Clinical trial results:
A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in non-dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa

Summary

EudraCT number	2016-000542-65
Trial protocol	HU BE GB DK AT CZ DE PT SE ES NL BG GR FR PL IT
Global end of trial date	19 April 2021

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	200808

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	02 August 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To compare daprodustat to darbepoetin alfa for cardiovascular (CV) safety (non-inferiority)
- To compare daprodustat to darbepoetin alfa for hemoglobin (Hgb) efficacy (non-inferiority)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 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	Hong Kong: 29
Country: Number of subjects enrolled	India: 144
Country: Number of subjects enrolled	Korea, Republic of: 323
Country: Number of subjects enrolled	Malaysia: 71
Country: Number of subjects enrolled	Philippines: 79
Country: Number of subjects enrolled	Singapore: 18
Country: Number of subjects enrolled	Taiwan: 120
Country: Number of subjects enrolled	Thailand: 64
Country: Number of subjects enrolled	Viet Nam: 140
Country: Number of subjects enrolled	Bulgaria: 128
Country: Number of subjects enrolled	Czechia: 40
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Hungary: 90
Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Romania: 49
Country: Number of subjects enrolled	Russian Federation: 82
Country: Number of subjects enrolled	South Africa: 25
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	Ukraine: 198
Country: Number of subjects enrolled	Australia: 72
Country: Number of subjects enrolled	Belgium: 43
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 17

Country: Number of subjects enrolled	Greece: 143
Country: Number of subjects enrolled	Israel: 37
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	New Zealand: 34
Country: Number of subjects enrolled	Portugal: 41
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 67
Country: Number of subjects enrolled	Argentina: 146
Country: Number of subjects enrolled	Brazil: 128
Country: Number of subjects enrolled	Colombia: 37
Country: Number of subjects enrolled	Mexico: 279
Country: Number of subjects enrolled	United States: 981
Worldwide total number of subjects	3872
EEA total number of subjects	750

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)	1678
From 65 to 84 years	1971
85 years and over	223

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study conducted across 39 countries. Participants were randomized to receive either daprodustat or darbepoetin alfa.

Pre-assignment

Screening details:

A total of 3872 participants were enrolled 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 treatment with daprodustat film-coated tablets at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily up to 51.1 month. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]).

Arm type	Experimental
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	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).

Arm title	Darbepoetin alfa

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 darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection at 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg) up to 51.1 month. Darbepoetin alfa IV injection was administered to participants undergoing hemodialysis. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).

Arm type	Active comparator

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 intravenous (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	Darbepoetin alfa
Started	1937	1935
Completed	1873	1870
Not completed	64	65
Unknown	1	-
Investigator Site Closed	6	13
Consent withdrawn by subject	32	23
Lost to follow-up	25	29

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 treatment with daprodustat film-coated tablets at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily up to 51.1 month. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]).	
Reporting group title	Darbepoetin alfa
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 darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection at 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg) up to 51.1 month. Darbepoetin alfa IV injection was administered to participants undergoing hemodialysis. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).	

Reporting group values	Daprodustat	Darbepoetin alfa	Total
Number of subjects	1937	1935	3872
Age categorical 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)	836	842	1678
From 65-84 years	994	977	1971
85 years and over	107	116	223
Age Continuous Units: Years			
arithmetic mean	64.8	64.9	
standard deviation	± 14.03	± 13.83	-
Sex: Female, Male Units: Participants			
Female	1102	1071	2173
Male	835	864	1699
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaskan Native	88	100	188
Asian - Central/South Asian Heritage	58	71	129
Asian - East Asian Heritage	245	232	477
Asian - Japanese Heritage	5	3	8
Asian - South East Asian Heritage	216	229	445
Black or African American	183	185	368
Native Hawaiian or Other Pacific Islander	7	7	14

White - Arabic/North African Heritage	19	18	37
White - White/Caucasian/European Heritage	1079	1037	2116
Mixed Asian Race	1	2	3
Mixed Race	36	51	87

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 treatment with daprodustat film-coated tablets at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily up to 51.1 month. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]).

Reporting group title	Darbepoetin alfa

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 darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection at 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg) up to 51.1 month. Darbepoetin alfa IV injection was administered to participants undergoing hemodialysis. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).

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],non-fatal stroke)was analyzed using Cox proportional hazards regression model with treatment group,current erythropoiesis-stimulating agents(ESA)use at randomization 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% 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 event)/365.25,based on CV follow-up time period.All Randomized (Intent-to-treat[ITT]) Population comprised of all randomized participants. Participants were analyzed according to treatment to which they were randomized.

End point type	Primary

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[1]	1935[2]		
Units: Events per 100 person years				
number (confidence interval 95%)	10.86 (9.80 to 12.02)	10.63 (9.58 to 11.77)		

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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.19

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 Hgb levels over the Evaluation Period (Week 28 to Week 52)

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

End point description:

Blood samples were collected from participants for Hgb measurements. Hgb during the evaluation period was defined as the mean of all available post-randomization Hgb values (on and off-treatment) during the evaluation period (Week 28 to Week 52). For the primary analysis missing post-Baseline Hgb 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. Analysis was performed using the Analysis of covariance (ANCOVA) model with terms for treatment, Baseline Hgb, current ESA use and region.

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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[4]	1935[5]		
Units: Grams per deciliter				
least squares mean (standard error)	0.74 (± 0.019)	0.66 (± 0.019)		

Notes:

[4] - All Randomized (ITT) Population.

[5] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified

Analysis type	non-inferiority[6]
Parameter estimate	Least square (LS) mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.13

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[7]	1935[8]		
Units: Events per 100 person years				
number (confidence interval 95%)	10.86 (9.80 to 12.02)	10.63 (9.58 to 11.77)		

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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.670884 [9]
Method	Wald test
Parameter estimate	Hazard ratio (HR)

Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.19

Notes:

[9] - The p-value was compared against 0.008333 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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[10]	1935[11]		
Units: Events per 100 person years				
number (confidence interval 95%)	12.34 (11.19 to 13.57)	11.77 (10.65 to 12.98)		

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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.800813 [12]
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.22

Notes:

[12] - The p-value was compared against 0.012500 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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[13]	1935[14]		
Units: Events per 100 person years				
number (confidence interval 95%)	13.16 (11.97 to 14.44)	12.22 (11.08 to 13.46)		

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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.886195 [15]
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %

sides	2-sided
lower limit	0.95
upper limit	1.24

Notes:

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

Secondary: Time to First Occurrence of chronic kidney disease (CKD) Progression during CV events follow-up time period

End point title	Time to First Occurrence of chronic kidney disease (CKD) Progression during CV events follow-up time period

End point description:

Progression of CKD defined as:40% decline in eGFR from Baseline or ESRD as defined by either initiating chronic dialysis for >=90 days or not initiating chronic dialysis when dialysis is indicated or kidney transplantation.Time to first occurrence of CKD progression was analyzed using Fine and Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use 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).First event person years=(cumulative total time to first event for participants who have event+cumulative total of censored time for participants without event)/365.25,based on CV follow-up time period.Only those participants with data available at indicated time points were analyzed.This analysis population was restricted to those with a Baseline eGFR

End point type	Secondary

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1220[16]	1265[17]		
Units: Events per 100 person years				
number (confidence interval 95%)	17.55 (15.74 to 19.51)	17.76 (15.97 to 19.70)		

Notes:

[16] - All Randomized (ITT) Population.

[17] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Subdistribution hazard ratio was estimated using Fine and Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36947
Method	Wald test
Parameter estimate	Subdistribution hazard ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.84
upper limit	1.13

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, current ESA use at randomization, 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 follow-up time period.

End point type	Secondary

End point timeframe:

Up to 4.3 person-years for vital status follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[18]	1935[19]		
Units: Events per 100 person years				
number (confidence interval 95%)	8.35 (7.43 to 9.35)	8.27 (7.35 to 9.26)		

Notes:

[18] - All Randomized (ITT) Population.

[19] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6197
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.2

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[20]	1935[21]		
Units: Events per 100 person years				
number (confidence interval 95%)	3.02 (2.48 to 3.65)	2.55 (2.06 to 3.13)		

Notes:

[20] - All Randomized (ITT) Population.

[21] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8976
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.58

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[22]	1935[23]		
Units: Events per 100 person years				
number (confidence interval 95%)	2.94 (2.40 to 3.56)	2.76 (2.24 to 3.36)		

Notes:

[22] - All Randomized (ITT) Population.

[23] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6581
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.4

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[24]	1935[25]		
Units: Events per 100 person years				
number (confidence interval 95%)	1.26 (0.92 to 1.69)	0.95 (0.66 to 1.33)		

Notes:

[24] - All Randomized (ITT) Population.

[25] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.894
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.07

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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[26]	1935[27]		
Units: Participants				
Occurrences per participant: 0	1493	1518		
Occurrences per participant: 1	318	317		
Occurrences per participant: 2	76	64		
Occurrences per participant: 3	26	22		
Occurrences per participant: 4	14	9		
Occurrences per participant: 5	5	3		
Occurrences per participant: 6	1	0		
Occurrences per participant: 7	4	1		
Occurrences per participant: 8	0	1		

Notes:

[26] - All Randomized (ITT) Population.

[27] - 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	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9422
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.23

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 Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8862
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.24

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 Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6789
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.39

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 Darbepoetin alfa

Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9016
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.19

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 Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8862
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.24

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 Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8989
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.92
upper limit	1.46

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[28]	1935[29]		
Units: Events per 100 person years				
number (confidence interval 95%)	5.36 (4.62 to 6.18)	4.98 (4.27 to 5.77)		

Notes:

[28] - All Randomized (ITT) Population.

[29] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7673
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.33

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) form 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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[30]	1935[31]		
Units: Events per 100 person years				
number (confidence interval 95%)	41.13 (38.59 to 43.80)	38.99 (36.54 to 41.56)		

Notes:

[30] - All Randomized (ITT) Population.

[31] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8601
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.15

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 electronic case record form with hospitalization duration of >=24 hours and admission date within 30days following previous discharge date of all-cause hospitalization event, where previous hospitalization was >=24hours.Time to first occurrence of all-cause hospital re-admission within 30days was analyzed using Cox proportional hazards regression model with treatment group, current ESA use at randomization and region as covariates.Time to the first occurrence was computed as(event date - randomization date)+1. Incidence rate per 100 person years calculated as(100*number of participants with at least 1event)/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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[32]	1935[33]		
Units: Events per 100 person years				
number (confidence interval 95%)	7.78 (6.87 to 8.79)	7.55 (6.65 to 8.55)		

Notes:

[32] - All Randomized (ITT) Population.

[33] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6207
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.22

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[34]	1935[35]		
Units: Events per 100 person years				
number (confidence interval 95%)	14.60 (13.33 to 15.96)	13.32 (12.11 to 14.61)		

Notes:

[34] - All Randomized (ITT) Population.

[35] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9393
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.26

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[36]	1935[37]		
Units: Events per 100 person years				
number (confidence interval 95%)	4.05 (3.41 to 4.78)	3.30 (2.73 to 3.96)		

Notes:

[36] - All Randomized (ITT) Population.

[37] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9412
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.56

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, current ESA use at randomization, 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 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[38]	1935[39]		
Units: Events per 100 person years				
number (confidence interval 95%)	1.81 (1.39 to 2.31)	1.43 (1.07 to 1.89)		

Notes:

[38] - All Randomized (ITT) Population.

[39] - 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, current ESA use at randomization, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8994
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.84

Secondary: Time to First Occurrence of Confirmed 40% Decline in eGFR during CV events follow-up time period

End point title	Time to First Occurrence of Confirmed 40% Decline in eGFR during CV events follow-up time period

End point description:

Time to first occurrence of confirmed 40% decline in eGFR was analyzed using a Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use 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. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1220[40]	1265[41]		
Units: Events per 100 person years				
number (confidence interval 95%)	8.21 (7.04 to 9.52)	8.90 (7.69 to 10.24)		

Notes:

[40] - All Randomized (ITT) Population.

[41] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Subdistribution hazard ratio was estimated using Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2073
Method	Wald test
Parameter estimate	Subdistribution hazard ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.13

Secondary: Time to First Occurrence of Chronic Dialysis during CV events follow-up time period

End point title	Time to First Occurrence of Chronic Dialysis during CV events follow-up time period

End point description:

Time to first occurrence of chronic dialysis was analyzed using a Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use and region as covariates. Chronic dialysis is defined by either initiating dialysis for >=90 days or not initiating chronic dialysis when dialysis is indicated. 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. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1220[42]	1265[43]		
Units: Events per 100 person years				
number (confidence interval 95%)	12.20 (10.74 to 13.81)	12.06 (10.63 to 13.62)		

Notes:

[42] - All Randomized (ITT) Population.

[43] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Subdistribution hazard ratio was estimated using Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5068
Method	Wald test
Parameter estimate	Subdistribution hazard ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.19

Secondary: Time to First Occurrence of Kidney Transplant during CV events follow-up time period

End point title	Time to First Occurrence of Kidney Transplant during CV events follow-up time period

End point description:

Time to first occurrence of kidney transplant were analyzed using a Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use 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. Only those participants with data available at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1220[44]	1265[45]		
Units: Events per 100 person years				
number (confidence interval 95%)	1.00 (0.63 to 1.50)	1.14 (0.75 to 1.66)		

Notes:

[44] - All Randomized (ITT) Population.

[45] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Subdistribution hazard ratio was estimated using Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3285
Method	Wald test
Parameter estimate	Subdistribution hazard ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.54

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

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

End point description:

Blood samples were collected from participants for Hgb measurements. Change from Baseline was defined as post-randomization 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, current ESA use, region, Baseline Hgb and Baseline Hgb 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1557[46]	1556[47]		
Units: Grams per deciliter				
least squares mean (standard error)	0.76 (± 0.029)	0.73 (± 0.029)		

Notes:

[46] - All Randomized (ITT) Population.

[47] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3113
Analysis specification	Pre-specified
Analysis type	non-inferiority[48]
Parameter estimate	LS mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.11

Notes:

[48] - 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. Hgb 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1491[49]	1520[50]		
Units: Participants	1167	1063		

Notes:

[49] - All Randomized (ITT) Population.

[50] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

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

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.2
upper limit	11.4

Secondary: Percentage of Time With Hgb 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 Hgb 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1461[51]	1483[52]		
Units: Percentage of days				
median (full range (min-max))	70.5 (0.0 to 100.0)	63.2 (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-darbepoetin alfa) and associated two-sided asymptotic 95% CI is presented.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2944
Analysis specification	Pre-specified
Analysis type	non-inferiority[53]
Parameter estimate	Mean difference (final values)
Point estimate	4.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.04
upper limit	7.11

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 Hgb 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 Hgb 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1461[54]	1483[55]		
Units: Percentage of days				
median (full range (min-max))	70.5 (0.0 to 100.0)	63.2 (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 Darbepoetin alfa
Number of subjects included in analysis	2944
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	van Elteren test
Parameter estimate	Probability
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.57

Secondary: Percentage of Time With Hgb 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 Hgb 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 (4.3 person-years for follow-up time period)

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1469[56]	1489[57]		
Units: Percentage of days				
median (full range (min-max))	66.1 (0.0 to 100.0)	62.1 (0.0 to 100.0)		

Notes:

[56] - All Randomized (ITT) Population.

[57] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

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

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2958
Analysis specification	Pre-specified
Analysis type	non-inferiority[58]
Parameter estimate	Median difference (final values)
Point estimate	3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	5.91

Notes:

[58] - 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 (4.3 person-years for follow-up time period)

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1469[59]	1489[60]		
Units: Percentage of days				
median (full range (min-max))	66.1 (0.0 to 100.0)	62.1 (0.0 to 100.0)		

Notes:

[59] - All Randomized (ITT) Population.

[60] - 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 Darbepoetin alfa
Number of subjects included in analysis	2958
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	van Elteren test
Parameter estimate	Probability
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.56

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 seated position 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 + current ESA use at randomization + 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 (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Week -4) and Week 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1913[61]	1884[62]		
Units: Millimeter of mercury				
least squares mean (standard error)				
SBP, n=1913, 1884	-0.62 (± 0.488)	-1.17 (± 0.479)		
DBP, n=1912, 1884	0.06 (± 0.267)	-0.59 (± 0.262)		
MAP, n=1912, 1884	-0.17 (± 0.300)	-0.77 (± 0.294)		

Notes:

[61] - All Randomized (ITT) Population.

[62] - 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 LS means between arms.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3797
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7916
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	1.9

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 LS means between arms.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3797
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9241
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided

lower limit	-0.22
upper limit	1.43

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 LS means between arms.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3797
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9581
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	1.38

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 seated position 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. Analysis was performed using ANCOVA model with terms for treatment group, current ESA use at randomization, 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 (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Week -4) and 51.1 months

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1919[63]	1884[64]		
Units: Millimeter of mercury				
least squares mean (standard error)				
SBP, n=1919, 1884	-1.19 (± 0.395)	-1.10 (± 0.398)		
DBP, n=1918, 1884	-0.26 (± 0.229)	-0.38 (± 0.231)		
MAP, n=1918, 1884	-0.57 (± 0.248)	-0.62 (± 0.251)		

Notes:
[63] - All Randomized (ITT) Population.
[64] - 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, current ESA use at randomization, region and Baseline value.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3803
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.442
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	1.02

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, current ESA use at randomization, region and Baseline value.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3803
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.549
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.74

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, current ESA use at randomization, region and Baseline value.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3803
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6369
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.75

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 event (based on post-dialysis) was defined 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, current ESA use at randomization 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 treatment (51.1 months)

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1919[65]	1884[66]		
Units: Events per 100 participant years				
number (confidence interval 95%)	138.50 (128.58 to 149.18)	157.35 (146.30 to 169.23)		

Notes:

[65] - All Randomized (ITT) Population.

[66] - 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 with treatment, current ESA use at randomization, and region as covariates and logarithm of time on treatment as an offset variable for the treatment group comparison.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3803

Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074
Method	Negative binomial model
Parameter estimate	Ratio of exacerbation rate
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	0.98

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 treatment (51.1 months)

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1919[67]	1884[68]		
Units: Participants	939	1012		

Notes:

[67] - All Randomized (ITT) Population.

[68] - 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 51.1 months

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1937[69]	1935[70]		
Units: Percentage of participants				
number (not applicable)	2.0	3.3		

Notes:

[69] - All Randomized (ITT) Population.

[70] - 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, current ESA use and region.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0113
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.94

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 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). 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 score represents 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1238[71]	1227[72]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=1238,1187	0.42 (± 0.169)	0.78 (± 0.172)		
Week 12, n=1237,1227	0.60 (± 0.171)	0.71 (± 0.172)		
Week 28, n=968,956	0.16 (± 0.197)	0.04 (± 0.198)		
Week 52, n=804,780	-0.32 (± 0.218)	-0.12 (± 0.221)		

Notes:

[71] - All Randomized (ITT) Population.

[72] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time,current ESA use at randomization, region,Baseline value and Baseline value by time and treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.932
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.11

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7423
Method	MMRM

Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.41

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3335
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.67

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6761
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.36

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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1238[73]	1227[74]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=1238,1187	0.08 (± 0.217)	0.37 (± 0.221)		
Week 12, n=1237,1227	0.02 (± 0.223)	0.18 (± 0.224)		
Week 28, n=968,956	-0.35 (± 0.244)	-0.02 (± 0.245)		
Week 52, n=804,780	-0.71 (± 0.290)	-0.35 (± 0.294)		

Notes:

[73] - All Randomized (ITT) Population.

[74] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8268
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.32

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6851
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0.47

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8316
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.35

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8032
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.46

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 (b pain), general health (GH), mental health (MH), role-emotional (RE) (role limitations caused by emotional problems), role-physical (RP) (role limitations caused by physical problems), social functioning (SF), physical functioning 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 (BL) 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1238[75]	1227[76]		
Units: Scores on a scale				
least squares mean (standard error)				
Bodily pain: Week 8, n=1238,1187	0.11 (± 0.221)	0.45 (± 0.225)		
Bodily pain: Week 12, n=1237,1227	0.35 (± 0.223)	0.50 (± 0.224)		
Bodily pain: Week 28, n=968,956	-0.48 (± 0.261)	0.02 (± 0.263)		
Bodily pain: Week 52, n=804,780	-0.34 (± 0.283)	0.13 (± 0.288)		

General health: Week 8, n=1238,1187	0.36 (± 0.171)	0.43 (± 0.174)		
General health: Week 12, n=1237,1227	0.28 (± 0.174)	0.48 (± 0.175)		
General health: Week 28, n=968,956	0.14 (± 0.200)	0.04 (± 0.201)		
General health: Week 52, n=804,780	-0.27 (± 0.220)	-0.19 (± 0.224)		
Mental health: Week 8, n=1238,1187	-0.19 (± 0.204)	0.12 (± 0.208)		
Mental health: Week 12, n=1237,1227	-0.07 (± 0.210)	-0.09 (± 0.211)		
Mental health: Week 28, n=968,956	-0.67 (± 0.231)	-0.37 (± 0.232)		
Mental health: Week 52, n=804,780	-0.85 (± 0.271)	-0.61 (± 0.275)		
Role-emotional: Week 8, n=1238,1187	0.45 (± 0.253)	0.54 (± 0.258)		
Role-emotional: Week 12, n=1237,1227	0.17 (± 0.258)	0.43 (± 0.259)		
Role-emotional: Week 28, n=968,956	-0.30 (± 0.290)	0.07 (± 0.292)		
Role-emotional: Week 52, n=804,780	-0.90 (± 0.339)	-0.38 (± 0.344)		
Role-physical: Week 8, n=1238,1187	0.33 (± 0.202)	0.83 (± 0.205)		
Role-physical: Week 12, n=1237,1227	0.40 (± 0.203)	0.73 (± 0.204)		
Role-physical: Week 28, n=968,956	0.06 (± 0.230)	0.00 (± 0.232)		
Role-physical: Week 52, n=804,780	-0.63 (± 0.259)	-0.44 (± 0.263)		
Social functioning: Week 8, n=1238,1187	0.19 (± 0.224)	0.82 (± 0.228)		
Social functioning: Week 12, n=1237,1227	0.21 (± 0.224)	0.53 (± 0.225)		
Social functioning: Week 28, n=968,956	0.04 (± 0.247)	0.17 (± 0.249)		
Social functioning: Week 52, n=804,780	-0.58 (± 0.282)	-0.20 (± 0.286)		

Notes:

[75] - All Randomized (ITT) Population.

[76] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

B pain,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8562
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.28

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

B pain,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8765
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.32

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

B pain,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9074
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.24

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

B pain,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6849
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0.47

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

GH,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5991
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.54

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

GH,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3614
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided

lower limit	-0.46
upper limit	0.66

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

GH,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7852
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.29

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

MH,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8526
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.27

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

GH,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL

value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6252
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.4

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

MH,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8262
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.33

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

MH,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4673
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.02
Confidence interval	

level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.61

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

MH,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.738
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.51

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

RE,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5997
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.62

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

RE,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7649
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.45

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

RE,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8175
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	0.43

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

RE,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8591
Method	MMRM
Parameter estimate	LS mean difference

Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	0.43

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

RP,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9588
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	0.06

Statistical analysis title	Statistical analysis 18

Statistical analysis description:

RP,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8761
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.23

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

RP,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4293
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.7

Statistical analysis title	Statistical analysis 20

Statistical analysis description:

RP,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6983
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.53

Statistical analysis title	Statistical analysis 21

Statistical analysis description:

SF,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9743

Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	0

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

SF,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time,current ESA use at randomization, region,BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8405
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.31

Statistical analysis title	Statistical analysis 23

Statistical analysis description:

SF,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6459
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.56

Statistical analysis title	Statistical analysis 24

Statistical analysis description:

SF,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8272
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.41

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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1238[77]	1227[78]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=1238,1187	0.35 (± 0.192)	0.90 (± 0.195)		
Week 12, n=1237,1227	0.62 (± 0.200)	0.74 (± 0.201)		
Week 28, n=968,956	0.22 (± 0.222)	0.32 (± 0.223)		

Week 52, n=804,780	-0.14 (± 0.250)	0.35 (± 0.253)		

Notes:

[77] - All Randomized (ITT) Population.

[78] - 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,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9786
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	-0.02

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,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6261
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.52

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,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9161
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	0.21

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,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6642
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.44

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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1238[79]	1227[80]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=1238,1187	0.51 (± 0.200)	0.83 (± 0.203)		
Week 12, n=1237,1227	0.65 (± 0.195)	0.52 (± 0.196)		
Week 28, n=968,956	0.05 (± 0.224)	-0.10 (± 0.225)		
Week 52, n=804,780	-0.69 (± 0.262)	-0.37 (± 0.266)		

Notes:

[79] - All Randomized (ITT) Population.

[80] - 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,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8703
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.24

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,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3167
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.67

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,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3155
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
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 model adjusted Week 52 data has been presented,with factors for treatment, time,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8069
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided

lower limit	-1.06
upper limit	0.41

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 minus 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443[81]	399[82]		
Units: Scores on a scale				
least squares mean (standard error)	-0.0253 (± 0.00842)	-0.0018 (± 0.00883)		

Notes:

[81] - All Randomized (ITT) Population.

[82] - 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, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	842
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9724
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.0234
Confidence interval	
level	95 %
sides	2-sided

lower limit	-0.0474
upper limit	0.0005

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

End point title	Change from Baseline in On-treatment EQ 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 imaginable health and 100 represents the best imaginable 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. 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443[83]	399[84]		
Units: Scores on a scale				
least squares mean (standard error)	-0.7 (± 0.78)	-1.4 (± 0.82)		

Notes:

[83] - All Randomized (ITT) Population.

[84] - 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, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	842
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2687
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	2.9

Secondary: Change from Baseline in On-treatment Chronic Kidney Disease- Anemia Symptoms Questionnaire (CKD-AQ) at Weeks 8, 12, 28, 52

End point title	Change from Baseline in On-treatment Chronic Kidney Disease-Anemia Symptoms Questionnaire (CKD-AQ) at Weeks 8, 12, 28, 52

End point description:

CKD-AQ is 21-item PRO measure assessing symptoms and symptom impact in participants with anemia associated with CKD. It had 3domains:1.Tired/Low Energy(LE)/Weak scale consisting of 10items;2.Chest Pain(CP)/Shortness of Breath(SOB) scale consisting of 4items;3.Cognitive(Cog) scale consisting of 3 items.4 CKD-AQ single items are:SOB,no activity; severity-short breath(S-SB), resting; difficulty standing (diff. std.)for long time(LT) and difficulty sleeping (diff sleep).Single-item were recorded based on a 0-100 scoring with 0=worst possible;100=best possible score. 3 domains scores were calculated as average of items in each domain;ranged from 0-100 where 0=worst possible;100=best possible score.Change from Baseline was calculated as on-treatment visit value-Baseline value.Baseline was defined as latest non-missing pre-dose assessment on or before randomization date.Only those participants with data available at indicated time points were analyzed(represented by n=X in category

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 8, 12, 28, 52

End point values	Daprodustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1341[85]	1360[86]		
Units: Scores on a scale				
least squares mean (standard error)				
Tired/Low energy/Weak domain: Week 8,n=1340,1294	1.72 (± 0.424)	2.94 (± 0.429)		
Tired/Low energy/Weak domain: Week 12,n=1341,1360	2.11 (± 0.437)	3.08 (± 0.434)		
Tired/Low energy/Weak domain: Week 28,n=1053,1047	1.27 (± 0.495)	1.87 (± 0.496)		
Tired/Low energy/Weak domain: Week 52,n=870,865	0.20 (± 0.554)	1.77 (± 0.556)		
Chest pain/SOB domain: Week 8,n=1340,1294	0.63 (± 0.358)	1.83 (± 0.363)		
Chest pain/ SOB domain: Week 12,n=1341,1360	0.88 (± 0.370)	1.53 (± 0.368)		
Chest pain/ SOB domain: Week 28,n=1053,1047	0.01 (± 0.424)	0.53 (± 0.425)		
Chest pain/ SOB domain: Week 52,n=870,865	-0.71 (± 0.471)	0.47 (± 0.473)		
Cognitive domain: Week 8,n=1340,1294	0.13 (± 0.413)	0.89 (± 0.419)		
Cognitive domain: Week 12,n=1341,1360	-0.17 (± 0.414)	1.01 (± 0.412)		
Cognitive domain: Week 28,n=1053,1047	-0.40 (± 0.468)	0.37 (± 0.469)		
Cognitive domain: Week 52,n=870,865	-2.00 (± 0.526)	-0.35 (± 0.527)		
SOB, no activity: Week 8,n=1340,1294	-0.1 (± 0.42)	1.0 (± 0.42)		
SOB, no activity: Week 12,n=1341,1360	0.1 (± 0.43)	0.4 (± 0.42)		

SOB, no activity: Week 28,n=1053,1047	-1.1 (± 0.50)	-0.2 (± 0.50)		
SOB, no activity: Week 52,n=870,865	-1.7 (± 0.57)	-1.6 (± 0.57)		
Severity-short breath, Resting: Week 8,n=1340,1294	-0.3 (± 0.40)	0.8 (± 0.40)		
Severity-short breath, Resting:Week 12,n=1341,1360	-0.3 (± 0.42)	0.0 (± 0.42)		
Severity-short breath, Resting:Week 28,n=1053,1047	-1.1 (± 0.48)	-0.7 (± 0.48)		
Severity-short breath, Resting:Week 52,n=870,865	-2.0 (± 0.53)	-0.5 (± 0.53)		
Diff std for long time: Week 8,n=1340,1294	1.0 (± 0.62)	2.5 (± 0.63)		
Diff std for long time: Week 12,n=1341,1360	0.7 (± 0.63)	1.6 (± 0.62)		
Diff std for long time: Week 28,n=1053,1047	0.4 (± 0.71)	1.7 (± 0.71)		
Diff std for long time: Week 52,n=870,865	-2.1 (± 0.76)	1.2 (± 0.76)		
Difficulty sleeping: Week 8,n=1340,1294	1.6 (± 0.60)	1.1 (± 0.61)		
Difficulty sleeping: Week 12,n=1341,1360	0.5 (± 0.60)	2.0 (± 0.59)		
Difficulty sleeping: Week 28,n=1053,1047	-0.7 (± 0.69)	-0.3 (± 0.70)		
Difficulty sleeping: Week 52,n=870,865	-2.6 (± 0.78)	-0.3 (± 0.78)		

Notes:

[85] - All Randomized (ITT) Population.

[86] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Tired/LE/Weak domain,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.978
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.03

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Tired/LE/Weak domain,Week28:Model was fitted from Baseline up to Week52 and model adjusted

Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8042
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.98
upper limit	0.77

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Tired/LE/Weak domain,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.977
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	-0.03

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Tired/LE/Weak domain,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.943
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.18
upper limit	0.23

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

CP/SOB,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9905
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.2

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

CP/SOB,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8939
Method	LS mean difference
Parameter estimate	LS mean difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	0.37

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

CP/SOB,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9615
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	0.13

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

CP/SOB,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.807
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.66

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Cog domain,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9781
Method	MMRM

Parameter estimate	LS mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	-0.03

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

Cog domain,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9015
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.91
upper limit	0.39

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

SOB, no activity,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9725
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

SOB, no activity,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8903
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0.5

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

SOB, no activity,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7188
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.8

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

Cog domain,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9864

Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	-0.19

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

Cog domain,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8778
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	0.53

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

S-SB,Resting, Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7462
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.9

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

SOB, no activity,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5011
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.6

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

S-SB,Resting, Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9716
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	0

Statistical analysis title	Statistical analysis 18

Statistical analysis description:

S-SB,Resting, Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa

Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6908
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.9

Statistical analysis title	Statistical analysis 21

Statistical analysis description:

Diff std for LT, Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9471
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	0.3

Statistical analysis title	Statistical analysis 23

Statistical analysis description:

Diff std for LT, Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8918
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided

lower limit	-3.2
upper limit	0.7

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

Diff std for LT, Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.833
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.9

Statistical analysis title	Statistical analysis 24

Statistical analysis description:

Diff std for LT, Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9986
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	-1.1

Statistical analysis title	Statistical analysis 20

Statistical analysis description:

S-SB,Resting, Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by

time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.977
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	0

Statistical analysis title	Statistical analysis 25

Statistical analysis description:

Diff sleep, Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3035
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	2.1

Statistical analysis title	Statistical analysis 28

Statistical analysis description:

Diff sleep, Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9832
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.4
Confidence interval	

level	95 %
sides	2-sided
lower limit	-4.5
upper limit	-0.2

Statistical analysis title	Statistical analysis 26

Statistical analysis description:

Diff sleep, Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9563
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0.2

Statistical analysis title	Statistical analysis 27

Statistical analysis description:

Diff sleep, Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6548
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	1.5

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 more disease severity. 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1341[87]	1362[88]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8, n=1341,1295	0.00 (± 0.022)	-0.02 (± 0.022)		
Week 12, n=1341,1362	0.03 (± 0.022)	-0.02 (± 0.022)		
Week 28, n=1054,1051	0.05 (± 0.025)	0.09 (± 0.025)		
Week 52, n=871,865	0.11 (± 0.028)	0.06 (± 0.029)		

Notes:

[87] - All Randomized (ITT) Population.

[88] - All Randomized (ITT) Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 8: Model was fitted from Baseline up to Week52 and model adjusted Week 8 data has been presented, with factors for treatment, time, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6917
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.08

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12: Model was fitted from Baseline up to Week52 and model adjusted Week 12 data has been presented, with factors for treatment, time, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.951
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.11

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week52 and model adjusted Week 28 data has been presented, with factors for treatment, time, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1136
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 4

Statistical analysis description:

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

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	2703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8859

Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.13

Secondary: Change from Baseline in Post-randomization estimated Glomerular Filtration Rate (eGFR) at Week 52

End point title	Change from Baseline in Post-randomization estimated Glomerular Filtration Rate (eGFR) at Week 52

End point description:

Blood samples were collected to analyze estimated glomerular filtration rate. Change from Baseline was calculated as post-Baseline 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	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1869[89]	1868[90]		
Units: mL per minute per 1.73 square meter				
least squares mean (standard error)	-2.88 (± 0.193)	-2.67 (± 0.193)		

Notes:

[89] - All Randomized (ITT) Population.

[90] - 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, current ESA use at randomization, region, Baseline value and Baseline value by time and treatment by time interactions.

Comparison groups	Daprodustat v Darbepoetin alfa
Number of subjects included in analysis	3737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7716
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	

level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.33

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 (non-STEAEs) were collected up to 4.3 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 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	Darbe
Reporting group description: -	
Reporting group title	Dapro

Reporting group description: -

Serious adverse events	Darbe	Dapro	
Total subjects affected by serious adverse events			
subjects affected / exposed	703 / 1933 (36.37%)	850 / 1937 (43.88%)	
number of deaths (all causes)	298	301	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	12 / 1933 (0.62%)	8 / 1937 (0.41%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	6 / 1933 (0.31%)	9 / 1937 (0.46%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriovenous fistula thrombosis			
subjects affected / exposed	9 / 1933 (0.47%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 10	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	6 / 1933 (0.31%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	5 / 1933 (0.26%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	6 / 1933 (0.31%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 1933 (0.00%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	3 / 1933 (0.16%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	3 / 1933 (0.16%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 1933 (0.05%)	5 / 1937 (0.26%)	
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	2 / 1933 (0.10%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritoneal dialysis complication			

subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	3 / 1933 (0.16%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	3 / 1933 (0.16%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodialysis complication			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxicity to various agents			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (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	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arteriovenous fistula maturation failure			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula occlusion			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site pseudoaneurysm			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft thrombosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart injury			

subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasal injury			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root injury lumbar			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural vomiting			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ulna fracture			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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	1 / 1933 (0.05%)	0 / 1937 (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 thrombosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 1933 (0.05%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticoagulation drug level above			

therapeutic			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (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	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acid base balance abnormal			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood glucose increased			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation test abnormal			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			

subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QRS complex prolonged			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzymes increased			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus test positive			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	26 / 1933 (1.35%)	37 / 1937 (1.91%)	
occurrences causally related to treatment / all	0 / 28	2 / 40	
deaths causally related to treatment / all	0 / 3	0 / 4	
Cardiac failure congestive			
subjects affected / exposed	20 / 1933 (1.03%)	29 / 1937 (1.50%)	
occurrences causally related to treatment / all	0 / 23	1 / 43	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	14 / 1933 (0.72%)	28 / 1937 (1.45%)	
occurrences causally related to treatment / all	0 / 17	1 / 35	
deaths causally related to treatment / all	0 / 1	0 / 4	
Angina unstable			

subjects affected / exposed	15 / 1933 (0.78%)	13 / 1937 (0.67%)	
occurrences causally related to treatment / all	0 / 17	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	11 / 1933 (0.57%)	10 / 1937 (0.52%)	
occurrences causally related to treatment / all	0 / 11	1 / 12	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	9 / 1933 (0.47%)	10 / 1937 (0.52%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	8 / 1933 (0.41%)	11 / 1937 (0.57%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 1933 (0.16%)	14 / 1937 (0.72%)	
occurrences causally related to treatment / all	0 / 3	2 / 14	
deaths causally related to treatment / all	0 / 0	0 / 9	
Cardiac failure acute			
subjects affected / exposed	5 / 1933 (0.26%)	9 / 1937 (0.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac arrest			
subjects affected / exposed	4 / 1933 (0.21%)	10 / 1937 (0.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 4	0 / 5	
Acute left ventricular failure			
subjects affected / exposed	1 / 1933 (0.05%)	12 / 1937 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	4 / 1933 (0.21%)	6 / 1937 (0.31%)	

occurrences causally related to treatment / all	0 / 4	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	3 / 1933 (0.16%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	2 / 1933 (0.10%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	1 / 3	
Myocardial ischaemia			
subjects affected / exposed	4 / 1933 (0.21%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus bradycardia			
subjects affected / exposed	3 / 1933 (0.16%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	2 / 1933 (0.10%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiorenal syndrome			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	

deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic valve incompetence			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis uraemic			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diastolic dysfunction			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic left ventricular failure			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve prolapse			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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			
Congenital cystic kidney disease			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Syringomyelia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	31 / 1933 (1.60%)	33 / 1937 (1.70%)	
occurrences causally related to treatment / all	0 / 34	2 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 1933 (0.00%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Evans syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-immune heparin associated thrombocytopenia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sideroblastic anaemia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	8 / 1933 (0.41%)	13 / 1937 (0.67%)	
occurrences causally related to treatment / all	0 / 8	0 / 13	

deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	9 / 1933 (0.47%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 9	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	4 / 1933 (0.21%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 1933 (0.16%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 1933 (0.10%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 2	
Seizure			
subjects affected / exposed	2 / 1933 (0.10%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 1933 (0.05%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxic encephalopathy			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	3 / 1933 (0.16%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhagic stroke			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar stroke			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dementia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	

occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemic coma			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basilar artery occlusion			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain stem infarction			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidotic hyperglycaemic coma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dizziness			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonic tremor			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gliosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paresis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbosacral radiculopathy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Putamen haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angle closure glaucoma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid ptosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhegmatogenous retinal detachment			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreoretinal traction syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	

deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	7 / 1933 (0.36%)	12 / 1937 (0.62%)	
occurrences causally related to treatment / all	0 / 7	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 2	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	6 / 1933 (0.31%)	12 / 1937 (0.62%)	
occurrences causally related to treatment / all	0 / 6	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	5 / 1933 (0.26%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	5 / 1933 (0.26%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	5 / 1933 (0.26%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 1933 (0.10%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 2	2 / 6	

deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	5 / 1933 (0.26%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 1933 (0.05%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	5 / 1933 (0.26%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 1933 (0.16%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 1933 (0.10%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 1933 (0.10%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 1933 (0.16%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oesophagitis			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	3 / 1933 (0.16%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic gastropathy			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal wall haematoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis ischaemic			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis microscopic			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastropathy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis haemorrhagic			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Intestinal obstruction			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vascular insufficiency			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oesophageal stenosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic disorder			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	35 / 1933 (1.81%)	54 / 1937 (2.79%)	
occurrences causally related to treatment / all	0 / 35	0 / 56	
deaths causally related to treatment / all	0 / 2	0 / 7	
Acute kidney injury			

subjects affected / exposed	47 / 1933 (2.43%)	70 / 1937 (3.61%)	
occurrences causally related to treatment / all	0 / 53	0 / 76	
deaths causally related to treatment / all	0 / 0	0 / 3	
Chronic kidney disease			
subjects affected / exposed	49 / 1933 (2.53%)	86 / 1937 (4.44%)	
occurrences causally related to treatment / all	0 / 52	0 / 90	
deaths causally related to treatment / all	0 / 0	0 / 6	
End stage renal disease			
subjects affected / exposed	36 / 1933 (1.86%)	48 / 1937 (2.48%)	
occurrences causally related to treatment / all	0 / 37	0 / 50	
deaths causally related to treatment / all	0 / 1	0 / 4	
Renal impairment			
subjects affected / exposed	11 / 1933 (0.57%)	20 / 1937 (1.03%)	
occurrences causally related to treatment / all	0 / 11	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	11 / 1933 (0.57%)	15 / 1937 (0.77%)	
occurrences causally related to treatment / all	0 / 11	0 / 16	
deaths causally related to treatment / all	0 / 1	0 / 3	
Nephropathy			
subjects affected / exposed	6 / 1933 (0.31%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	4 / 1933 (0.21%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 1933 (0.10%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	

occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic end stage renal disease			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic nephropathy			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis chronic			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis membranous			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercapillary glomerulosclerosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive nephropathy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal tubular necrosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	5 / 1933 (0.26%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin ulcer			
subjects affected / exposed	6 / 1933 (0.31%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic skin ulcer			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Actinic keratosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cutaneous calcification			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic ulcer			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythrodermic psoriasis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peau d'orange			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	9 / 1933 (0.47%)	9 / 1937 (0.46%)	
occurrences causally related to treatment / all	0 / 12	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 1933 (0.05%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lead dislodgement			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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			
Back pain			

subjects affected / exposed	4 / 1933 (0.21%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	4 / 1933 (0.21%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 1933 (0.10%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	3 / 1933 (0.16%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	

occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty tophus			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle twitching			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myositis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcopenia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 secondary			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperprolactinaemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid hyperplasia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	25 / 1933 (1.29%)	26 / 1937 (1.34%)	
occurrences causally related to treatment / all	0 / 26	0 / 26	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fluid overload			
subjects affected / exposed	23 / 1933 (1.19%)	25 / 1937 (1.29%)	
occurrences causally related to treatment / all	0 / 24	0 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	13 / 1933 (0.67%)	16 / 1937 (0.83%)	
occurrences causally related to treatment / all	0 / 16	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	16 / 1933 (0.83%)	10 / 1937 (0.52%)	
occurrences causally related to treatment / all	0 / 20	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	5 / 1933 (0.26%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 2	
Diabetic ketoacidosis			
subjects affected / exposed	3 / 1933 (0.16%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	5 / 1933 (0.26%)	3 / 1937 (0.15%)	
occurrences causally related to	0 / 6	0 / 5	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	3 / 1933 (0.16%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	6 / 1933 (0.31%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	4 / 1933 (0.21%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 1933 (0.10%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	1 / 1933 (0.05%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	

deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Fluid retention			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal loss of weight			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acidosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperinsulinaemic hypoglycaemia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemic syndrome			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudohyponatraemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refeeding syndrome			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Starvation ketoacidosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	75 / 1933 (3.88%)	78 / 1937 (4.03%)	
occurrences causally related to treatment / all	0 / 81	0 / 90	
deaths causally related to treatment / all	0 / 4	0 / 10	
COVID-19			
subjects affected / exposed	33 / 1933 (1.71%)	39 / 1937 (2.01%)	
occurrences causally related to treatment / all	0 / 33	0 / 39	
deaths causally related to treatment / all	0 / 4	0 / 10	
Urinary tract infection			
subjects affected / exposed	36 / 1933 (1.86%)	33 / 1937 (1.70%)	
occurrences causally related to treatment / all	0 / 38	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	10 / 1933 (0.52%)	21 / 1937 (1.08%)	
occurrences causally related to treatment / all	0 / 15	0 / 28	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	19 / 1933 (0.98%)	14 / 1937 (0.72%)	
occurrences causally related to treatment / all	0 / 19	1 / 15	
deaths causally related to treatment / all	0 / 1	1 / 5	
Cellulitis			
subjects affected / exposed	14 / 1933 (0.72%)	19 / 1937 (0.98%)	
occurrences causally related to	0 / 15	0 / 22	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	10 / 1933 (0.52%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	10 / 1933 (0.52%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Osteomyelitis			
subjects affected / exposed	8 / 1933 (0.41%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	10 / 1933 (0.52%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	6 / 1933 (0.31%)	8 / 1937 (0.41%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	7 / 1933 (0.36%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	5 / 1933 (0.26%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	5 / 1933 (0.26%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	

deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	6 / 1933 (0.31%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 2	
Bronchitis			
subjects affected / exposed	7 / 1933 (0.36%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	7 / 1933 (0.36%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	6 / 1933 (0.31%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			
subjects affected / exposed	6 / 1933 (0.31%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	3 / 1933 (0.16%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	5 / 1933 (0.26%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 1933 (0.05%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pneumonia bacterial			
subjects affected / exposed	4 / 1933 (0.21%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	1 / 1933 (0.05%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyelonephritis chronic			
subjects affected / exposed	3 / 1933 (0.16%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 1933 (0.05%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	4 / 1933 (0.21%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site infection			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 1933 (0.00%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 1933 (0.00%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 1933 (0.00%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	

deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	3 / 1933 (0.16%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diabetic foot infection			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal peritonitis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (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	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	

deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site infection			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic sinusitis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium bacteraemia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis klebsiella			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue haemorrhagic fever			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis intestinal perforated			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis intestinal haemorrhagic			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema infected			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous pyelonephritis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.00%)	1 / 1937 (0.05%)	
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	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Escherichia coli			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacillus			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes ophthalmic			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site abscess			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective tenosynovitis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral discitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Orchitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

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 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia adenoviral			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas bronchitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal graft infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal cyst infection			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic arthritis staphylococcal			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia sepsis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sphingomonas paucimobilis infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteritis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 infection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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 / 1933 (0.57%)	15 / 1937 (0.77%)	
occurrences causally related to treatment / all	1 / 14	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	8 / 1933 (0.41%)	8 / 1937 (0.41%)	
occurrences causally related to treatment / all	0 / 8	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	9 / 1933 (0.47%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	5 / 1933 (0.26%)	10 / 1937 (0.52%)	
occurrences causally related to treatment / all	0 / 5	0 / 10	

deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	8 / 1933 (0.41%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	8 / 1933 (0.41%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	4 / 1933 (0.21%)	5 / 1937 (0.26%)	
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	1 / 1933 (0.05%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 1933 (0.16%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 1933 (0.10%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	2 / 1933 (0.10%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intermittent claudication			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aortic aneurysm			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis hypotension			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accelerated hypertension			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Aortic intramural haematoma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant cell arteritis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery stenosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 1933 (0.10%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 1933 (0.10%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	4 / 1933 (0.21%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	

deaths causally related to treatment / all	0 / 1	0 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
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	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
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 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 1933 (0.00%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of bladder			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrosarcoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer stage 0			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematological malignancy			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hodgkin's disease			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage I			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Meningioma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Monoclonal gammopathy			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer recurrent			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer recurrent			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory anaemia with an excess of blasts			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal neoplasm			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the vulva			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Immobile			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Death			
subjects affected / exposed	4 / 1933 (0.21%)	13 / 1937 (0.67%)	
occurrences causally related to treatment / all	1 / 4	1 / 13	
deaths causally related to treatment / all	1 / 4	1 / 13	
Non-cardiac chest pain			
subjects affected / exposed	6 / 1933 (0.31%)	9 / 1937 (0.46%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 1933 (0.05%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 6	
Oedema peripheral			
subjects affected / exposed	4 / 1933 (0.21%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 1933 (0.10%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	4 / 1933 (0.21%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 1933 (0.21%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	1 / 1933 (0.05%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Catheter site extravasation			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site inflammation			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discomfort			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait inability			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrobiosis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic mass			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular device occlusion			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	4 / 1933 (0.21%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 1933 (0.00%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
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			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast mass			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heavy menstrual bleeding			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermenstrual bleeding			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal swelling			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	11 / 1933 (0.57%)	11 / 1937 (0.57%)	
occurrences causally related to treatment / all	0 / 13	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pleural effusion			
subjects affected / exposed	11 / 1933 (0.57%)	9 / 1937 (0.46%)	
occurrences causally related to treatment / all	0 / 12	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	7 / 1933 (0.36%)	13 / 1937 (0.67%)	
occurrences causally related to treatment / all	0 / 7	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	12 / 1933 (0.62%)	4 / 1937 (0.21%)	
occurrences causally related to treatment / all	0 / 14	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Respiratory failure			
subjects affected / exposed	4 / 1933 (0.21%)	7 / 1937 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pulmonary oedema			
subjects affected / exposed	7 / 1933 (0.36%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	

deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 1933 (0.26%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 1933 (0.10%)	6 / 1937 (0.31%)	
occurrences causally related to treatment / all	1 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	3 / 1933 (0.16%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 1933 (0.00%)	5 / 1937 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	3 / 1933 (0.16%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchospasm			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 1933 (0.10%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Apnoea			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory disease			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.05%)	0 / 1937 (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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Painful respiration			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertensive crisis			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory alkalosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (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 / 1933 (0.05%)	0 / 1937 (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	2 / 1933 (0.10%)	2 / 1937 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 1933 (0.05%)	3 / 1937 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	2 / 1933 (0.10%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 1933 (0.05%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Biliary colic			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptogenic cirrhosis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemobilia			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic mass			
subjects affected / exposed	0 / 1933 (0.00%)	1 / 1937 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-alcoholic steatohepatitis			
subjects affected / exposed	1 / 1933 (0.05%)	0 / 1937 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Darbe	Dapro	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	825 / 1933 (42.68%)	851 / 1937 (43.93%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	88 / 1933 (4.55%)	104 / 1937 (5.37%)	
occurrences (all)	119	128	
Vascular disorders			
Hypertension			
subjects affected / exposed	264 / 1933 (13.66%)	247 / 1937 (12.75%)	
occurrences (all)	339	317	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	162 / 1933 (8.38%)	198 / 1937 (10.22%)	
occurrences (all)	199	239	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	88 / 1933 (4.55%)	127 / 1937 (6.56%)	
occurrences (all)	96	150	

Diarrhoea			
subjects affected / exposed	139 / 1933 (7.19%)	149 / 1937 (7.69%)	
occurrences (all)	172	181	
Nausea			
subjects affected / exposed	84 / 1933 (4.35%)	103 / 1937 (5.32%)	
occurrences (all)	101	120	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	105 / 1933 (5.43%)	82 / 1937 (4.23%)	
occurrences (all)	110	95	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	122 / 1933 (6.31%)	128 / 1937 (6.61%)	
occurrences (all)	141	148	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	153 / 1933 (7.92%)	164 / 1937 (8.47%)	
occurrences (all)	199	245	
Nasopharyngitis			
subjects affected / exposed	133 / 1933 (6.88%)	118 / 1937 (6.09%)	
occurrences (all)	180	163	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2016	Amendment 1 (Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden and the United Kingdom): Clarified end of the study timing; removed requirement to reduce ESA dose if Week -8 Hgb is >11.5 g/dL; further iron management guidance; new exploratory objective for delayed graft function after deceased donor kidney transplantation
12 October 2016	Amendment 2 (Key changes): Applied changes from Amendment 1; added new timepoints at Week -4 and Week 2 for collection of iron therapy and at Week 52 for Kt/Vurea; changes to ambulatory blood pressure monitoring (ABPM) assessments; clarification for those randomized to rhEPO who transition from HD to PD will change from epoetin alfa to darbepoetin alfa; added country-specific requirements for France and Czech Republic
08 February 2017	Amendment 2/France-01: Added France only requirements for additional ultrasound added to end of study and for participants who transition to dialysis to permanently discontinue randomized treatment.
05 October 2017	Amendment 3 (Key changes): Added retest for Hgb and TSAT for entry; broadened exclusion to include participation in interventional study with investigational agent or device; added provisions for use of local standard of care; revised statistical section to change from two-sided testing at the 5% level to one-sided 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; added provision for possible change to Dose Adjustment Algorithm based review of blinded instream aggregate Hgb data; updated Risk Assessment to align with Investigator's Brochure, version 8; simplified ABPM sub-study
09 October 2017	Amendment 3/France-01: Apply changes from global amendment 3
16 August 2019	Amendment 4: Added retest values for Hgb entry at Day 1, an additional retest opportunity for TSAT for eligibility at W-8, and revised the definition of current uncontrolled hypertension; added autosomal dominant polycystic kidney disease (ADPKD) risk information and requirements for patients with ADPKD; added new adverse event of special interest of worsening of hypertension; added secondary objective/endpoint to assess renal progression via change in eGFR; updated Risk Assessment to align with Investigator's Brochure, version 10; stated recruitment in the ABPM sub-study is closed; PK sub-study entry criteria to exclude patients transitioning or already transitioned to dialysis
16 August 2019	Amendment 4/France-01: Apply changes from global amendment 4 plus update France administrative considerations
30 July 2020	Amendment 5: Revised MACE NI margin and target MACE as a result of the NI margin change; updated analysis of the Hgb co-primary endpoint and multiplicity adjustment strategy from Hommel to Holm-Bonferroni based on FDA feedback; updated pregnancy reporting timelines to align with revised Sponsor timings
30 July 2020	Amendment No. 05/FRA-01: Apply changes from global amendment 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported