 g/dL; guidance to iron management; new exploratory objective to compare daprodustat to rhEPO on delayed graft function after deceased donor kidney transplantation
12 October 2016	Amendment 2: Main changes include new timepoints at Run-in (Week -4) and Week 2 for collection of iron therapy and at Week 52 for Kt/Vurea. Changes to ABPM assessments and prompts for recording awaking and sleeping times; clarification for those randomized to rhEPO who transition from HD to PD will change from epoetin alfa to darbepoetin alfa.
08 February 2017	Amendment 2/France1: Additional ultrasound added to France; PD participants are not eligible for France.
05 October 2017	Amendment 3: Added retest for Hgb and TSAT to determine eligibility; broadened exclusion to include participation in interventional study with investigational agent or device; revised statistical section to change from two-sided testing at the 5% level to onesided testing at the 2.5% level; correct the comparator for the Null and Alternative hypotheses; changed significance levels to p-values; added description of the adjustments to statistical model; updated hyporesponder analyses; added text regarding the interim analysis process; added exploratory endpoints around Hgb variability, iron parameters, transfusions and dose adjustment scheme; provision for possible adjustment to Dose Adjustment Algorithm triggers for Hgb values 7.5 g/dL to <9.5 g/dL based on the review of blinded instream aggregate Hgb data
09 October 2017	Amendment 3/France1: Changes from amendment 3 to France
30 July 2020	Amendment 4: Revised MACE non-inferiority margin NI margin; revised target MACE as a result of the change to the NI margin; updated the analysis of the hemoglobin co-primary endpoint based on FDA feedback; multiplicity adjustment strategy updated from Hommel to Holm-Bonferroni based on FDA feedback; added AESI of worsening of hypertension
30 July 2020	Amendment 4/France1: changes from amendment 4 to France

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported