



Clinical trial results:

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients

Summary

EudraCT number	2014-000780-40
Trial protocol	SE CZ SK HU ES BG PL
Global end of trial date	26 September 2018

Results information

Result version number	v2
This version publication date	31 October 2019
First version publication date	12 October 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D5740C00002
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02174731
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	101 Orchard Ridge Drive, Gaithersburg, Maryland, United States, 20878
Public contact	Global Clinical Lead, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.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	26 September 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of roxadustat for the treatment of anemia in chronic kidney disease (CKD) participants on dialysis.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Sample.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 34
Country: Number of subjects enrolled	Bulgaria: 139
Country: Number of subjects enrolled	Canada: 55
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	Hungary: 63
Country: Number of subjects enrolled	India: 86
Country: Number of subjects enrolled	Mexico: 109
Country: Number of subjects enrolled	Peru: 76
Country: Number of subjects enrolled	Philippines: 85
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Russian Federation: 91
Country: Number of subjects enrolled	Slovakia: 32
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Thailand: 45
Country: Number of subjects enrolled	Ukraine: 240
Country: Number of subjects enrolled	United States: 776
Country: Number of subjects enrolled	Vietnam: 152

Worldwide total number of subjects	2106
EEA total number of subjects	357

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)	1581
From 65 to 84 years	501
85 years and over	24

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 197 centers in 18 countries worldwide across the United States (US), Canada, Latin America, Australia, Asia and Europe between 01 July 2014 and 26 September 2018. Participants with CKD who were on dialysis were recruited in this study.

Pre-assignment

Screening details:

Study had a screening period (up to 6 weeks), treatment period (up to 4 years) and follow-up period (4 weeks after treatment period for those who completed treatment). 2133 participants were randomized, of which 2106 were included in the analysis and 27 were excluded. Only participants included in the analysis are presented in the participant flow.

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	Roxadustat

Arm description:

Participants received roxadustat tablets orally three times a week (TIW) throughout the treatment period (up to 4 years). For hemodialysis (HD) participants, it was recommended that roxadustat was taken after completion of the HD session. For participants treated with an erythropoietin analogue at study entry, selection of initial roxadustat dose was based on the participant's erythropoietin analogue dose at screening Visit 1. Participants not treated with an erythropoietin analogue at study entry initiated roxadustat using a tiered, weight-based dosing scheme. Doses were titrated to achieve and maintain hemoglobin (Hb) values of 11 ± 1 grams per deciliter (g/dL). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks using a dose adjustment algorithm.

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

Dosage and administration details:

Roxadustat tablets orally TIW throughout the treatment period (up to 4 years). Doses were titrated to achieve and maintain Hb values of 11 ± 1 g/dL.

Arm title	Epoetin alfa
------------------	--------------

Arm description:

Participants received epoetin alfa (only use of Procrit®, Eprex® and Epogen® permitted in the study) subcutaneous (SC) or intravenous (IV) injection TIW, except for participants treated with epoetin alfa in a less frequent regimen prior to study entry. For participants treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was the actual dose administered at screening Visit 1. Participants treated with darbepoetin alfa or methoxy polyethylene glycol-epoetin beta prior to study entry initially received epoetin alfa at doses based on a conversion factor. For participants not treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was 50 international unit per kilogram (IU/kg) TIW. Dose adjustments were to be consistent with local approved prescribing information.

Arm type	Active comparator
----------	-------------------

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

Dosage and administration details:

Eprex® injections TIW throughout the treatment period (up to 4 years). Dose adjustments were to be consistent with local approved prescribing information.

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

Dosage and administration details:

Procrit® injections TIW throughout the treatment period (up to 4 years). Dose adjustments were to be consistent with local approved prescribing information.

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

Dosage and administration details:

Epogen® injections TIW throughout the treatment period (up to 4 years). Dose adjustments were to be consistent with local approved prescribing information.

Number of subjects in period 1	Roxadustat	Epoetin alfa
Started	1051	1055
Received treatment	1048	1053
Completed	982	990
Not completed	69	65
Incorrect enrolment before randomization	-	1
Participant decision	67	64
Missing	2	-

Baseline characteristics

Reporting groups

Reporting group title	Roxadustat
-----------------------	------------

Reporting group description:

Participants received roxadustat tablets orally three times a week (TIW) throughout the treatment period (up to 4 years). For hemodialysis (HD) participants, it was recommended that roxadustat was taken after completion of the HD session. For participants treated with an erythropoietin analogue at study entry, selection of initial roxadustat dose was based on the participant's erythropoietin analogue dose at screening Visit 1. Participants not treated with an erythropoietin analogue at study entry initiated roxadustat using a tiered, weight-based dosing scheme. Doses were titrated to achieve and maintain hemoglobin (Hb) values of 11 ± 1 grams per deciliter (g/dL). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks using a dose adjustment algorithm.

Reporting group title	Epoetin alfa
-----------------------	--------------

Reporting group description:

Participants received epoetin alfa (only use of Procrit®, Eprex® and Epogen® permitted in the study) subcutaneous (SC) or intravenous (IV) injection TIW, except for participants treated with epoetin alfa in a less frequent regimen prior to study entry. For participants treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was the actual dose administered at screening Visit 1. Participants treated with darbepoetin alfa or methoxy polyethylene glycol-epoetin beta prior to study entry initially received epoetin alfa at doses based on a conversion factor. For participants not treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was 50 international unit per kilogram (IU/kg) TIW. Dose adjustments were to be consistent with local approved prescribing information.

Reporting group values	Roxadustat	Epoetin alfa	Total
Number of subjects	1051	1055	2106
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	798	783	1581
From 65-84 years	241	260	501
85 years and over	12	12	24
Age Continuous Units: years			
arithmetic mean	53.5	54.5	-
standard deviation	± 15.30	± 14.97	-
Sex: Female, Male Units: Subjects			
Female	426	429	855
Male	625	626	1251
Race/Ethnicity, Customized Units: Subjects			
White	597	598	1195
Black of African American	148	158	306
Asian	208	198	406

Native Hawaiian or other Pacific Islander	5	3	8
American Indian or Alaska Native	50	62	112
Other	43	36	79
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	268	271	539
Not Hispanic or Latino	783	784	1567
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Roxadustat
-----------------------	------------

Reporting group description:

Participants received roxadustat tablets orally three times a week (TIW) throughout the treatment period (up to 4 years). For hemodialysis (HD) participants, it was recommended that roxadustat was taken after completion of the HD session. For participants treated with an erythropoietin analogue at study entry, selection of initial roxadustat dose was based on the participant's erythropoietin analogue dose at screening Visit 1. Participants not treated with an erythropoietin analogue at study entry initiated roxadustat using a tiered, weight-based dosing scheme. Doses were titrated to achieve and maintain hemoglobin (Hb) values of 11 ± 1 grams per deciliter (g/dL). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks using a dose adjustment algorithm.

Reporting group title	Epoetin alfa
-----------------------	--------------

Reporting group description:

Participants received epoetin alfa (only use of Procrit®, Eprex® and Epogen® permitted in the study) subcutaneous (SC) or intravenous (IV) injection TIW, except for participants treated with epoetin alfa in a less frequent regimen prior to study entry. For participants treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was the actual dose administered at screening Visit 1. Participants treated with darbepoetin alfa or methoxy polyethylene glycol-epoetin beta prior to study entry initially received epoetin alfa at doses based on a conversion factor. For participants not treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was 50 international unit per kilogram (IU/kg) TIW. Dose adjustments were to be consistent with local approved prescribing information.

Primary: US Food and Drug Administration (FDA) Analysis: Mean Change From Baseline in Hb Averaged Over Week 28 to Week 52

End point title	US Food and Drug Administration (FDA) Analysis: Mean Change From Baseline in Hb Averaged Over Week 28 to Week 52
-----------------	--

End point description:

Baseline Hb was defined as the mean of the three last central laboratory Hb values from the screening and randomization visits. Mean change in Hb from baseline to the participants mean level from Week 28 to Week 52 was analyzed using a missing at random (MAR) based multiple imputation analysis of covariance (ANCOVA). Baseline Hb was used as a covariate and treatment group, cardiovascular (CV) history, geographic region and dialysis duration as fixed effects. The adjusted least squares (LS) mean estimates of change from baseline during Week 28 to Week 52 are presented. The Intention-To-Treat (ITT) analysis set included all participants who were randomized to investigational product (IP) irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

End point type	Primary
----------------	---------

End point timeframe:

Baseline (Day 1, Week 0), Week 28 to 52

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1003	1016		
Units: g/dL				
least squares mean (standard error)	0.77 (\pm 0.041)	0.68 (\pm 0.040)		

Statistical analyses

Statistical analysis title	Treatment Difference in Hb
Comparison groups	Epoetin alfa v Roxadustat
Number of subjects included in analysis	2019
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.044

Notes:

[1] - Non-inferiority of roxadustat versus epoetin alfa was declared if the lower bound of the 95% confidence interval (CI) of the difference between roxadustat and epoetin alfa exceeded -0.75. Non-inferiority p-value is 1-sided. Difference between groups (roxadustat minus Epoetin alfa) in LS mean changes.

Primary: European Union (EU) Health Authorities Analysis: Change in Hb From Baseline to the Mean Level During the Evaluation Period (Week 28 to Week 36) Without Having Received Rescue Therapy Within 6 Weeks Prior to and During the 8Week Evaluation Period

End point title	European Union (EU) Health Authorities Analysis: Change in Hb From Baseline to the Mean Level During the Evaluation Period (Week 28 to Week 36) Without Having Received Rescue Therapy Within 6 Weeks Prior to and During the 8Week Evaluation Period
-----------------	---

End point description:

Baseline Hb was defined as mean of three last central laboratory Hb values from screening and randomization visits. Mean change in Hb from baseline to participants mean level from Week 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period was analysed using Mixed Model of Repeated Measures (MMRM). Baseline Hb was used as a covariate and treatment group, CV history, geographic region and dialysis duration as fixed effects. Adjusted LS mean estimates of change from baseline during Week 28 to Week 36 are presented for participants that did not receive rescue therapy within 6 weeks prior to and during this 8 week evaluation period. Per Protocol Set (PPS) included all randomized participants without important protocol deviations who had received at least 8 weeks of study treatment and had valid corresponding Hb measurements. Participants from PPS, with data available for analysis are presented.

End point type	Primary
----------------	---------

End point timeframe:

Baseline (Day 1, Week 0), Week 28 to 36

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	836	864		
Units: g/dL				
least squares mean (standard error)	0.88 (± 0.044)	0.74 (± 0.043)		

Statistical analyses

Statistical analysis title	Treatment Difference in Hb
Comparison groups	Roxadustat v Epoetin alfa
Number of subjects included in analysis	1700
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.056

Notes:

[2] - Non-inferiority of roxadustat versus epoetin alfa was declared if the lower bound of the 95% CI of the difference between roxadustat and epoetin alfa exceeded -0.75. Non-inferiority p-value is 1-sided. Difference between groups (roxadustat minus Epoetin alfa) in LS mean change.

Secondary: Proportion of Total Time of Hb Within the Interval of ≥ 10 g/dL From Week 28 to Week 52

End point title	Proportion of Total Time of Hb Within the Interval of ≥ 10 g/dL From Week 28 to Week 52
-----------------	--

End point description:

The proportion of total time was computed as follows: For each participant, the recorded Hb values were first linearly interpolated between measurements. The time this interpolated curve was ≥ 10 g/dL was computed and subsequently divided by the time between the measurements from Week 28 to Week 52. The difference between roxadustat and epoetin alfa were compared using ANCOVA. Baseline Hb was used as a covariate and the treatment groups, CV history, geographic region and dialysis duration as fixed effects. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Participants without any Hb measurements from Week 28 were not included in the analysis.

End point type	Secondary
----------------	-----------

End point timeframe:
Week 28 to 52

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	896	941		
Units: proportion of total time				
least squares mean (standard error)	0.79 (\pm 0.012)	0.76 (\pm 0.012)		

Statistical analyses

Statistical analysis title	Treatment Difference in Total Time of Hb
Comparison groups	Roxadustat v Epoetin alfa
Number of subjects included in analysis	1837
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.013

Notes:

[3] - Non-inferiority of roxadustat versus epoetin alfa was declared if the lower bound of the 95% CI of the difference between roxadustat and epoetin alfa exceeded -0.15. Non-inferiority p-value is 1-sided. Difference between groups (roxadustat minus Epoetin alfa) in LS mean.

Secondary: Proportion of Total Time of Hb Within the Interval of 10 to 12 g/dL From Week 28 to Week 52

End point title	Proportion of Total Time of Hb Within the Interval of 10 to 12 g/dL From Week 28 to Week 52
-----------------	---

End point description:

The proportion of total time was computed as follows: For each participant, the recorded Hb values were first linearly interpolated between measurements. The time this interpolated curve was within 10-12 g/dL was computed and subsequently divided by the time between the measurement from Week 28 to 52. The difference between roxadustat and epoetin alfa were compared using ANCOVA. Baseline Hb was used as a covariate and the treatment groups, CV history, geographic region and dialysis duration as fixed effects. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Participants without any Hb measurements from Week 28 were not included in the analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 28 to 52

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	896	941		
Units: proportion of total time				
least squares mean (standard error)	0.65 (\pm 0.013)	0.63 (\pm 0.012)		

Statistical analyses

Statistical analysis title	Treatment Difference in Total Time of Hb
Comparison groups	Roxadustat v Epoetin alfa
Number of subjects included in analysis	1837
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[4] - Non-inferiority of roxadustat versus epoetin alfa was declared if the lower bound of the 95% CI of the difference between roxadustat and epoetin alfa exceeded -0.15. Non-inferiority p-value is 1-sided. Difference between groups (roxadustat minus Epoetin alfa) in LS mean.

Secondary: Mean Change in Low-Density Lipoprotein (LDL) Cholesterol From Baseline to Week 24

End point title	Mean Change in Low-Density Lipoprotein (LDL) Cholesterol From Baseline to Week 24
-----------------	---

End point description:

Baseline LDL was defined as the last result obtained prior to randomization. Mean changes in LDL cholesterol from baseline to Week 24 was analysed using ANCOVA. Baseline Hb and baseline LDL were used as covariates and treatment groups, CV history, geographic region and dialysis duration as fixed effects. The adjusted LS mean estimates of change from baseline to Week 24 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1, Week 0) to Week 24

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	902	937		
Units: millimole per liter				
least squares mean (standard error)	-0.38 (± 0.026)	-0.05 (± 0.026)		

Statistical analyses

Statistical analysis title	Treatment Difference in LDL Cholesterol
Comparison groups	Roxadustat v Epoetin alfa
Number of subjects included in analysis	1839
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	-0.27
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[5] - Superiority was also declared as the lower bound of the 95% CI exceeded 0 and p-value was lower than 0.05. Difference between groups (roxadustat minus Epoetin alfa) in LS mean.

Secondary: Mean Change in Hb From Baseline to the Participant's Mean Level Between Week 28 to Week 52 in Participants With Baseline High-Sensitivity C-Reactive Protein (hsCRP) Greater Than the Upper Limit of Normal (ULN)

End point title	Mean Change in Hb From Baseline to the Participant's Mean Level Between Week 28 to Week 52 in Participants With Baseline High-Sensitivity C-Reactive Protein (hsCRP) Greater Than the Upper Limit of Normal (ULN)
-----------------	---

End point description:

Baseline hsCRP was quantified from stored biomarker samples obtained at randomization. Baseline Hb is defined as the mean of the three last central laboratory Hb values from the screening and randomization visits. Changes in Hb from baseline to mean value during Weeks 28 to 52 in participants with baseline hsCRP >ULN was analyzed using a MAR based multiple imputation ANCOVA. Baseline Hb was used as a covariate and treatment group, CV history, geographic region and dialysis duration as fixed effects. The adjusted LS mean estimates of change from baseline during Week 28 to Week 52 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Only participants who consented to the use of donated biomarker samples and had baseline hsCRP >ULN were included in the analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1, Week 0), Week 28 to 52

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	301		
Units: g/dL				
least squares mean (standard error)	0.80 (\pm 0.077)	0.59 (\pm 0.076)		

Statistical analyses

Statistical analysis title	Treatment Difference in Hb
Comparison groups	Roxadustat v Epoetin alfa
Number of subjects included in analysis	581
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[6]
P-value	< 0.001 ^[7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.36
Variability estimate	Standard error of the mean
Dispersion value	0.081

Notes:

[6] - Non-inferiority of roxadustat versus epoetin alfa was declared if the lower bound of the 95% CI of the difference between roxadustat and epoetin alfa exceeded -0.75. Non-inferiority p-value is 1-sided. Difference between groups (roxadustat minus Epoetin alfa) in LS mean.

[7] - MAR-based multiple imputation.

Secondary: Mean Monthly IV Iron Use From Week 36 to End of Study (EOS)

End point title	Mean Monthly IV Iron Use From Week 36 to End of Study (EOS)
-----------------	---

End point description:

Oral iron supplementation was allowed for both treatment groups without restriction. Oral iron was recommended for dietary supplementation to support erythropoiesis and as the first line treatment for prevention and treatment of iron deficiency, unless the participant was intolerant to this route of treatment. In participants receiving roxadustat, the Investigator was allowed to initiate the use of an approved IV iron supplement if a participant's Hb value had not sufficiently responded to 2 or more dose increases of the IP, and ferritin <100 nanogram per milliliter (ng/mL) or transferrin saturation (TSAT) <20%. IP treatment was allowed to continue during IV iron administration. Discontinuation of IV iron supplementation was recommended once the participant was no longer considered to be iron deficient (ferritin >100 ng/mL and TSAT >20%). Results for participants in ITT analysis set were presented.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 36 to EOS (4 weeks after the treatment period)

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	885	920		
Units: mg				
arithmetic mean (standard deviation)	58.71 (\pm 236.12)	91.37 (\pm 225.64)		

Statistical analyses

Statistical analysis title	Treatment Difference in Iron use
Comparison groups	Roxadustat v Epoetin alfa
Number of subjects included in analysis	1805
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon Rank Sum Test

Secondary: Time-To-First Administration of RBC Transfusion as Rescue Therapy

End point title	Time-To-First Administration of RBC Transfusion as Rescue Therapy
-----------------	---

End point description:

Time-to-first RBC transfusion as rescue therapy was calculated as (date of first occurrence of any RBC transfusion as rescue therapy, or date of censoring if no event had occurred) - (date of first dose of IP) + 1. Event rate was calculated as (number of participants with event) divided by (the total number of days at risk for event across all participants in given group divided by 365.25) multiplied by 100. The event rate is presented for participants with events. The on-treatment+3 days safety analysis set included all participants who received at least 1 dose of randomized IP, except for those excluded from analysis. Participants were censored at 3 days after the last administration of the IP.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1, Week 0) up to EOS (4 weeks after the treatment period)

End point values	Roxadustat	Epoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1048	1053		
Units: event rate				
number (not applicable)	6.0	7.2		

Statistical analyses

Statistical analysis title	Treatment Difference in RBC Transfusion
Comparison groups	Roxadustat v Epoetin alfa

Number of subjects included in analysis	2101
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[8]
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.07

Notes:

[8] - Non-inferiority of roxadustat versus epoetin alfa was declared if the upper bound of the HR 95% CI of the difference between roxadustat and epoetin alfa was less than or equal to 1.8. Non-inferiority p-value is 1-sided. The CIs were from Wald and ties were calculated using the Efron method.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of IP administration (Day 1, Week 0) to 28 days after the last administration of the IP, with treatment duration up to 4 years.

Adverse event reporting additional description:

The on-treatment+28 days safety analysis set included all participants who received at least 1 dose of randomized IP, except for those excluded from analysis. Participants were censored at 28 days after the last administration of the IP.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20.0
--------------------	------

Reporting groups

Reporting group title	Epoetin alfa
-----------------------	--------------

Reporting group description:

Participants received epoetin alfa (only use of Procrit®, Eprex® and Epogen® permitted in the study) SC or IV injection TIW, except for participants treated with epoetin alfa in a less frequent regimen prior to study entry. For participants treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was the actual dose administered at screening Visit 1. Participants treated with darbepoetin alfa or methoxy polyethylene glycol-epoetin beta prior to study entry initially received epoetin alfa at doses based on a conversion factor. For participants not treated with an erythropoietin analogue at study entry, the initial dose of epoetin alfa was 50 IU/kg TIW. Dose adjustments were to be consistent with local approved prescribing information.

Reporting group title	Roxadustat
-----------------------	------------

Reporting group description:

Participants received roxadustat tablets orally TIW throughout the treatment period (up to 4 years). For HD participants, it was recommended that roxadustat was taken after completion of the HD session. For participants treated with an erythropoietin analogue at study entry, selection of initial roxadustat dose was based on the participant's erythropoietin analogue dose at screening Visit 1. Participants not treated with an erythropoietin analogue at study entry initiated roxadustat using a tiered, weight-based dosing scheme. Doses were titrated to achieve and maintain Hb values of 11±1 g/dL. Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks using a dose adjustment algorithm.

Serious adverse events	Epoetin alfa	Roxadustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	606 / 1053 (57.55%)	604 / 1048 (57.63%)	
number of deaths (all causes)	231	247	
number of deaths resulting from adverse events	187	167	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
5q minus syndrome			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Adenocarcinoma of colon		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Adrenal neoplasm		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
B-cell lymphoma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Basal cell carcinoma		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Benign neoplasm of thyroid gland		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bladder cancer stage IV		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Bladder neoplasm		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Brain neoplasm		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Breast cancer female		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer metastatic		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cervix carcinoma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cholangiocarcinoma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Colon cancer		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Colon cancer metastatic		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Gastrointestinal carcinoma		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Gastrointestinal stromal tumour		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Invasive ductal breast carcinoma		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung adenocarcinoma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage IV		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Lung neoplasm		
subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Lung neoplasm malignant		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lymphoma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Malignant pleural effusion		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases to lung		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases to peritoneum		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Myelodysplastic syndrome		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal carcinoma		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteochondroma		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic carcinoma		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Papillary thyroid cancer		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Parathyroid tumour		

subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Parathyroid tumour benign		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Plasma cell myeloma		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Prostate cancer recurrent		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal neoplasm		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cell carcinoma		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal neoplasm		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Skin angiosarcoma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Skin cancer		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	6 / 1053 (0.57%)	6 / 1048 (0.57%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 1053 (0.09%)	4 / 1048 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis			
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bleeding varicose vein			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Blood pressure inadequately controlled		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Brachiocephalic vein occlusion		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Brachiocephalic vein stenosis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Brachiocephalic vein thrombosis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Circulatory collapse		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Deep vein thrombosis		
subjects affected / exposed	0 / 1053 (0.00%)	11 / 1048 (1.05%)
occurrences causally related to treatment / all	0 / 0	1 / 11
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic microangiopathy		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dry gangrene		

subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
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	3 / 1053 (0.28%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haematoma		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhage		
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertension		
subjects affected / exposed	12 / 1053 (1.14%)	12 / 1048 (1.15%)
occurrences causally related to treatment / all	0 / 13	1 / 16
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive crisis		
subjects affected / exposed	36 / 1053 (3.42%)	24 / 1048 (2.29%)
occurrences causally related to treatment / all	1 / 38	4 / 32
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive emergency		
subjects affected / exposed	31 / 1053 (2.94%)	24 / 1048 (2.29%)
occurrences causally related to treatment / all	1 / 33	2 / 26
deaths causally related to treatment / all	0 / 1	0 / 0
Hypotension		
subjects affected / exposed	18 / 1053 (1.71%)	17 / 1048 (1.62%)
occurrences causally related to treatment / all	0 / 20	0 / 18
deaths causally related to treatment / all	0 / 1	0 / 1
Hypovolaemic shock		

subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Iliac artery occlusion		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Jugular vein thrombosis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
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 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Orthostatic hypotension		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral arterial occlusive disease		
subjects affected / exposed	3 / 1053 (0.28%)	6 / 1048 (0.57%)
occurrences causally related to treatment / all	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery aneurysm		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery occlusion		

subjects affected / exposed	1 / 1053 (0.09%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery stenosis		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral artery thrombosis		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral ischaemia		
subjects affected / exposed	5 / 1053 (0.47%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral vascular disorder		
subjects affected / exposed	6 / 1053 (0.57%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Phlebitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Shock		
subjects affected / exposed	1 / 1053 (0.09%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0
Shock haemorrhagic		
subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1
Steal syndrome		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Superior vena cava stenosis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Superior vena cava syndrome		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thrombophlebitis		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Thrombophlebitis superficial		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular compression		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Vena cava thrombosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Venous aneurysm		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous stenosis			
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	4 / 1053 (0.38%)	5 / 1048 (0.48%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	4 / 1053 (0.38%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of device insertion			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	23 / 1053 (2.18%)	21 / 1048 (2.00%)
occurrences causally related to treatment / all	0 / 23	0 / 21
deaths causally related to treatment / all	0 / 23	0 / 21
Device related thrombosis		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Fatigue		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
General physical health deterioration		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Generalised oedema		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhagic cyst		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Impaired healing		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Inflammation		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza like illness		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Multiple organ dysfunction syndrome		
subjects affected / exposed	4 / 1053 (0.38%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 4	0 / 2
Non-cardiac chest pain		
subjects affected / exposed	9 / 1053 (0.85%)	12 / 1048 (1.15%)
occurrences causally related to treatment / all	0 / 11	1 / 15
deaths causally related to treatment / all	0 / 0	0 / 0
Oedema		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oedema peripheral		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral swelling		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pyrexia		
subjects affected / exposed	8 / 1053 (0.76%)	8 / 1048 (0.76%)
occurrences causally related to treatment / all	0 / 10	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Sudden cardiac death		
subjects affected / exposed	3 / 1053 (0.28%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 3	0 / 3
Sudden death		

subjects affected / exposed	5 / 1053 (0.47%)	6 / 1048 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 5	0 / 6	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media allergy			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis membrane reaction			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicocele			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	7 / 1053 (0.66%)	6 / 1048 (0.57%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	

Acute respiratory failure			
subjects affected / exposed	9 / 1053 (0.85%)	13 / 1048 (1.24%)	
occurrences causally related to treatment / all	0 / 10	0 / 13	
deaths causally related to treatment / all	0 / 3	0 / 4	
Aspiration			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	7 / 1053 (0.66%)	6 / 1048 (0.57%)	
occurrences causally related to treatment / all	0 / 14	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	7 / 1053 (0.66%)	9 / 1048 (0.86%)
occurrences causally related to treatment / all	0 / 9	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0
Epistaxis		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Haemoptysis		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haemothorax		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxia		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural effusion		
subjects affected / exposed	14 / 1053 (1.33%)	15 / 1048 (1.43%)
occurrences causally related to treatment / all	0 / 19	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 1
Pleurisy		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia aspiration		

subjects affected / exposed	3 / 1053 (0.28%)	7 / 1048 (0.67%)
occurrences causally related to treatment / all	0 / 3	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonitis		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pneumothorax		
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Productive cough		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary alveolar haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary artery thrombosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary congestion		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary embolism		
subjects affected / exposed	8 / 1053 (0.76%)	6 / 1048 (0.57%)
occurrences causally related to treatment / all	1 / 8	1 / 6
deaths causally related to treatment / all	1 / 3	1 / 2
Pulmonary fibrosis		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	20 / 1053 (1.90%)	10 / 1048 (0.95%)	
occurrences causally related to treatment / all	0 / 22	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	9 / 1053 (0.85%)	5 / 1048 (0.48%)	
occurrences causally related to treatment / all	0 / 9	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Respiratory tract haemorrhage			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Confusional state		
subjects affected / exposed	1 / 1053 (0.09%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Delirium		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Depression		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hallucination		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hallucination, visual		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Illusion		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Major depression		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mental status changes		

subjects affected / exposed	6 / 1053 (0.57%)	6 / 1048 (0.57%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
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 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 1053 (0.09%)	5 / 1048 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	3 / 1053 (0.28%)	5 / 1048 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			

subjects affected / exposed	1 / 1053 (0.09%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation test abnormal			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Echocardiogram abnormal			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			

subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human rhinovirus test positive			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulse absent			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respirovirus test positive			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress echocardiogram abnormal			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial fluid crystal present			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Anastomotic ulcer		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ankle fracture		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous fistula aneurysm		
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous fistula occlusion		
subjects affected / exposed	3 / 1053 (0.28%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous fistula site complication		
subjects affected / exposed	5 / 1053 (0.47%)	9 / 1048 (0.86%)
occurrences causally related to treatment / all	0 / 6	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 0
Arteriovenous fistula site haemorrhage		
subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous fistula thrombosis		
subjects affected / exposed	31 / 1053 (2.94%)	37 / 1048 (3.53%)
occurrences causally related to treatment / all	2 / 35	4 / 46
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous graft aneurysm		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous graft site stenosis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous graft thrombosis		
subjects affected / exposed	10 / 1053 (0.95%)	6 / 1048 (0.57%)
occurrences causally related to treatment / all	1 / 13	1 / 13
deaths causally related to treatment / all	0 / 0	0 / 0
Chest injury		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Clavicle fracture		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
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 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Concussion		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Contusion		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Craniocerebral injury		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Craniofacial fracture		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Extradural haematoma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Facial bones fracture		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fall		
subjects affected / exposed	6 / 1053 (0.57%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral neck fracture		
subjects affected / exposed	2 / 1053 (0.19%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Femur fracture		
subjects affected / exposed	6 / 1053 (0.57%)	6 / 1048 (0.57%)
occurrences causally related to treatment / all	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Fibula fracture		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Foot fracture		

subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Forearm fracture		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Foreign body		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fracture displacement		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Frostbite		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal stoma complication		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Graft thrombosis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemodialysis-induced symptom		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Head injury		

subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hip fracture		
subjects affected / exposed	6 / 1053 (0.57%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Humerus fracture		
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Injury		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Joint injury		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Kidney rupture		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Laceration		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Limb injury		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lower limb fracture		

subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (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 / 1053 (0.09%)	0 / 1048 (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 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle rupture		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nerve root injury		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Patella fracture		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pelvic fracture		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Perirenal haematoma		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peritoneal dialysis complication		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Post concussion syndrome		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural haematoma		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural haemorrhage		
subjects affected / exposed	4 / 1053 (0.38%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural urine leak		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative wound complication		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Procedural haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Procedural hypotension		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Procedural pain		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pubis fracture		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	3 / 1053 (0.28%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Rib fracture		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Shunt stenosis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Shunt thrombosis		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal compression fracture		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Subarachnoid haemorrhage		
subjects affected / exposed	2 / 1053 (0.19%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 2	1 / 4
deaths causally related to treatment / all	0 / 2	0 / 0
Subcutaneous haematoma		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Subdural haematoma		
subjects affected / exposed	6 / 1053 (0.57%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0
Subdural haemorrhage		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Tendon injury		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
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	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tibia fracture		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Toxicity to various agents		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Traumatic haematoma		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Ulna fracture		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	4 / 1053 (0.38%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site occlusion			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site pseudoaneurysm			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis			
subjects affected / exposed	13 / 1053 (1.23%)	16 / 1048 (1.53%)	
occurrences causally related to treatment / all	1 / 15	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular injury			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm ruptured			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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			
Fibrous dysplasia of bone			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 1053 (0.09%)	6 / 1048 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute left ventricular failure			
subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Acute myocardial infarction			
subjects affected / exposed	41 / 1053 (3.89%)	39 / 1048 (3.72%)	
occurrences causally related to treatment / all	0 / 46	3 / 49	
deaths causally related to treatment / all	0 / 9	0 / 7	
Angina pectoris			
subjects affected / exposed	8 / 1053 (0.76%)	8 / 1048 (0.76%)	
occurrences causally related to treatment / all	0 / 8	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	6 / 1053 (0.57%)	5 / 1048 (0.48%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	3 / 1053 (0.28%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 1053 (0.00%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	18 / 1053 (1.71%)	10 / 1048 (0.95%)	
occurrences causally related to treatment / all	0 / 21	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial flutter			

subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial tachycardia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial thrombosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block		
subjects affected / exposed	0 / 1053 (0.00%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block complete		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular dissociation		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bradycardia		
subjects affected / exposed	2 / 1053 (0.19%)	6 / 1048 (0.57%)
occurrences causally related to treatment / all	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Bundle branch block left		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac arrest		

subjects affected / exposed	7 / 1053 (0.66%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 4	0 / 2
Cardiac asthma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac disorder		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure		
subjects affected / exposed	10 / 1053 (0.95%)	13 / 1048 (1.24%)
occurrences causally related to treatment / all	0 / 10	0 / 14
deaths causally related to treatment / all	0 / 5	0 / 0
Cardiac failure acute		
subjects affected / exposed	5 / 1053 (0.47%)	10 / 1048 (0.95%)
occurrences causally related to treatment / all	0 / 5	0 / 11
deaths causally related to treatment / all	0 / 1	0 / 5
Cardiac failure chronic		
subjects affected / exposed	5 / 1053 (0.47%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure congestive		
subjects affected / exposed	29 / 1053 (2.75%)	24 / 1048 (2.29%)
occurrences causally related to treatment / all	0 / 43	0 / 35
deaths causally related to treatment / all	0 / 3	0 / 3
Cardiac perforation		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac tamponade		

subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac valve disease		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
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	4 / 1053 (0.38%)	7 / 1048 (0.67%)
occurrences causally related to treatment / all	0 / 4	1 / 7
deaths causally related to treatment / all	0 / 3	1 / 4
Cardiogenic shock		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2
Cardiomegaly		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiopulmonary failure		
subjects affected / exposed	4 / 1053 (0.38%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 2
Cardiovascular disorder		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Cardiovascular insufficiency		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Congestive cardiomyopathy		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cor pulmonale acute		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Coronary artery disease		
subjects affected / exposed	16 / 1053 (1.52%)	17 / 1048 (1.62%)
occurrences causally related to treatment / all	0 / 18	0 / 17
deaths causally related to treatment / all	0 / 2	0 / 1
Coronary artery stenosis		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive heart disease		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intracardiac thrombus		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Left ventricular dysfunction		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
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 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Mitral valve incompetence		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial infarction		
subjects affected / exposed	6 / 1053 (0.57%)	14 / 1048 (1.34%)
occurrences causally related to treatment / all	0 / 6	0 / 15
deaths causally related to treatment / all	0 / 2	0 / 8
Myocardial ischaemia		
subjects affected / exposed	6 / 1053 (0.57%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 3	0 / 1
Nodal arrhythmia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Palpitations		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pericardial effusion		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (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	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pericarditis uraemic		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulseless electrical activity		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Right ventricular failure		
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Sinus bradycardia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sinus node dysfunction		
subjects affected / exposed	4 / 1053 (0.38%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular extrasystoles		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular tachycardia		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tachyarrhythmia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tachycardia		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tachycardia paroxysmal		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tricuspid valve disease		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Trifascicular block		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular arrhythmia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Ventricular extrasystoles		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular fibrillation		
subjects affected / exposed	4 / 1053 (0.38%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 4	0 / 1
Ventricular hypokinesia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular tachycardia		

subjects affected / exposed	4 / 1053 (0.38%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 1053 (0.00%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia haemorrhage			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain injury			
subjects affected / exposed	0 / 1053 (0.00%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain oedema			
subjects affected / exposed	0 / 1053 (0.00%)	4 / 1048 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Brain stem stroke			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery aneurysm			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Carotid artery stenosis		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral haemorrhage		
subjects affected / exposed	2 / 1053 (0.19%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 2
Cerebral infarction		
subjects affected / exposed	4 / 1053 (0.38%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 4	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral ischaemia		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral small vessel ischaemic disease		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebrovascular accident		
subjects affected / exposed	12 / 1053 (1.14%)	14 / 1048 (1.34%)
occurrences causally related to treatment / all	0 / 12	1 / 14
deaths causally related to treatment / all	0 / 5	0 / 1
Cerebrovascular insufficiency		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cervical cord compression		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cognitive disorder		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Coma		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic hyperglycaemic coma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Dizziness		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Embolic stroke		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalopathy		
subjects affected / exposed	6 / 1053 (0.57%)	8 / 1048 (0.76%)
occurrences causally related to treatment / all	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Epilepsy		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Generalised tonic-clonic seizure		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhage intracranial		
subjects affected / exposed	2 / 1053 (0.19%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 1
Haemorrhagic stroke		
subjects affected / exposed	6 / 1053 (0.57%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 5	0 / 2
Headache		
subjects affected / exposed	1 / 1053 (0.09%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiparesis		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hydrocephalus		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive encephalopathy		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoglycaemic encephalopathy		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Hypoxic-ischaemic encephalopathy		

subjects affected / exposed	4 / 1053 (0.38%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Intracranial aneurysm		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intracranial haematoma		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Ischaemic stroke		
subjects affected / exposed	11 / 1053 (1.04%)	10 / 1048 (0.95%)
occurrences causally related to treatment / all	0 / 12	1 / 10
deaths causally related to treatment / all	0 / 2	0 / 2
Lacunar infarction		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lacunar stroke		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar radiculopathy		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolic encephalopathy		
subjects affected / exposed	3 / 1053 (0.28%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Myoclonus		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Partial seizures		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Polyneuropathy		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Posterior reversible encephalopathy syndrome		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Postresuscitation encephalopathy		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Presyncope		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sciatic nerve neuropathy		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sciatica		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Seizure		

subjects affected / exposed	7 / 1053 (0.66%)	13 / 1048 (1.24%)
occurrences causally related to treatment / all	0 / 7	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal cord compression		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Subdural hygroma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Syncope		
subjects affected / exposed	11 / 1053 (1.04%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	1 / 13	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Tardive dyskinesia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tonic convulsion		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Toxic encephalopathy		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transient ischaemic attack		
subjects affected / exposed	6 / 1053 (0.57%)	10 / 1048 (0.95%)
occurrences causally related to treatment / all	0 / 6	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0
Vertebral artery stenosis		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
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	1 / 1053 (0.09%)	0 / 1048 (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	2 / 1053 (0.19%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aplasia pure red cell			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow reticulin fibrosis			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hilar lymphadenopathy			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			

subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery embolism			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
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	2 / 1053 (0.19%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	10 / 1053 (0.95%)	10 / 1048 (0.95%)	
occurrences causally related to treatment / all	0 / 10	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 1053 (0.00%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall mass			

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Acute abdomen		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ascites		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic gastritis		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis		
subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis ischaemic		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Constipation		
subjects affected / exposed	0 / 1053 (0.00%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Dental caries		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic gastroparesis		

subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Diarrhoea		
subjects affected / exposed	7 / 1053 (0.66%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticular perforation		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulum intestinal		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer		
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer perforation		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenitis		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dyspepsia		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Enteritis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Enterocolitis haemorrhagic		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enterocutaneous fistula		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Erosive duodenitis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Faecaloma		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Faeces discoloured		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Flatulence		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Food poisoning		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric disorder		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric haemorrhage		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Gastric ulcer		
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer haemorrhage		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
subjects affected / exposed	5 / 1053 (0.47%)	11 / 1048 (1.05%)
occurrences causally related to treatment / all	0 / 5	1 / 15
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis erosive		
subjects affected / exposed	4 / 1053 (0.38%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis haemorrhagic		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroduodenitis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal erosion		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal haemorrhage		
subjects affected / exposed	21 / 1053 (1.99%)	22 / 1048 (2.10%)
occurrences causally related to treatment / all	0 / 25	1 / 24
deaths causally related to treatment / all	0 / 0	0 / 2
Gastrointestinal perforation		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Gastrointestinal polyp haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 1053 (0.09%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Haematemesis		
subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhagic erosive gastritis		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhoidal haemorrhage		
subjects affected / exposed	4 / 1053 (0.38%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhoids		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	1 / 1053 (0.09%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus paralytic		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Impaired gastric emptying		
subjects affected / exposed	4 / 1053 (0.38%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 4	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Incarcerated inguinal hernia		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Inflammatory bowel disease		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Inguinal hernia		

subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal ischaemia		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal metaplasia		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal obstruction		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal perforation		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intra-abdominal haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestine polyp		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower gastrointestinal haemorrhage		

subjects affected / exposed	2 / 1053 (0.19%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Malabsorption		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Mallory-Weiss syndrome		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Melaena		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nausea		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal motility disorder		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophagitis		
subjects affected / exposed	1 / 1053 (0.09%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic disorder		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic necrosis		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis		
subjects affected / exposed	1 / 1053 (0.09%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis acute		
subjects affected / exposed	5 / 1053 (0.47%)	6 / 1048 (0.57%)
occurrences causally related to treatment / all	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 3
Pancreatitis chronic		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Peptic ulcer haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritoneal haemorrhage		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Proctitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal haemorrhage		

subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	8 / 1053 (0.76%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 9	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	9 / 1053 (0.85%)	8 / 1048 (0.76%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	5 / 1053 (0.47%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dyskinesia			

subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholangitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis		
subjects affected / exposed	4 / 1053 (0.38%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis acute		
subjects affected / exposed	6 / 1053 (0.57%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis chronic		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholelithiasis		
subjects affected / exposed	0 / 1053 (0.00%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Drug-induced liver injury		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic cirrhosis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disease			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ulcer			

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Drug reaction with eosinophilia and systemic symptoms		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ecchymosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pruritus		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rash		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Red man syndrome		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Skin ulcer		
subjects affected / exposed	6 / 1053 (0.57%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Stevens-Johnson syndrome		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Toxic epidermal necrolysis		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	11 / 1053 (1.04%)	13 / 1048 (1.24%)	
occurrences causally related to treatment / all	0 / 12	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 5	
Calculus urinary			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 1053 (0.09%)	7 / 1048 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 7	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysuria			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			

subjects affected / exposed	1 / 1053 (0.09%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 4
Glomerulonephritis chronic		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Haematuria		
subjects affected / exposed	4 / 1053 (0.38%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hydronephrosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nephrolithiasis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cyst		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cyst haemorrhage		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cyst ruptured		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal failure		

subjects affected / exposed	4 / 1053 (0.38%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Renal haematoma			
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 1053 (0.09%)	5 / 1048 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism secondary			
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism tertiary			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 1053 (0.19%)	5 / 1048 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calcification of muscle			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	4 / 1053 (0.38%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle haemorrhage		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle spasms		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	3 / 1053 (0.28%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		
subjects affected / exposed	4 / 1053 (0.38%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal pain		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Myalgia		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neuropathic arthropathy		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteitis deformans		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthritis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteochondritis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteochondrosis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pain in extremity		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rhabdomyolysis		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Soft tissue necrosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal column stenosis		

subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal ligament ossification			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Abscess of salivary gland		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abscess soft tissue		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Acute endocarditis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Appendicitis		
subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Appendicitis perforated		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriosclerotic gangrene		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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 infection		
subjects affected / exposed	3 / 1053 (0.28%)	6 / 1048 (0.57%)
occurrences causally related to treatment / all	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriovenous graft site infection		

subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Arthritis bacterial		
subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arthritis infective		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bacteraemia		
subjects affected / exposed	2 / 1053 (0.19%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial colitis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial infection		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial pyelonephritis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial sepsis		
subjects affected / exposed	1 / 1053 (0.09%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Bacteriuria		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Balanoposthitis infective		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bone tuberculosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis		
subjects affected / exposed	5 / 1053 (0.47%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0
Campylobacter colitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Candida pneumonia		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Catheter site abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Catheter site infection		
subjects affected / exposed	1 / 1053 (0.09%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Cellulitis		

subjects affected / exposed	16 / 1053 (1.52%)	12 / 1048 (1.15%)
occurrences causally related to treatment / all	0 / 18	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0
Cellulitis of male external genital organ		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic hepatitis C		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic tonsillitis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Citrobacter sepsis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Clostridium difficile colitis		
subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Clostridium difficile infection		

subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cystitis		
subjects affected / exposed	0 / 1053 (0.00%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Device related infection		
subjects affected / exposed	11 / 1053 (1.04%)	11 / 1048 (1.05%)
occurrences causally related to treatment / all	0 / 15	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0
Device related sepsis		
subjects affected / exposed	7 / 1053 (0.66%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic foot infection		
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic gangrene		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diarrhoea infectious		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulitis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
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 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Endocarditis		
subjects affected / exposed	2 / 1053 (0.19%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1
Endocarditis bacterial		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Endophthalmitis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
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 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Erysipelas		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia bacteraemia		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia urinary tract infection		

subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Fungal infection		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fungal peritonitis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fungal sepsis		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gangrene		
subjects affected / exposed	11 / 1053 (1.04%)	9 / 1048 (0.86%)
occurrences causally related to treatment / all	0 / 13	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Gas gangrene		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	6 / 1053 (0.57%)	11 / 1048 (1.05%)
occurrences causally related to treatment / all	0 / 6	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis aeromonas		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis bacterial		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis viral		
subjects affected / exposed	3 / 1053 (0.28%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal bacterial infection		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal infection		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal viral infection		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Graft infection		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
HIV infection		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Helicobacter gastritis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis B		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis C		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Herpes zoster		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Herpes zoster infection neurological		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Implant site cellulitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infected cyst		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infected fistula		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Infected seroma		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infected skin ulcer		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infection		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infectious pleural effusion		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infective exacerbation of bronchiectasis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza		
subjects affected / exposed	2 / 1053 (0.19%)	5 / 1048 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral discitis		
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Joint abscess		

subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Labyrinthitis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Localised infection		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection viral		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lyme disease		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
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	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mycobacterium abscessus infection		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Necrotising fasciitis		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Neurocysticercosis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal candidiasis		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
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	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis		
subjects affected / exposed	10 / 1053 (0.95%)	10 / 1048 (0.95%)
occurrences causally related to treatment / all	0 / 10	0 / 17
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis acute		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Otitis media		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Parainfluenzae virus infection		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Parasitic gastroenteritis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Paraspinal abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pelvic abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Perineal abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Periorbital cellulitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonitis		
subjects affected / exposed	24 / 1053 (2.28%)	24 / 1048 (2.29%)
occurrences causally related to treatment / all	0 / 37	0 / 28
deaths causally related to treatment / all	0 / 0	0 / 1
Peritonsillar abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pilonidal cyst		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	78 / 1053 (7.41%)	70 / 1048 (6.68%)
occurrences causally related to treatment / all	0 / 92	1 / 80
deaths causally related to treatment / all	0 / 5	0 / 4
Pneumonia bacterial		
subjects affected / exposed	3 / 1053 (0.28%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia respiratory syncytial viral		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia staphylococcal		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia streptococcal		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pneumonia viral		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative wound infection		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary tuberculosis		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pyelonephritis		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis acute		
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis chronic		
subjects affected / exposed	1 / 1053 (0.09%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Pyonephrosis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory syncytial virus infection		
subjects affected / exposed	2 / 1053 (0.19%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection		

subjects affected / exposed	7 / 1053 (0.66%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection viral		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Retroperitoneal abscess		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rhinovirus infection		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	40 / 1053 (3.80%)	40 / 1048 (3.82%)
occurrences causally related to treatment / all	0 / 46	0 / 44
deaths causally related to treatment / all	0 / 12	0 / 12
Septic embolus		
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1
Septic encephalopathy		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Septic shock		
subjects affected / exposed	13 / 1053 (1.23%)	12 / 1048 (1.15%)
occurrences causally related to treatment / all	0 / 15	0 / 13
deaths causally related to treatment / all	0 / 9	0 / 6
Shunt infection		

subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Skin infection		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal bacteraemia		
subjects affected / exposed	0 / 1053 (0.00%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal infection		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal osteomyelitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Staphylococcal sepsis		
subjects affected / exposed	3 / 1053 (0.28%)	4 / 1048 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 0
Stenotrophomonas infection		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Systemic viral infection		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tetanus		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tonsillitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tracheobronchitis		
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tuberculosis		
subjects affected / exposed	3 / 1053 (0.28%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection		
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		
subjects affected / exposed	13 / 1053 (1.23%)	8 / 1048 (0.76%)
occurrences causally related to treatment / all	0 / 13	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Urosepsis		
subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Varicella		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (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	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Viral infection		
subjects affected / exposed	4 / 1053 (0.38%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Viral pericarditis		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Viral upper respiratory tract infection		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vulval abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Vulval cellulitis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Vulvovaginal candidiasis		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Wound abscess		
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Wound infection		

subjects affected / exposed	3 / 1053 (0.28%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Adult failure to thrive			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calciphylaxis			
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 1053 (0.09%)	2 / 1048 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 1053 (0.19%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 1053 (0.09%)	0 / 1048 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	3 / 1053 (0.28%)	7 / 1048 (0.67%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

subjects affected / exposed	29 / 1053 (2.75%)	32 / 1048 (3.05%)
occurrences causally related to treatment / all	0 / 35	0 / 55
deaths causally related to treatment / all	0 / 0	0 / 1
Fluid retention		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gout		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypercalcaemia		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemia		
subjects affected / exposed	2 / 1053 (0.19%)	8 / 1048 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome		
subjects affected / exposed	0 / 1053 (0.00%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperkalaemia		
subjects affected / exposed	21 / 1053 (1.99%)	27 / 1048 (2.58%)
occurrences causally related to treatment / all	0 / 26	0 / 32
deaths causally related to treatment / all	0 / 2	0 / 2
Hyperphosphataemia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypervolaemia		

subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypocalcaemia		
subjects affected / exposed	2 / 1053 (0.19%)	2 / 1048 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoglycaemia		
subjects affected / exposed	11 / 1053 (1.04%)	19 / 1048 (1.81%)
occurrences causally related to treatment / all	0 / 11	0 / 22
deaths causally related to treatment / all	0 / 0	0 / 0
Hypokalaemia		
subjects affected / exposed	2 / 1053 (0.19%)	3 / 1048 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hyponatraemia		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypovolaemia		
subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Malnutrition		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolic acidosis		
subjects affected / exposed	4 / 1053 (0.38%)	0 / 1048 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0
Type 1 diabetes mellitus		

subjects affected / exposed	1 / 1053 (0.09%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Type 2 diabetes mellitus		
subjects affected / exposed	0 / 1053 (0.00%)	1 / 1048 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Epoetin alfa	Roxadustat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	799 / 1053 (75.88%)	826 / 1048 (78.82%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	85 / 1053 (8.07%)	85 / 1048 (8.11%)	
occurrences (all)	124	130	
Hypotension			
subjects affected / exposed	54 / 1053 (5.13%)	64 / 1048 (6.11%)	
occurrences (all)	83	79	
Nervous system disorders			
Headache			
subjects affected / exposed	56 / 1053 (5.32%)	79 / 1048 (7.54%)	
occurrences (all)	85	91	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	101 / 1053 (9.59%)	114 / 1048 (10.88%)	
occurrences (all)	153	159	
Nausea			
subjects affected / exposed	65 / 1053 (6.17%)	61 / 1048 (5.82%)	
occurrences (all)	94	72	
Vomiting			
subjects affected / exposed	52 / 1053 (4.94%)	60 / 1048 (5.73%)	
occurrences (all)	64	69	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	62 / 1053 (5.89%) 76	61 / 1048 (5.82%) 77	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	61 / 1053 (5.79%) 95	43 / 1048 (4.10%) 67	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	54 / 1053 (5.13%) 77	70 / 1048 (6.68%) 102	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2014	<p>Roxadustat dosing and dose adjustment: 120 mg start dose, and 120 mg and 350 mg dose steps removed. Roxadustat dosing algorithm: 0.8 changed to 1.0. Single dose adjustment algorithm used throughout treatment period. Dose cap reduced from lower of 3.5 mg/kg or 400 mg to 3.0 mg/kg or 400 mg. Definition of excessive erythropoiesis simplified. Visit 1 changed to a phone call. Removed visits at Week 3, 5, and 7. Visits every 4 weeks after Week 52. Visit window from ± 2 days to -4 days to 2 days. Inclusion criteria #5 and #6: Ferritin raised to ≥ 100 ng/mL and transferrin saturation raised to $\geq 20\%$. Exclusion criteria #3 deleted, #9 changed from Bosniak category II to IIF, #10 added definition of uncontrolled hypertension in dialysis subjects, and #13 added "that is determined to be principal cause of anemia". Replaced statins text: "When coadministered with roxadustat, hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) exposure was increased 2- to 3-fold. Investigators should consider this interaction and local prescribing information when deciding on appropriate statin dose for individual participants, bearing in mind impact of ethnicity, other concomitant medications, renal and hepatic function. Recommended maximum daily statin doses are: simvastatin 20 mg, atorvastatin 40 mg, rosuvastatin 10 mg, pravastatin 40 mg, fluvastatin 40 mg (20 mg if estimated glomerular filtration rate (eGFR) <30), pitavastatin 2 mg (1 mg if eGFR <30.)". Euro quality of life health utility index continued every 24 weeks after Week 52 and added at next visit after composite safety endpoint (CSE) event. Removed annual study discontinuation rate of 8.5% and changed estimated time to 1.4 years instead of 1.5 years. Study center number changed from 400 to approximately 250. Priority of secondary objectives changed: rescue therapy placed before self reported health status. Changed ANCOVA to MMRM for efficacy analysis. "Recombinant erythropoietin" replaced with "erythropoietin analogue".</p>
19 September 2018	<p>Previous primary efficacy objective and its outcome measures is designated for US FDA. A second outcome measure designated for the EU health authority (Hb change from baseline to average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period) was added. Added that hepcidin and hsCRP were to be analyzed from biomarker samples. Full Analysis Set: renamed as "ITT Analysis Set", and text revised to clarify how event of interest will be counted in respect of IP discontinuation according to ITT principle. "Patients" changed to "subjects" throughout corresponding protocol section (Section 8). Per Protocol Set: an additional criterion was added ("participants receiving at least 8 weeks of study treatment"), censoring rules for participants with an important protocol deviation were clarified, and the treatment groups to which PPS participants belong were specified. Full Analysis Set: section newly created allowing for an additional analysis set. Participants who will not be included in any analysis set: section newly created to specify participants not included in any analysis set, and their reason for exclusion. Primary efficacy endpoint text changed as follows: A new subsection with 2 parts, one for the US FDA and other for the EU health authority was created. Secondary efficacy endpoints changed as follows: Endpoint for time to first RBC transfusion or erythropoiesis stimulating agent as rescue therapy was changed to exploratory endpoint. Additional endpoints related to Hb response, lipid reduction, RBC rescue therapy use, and IV iron use were added. Primary safety objective/additional safety composite endpoints changed as follows: A new section entitled "Adjudicated CV Events Analyses for Safety Assessments" was created. Time to event analyses including time to first major adverse CV events+, time to first CSE, and time to first rescue therapy (composite) were removed.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

27 participants were excluded from the analysis due to GCP violations or system technical issues (17 in the roxadustat group and 10 in the epoetin alfa group).

Notes: