



Clinical trial results:

Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 µg Once-Every-3-Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy

Summary

EudraCT number	2007-005792-34
Trial protocol	GB IE CZ AT BE ES DE NL GR IT SI BG
Global end of trial date	07 June 2017

Results information

Result version number	v1 (current)
This version publication date	23 June 2018
First version publication date	23 June 2018

Trial information

Trial identification

Sponsor protocol code	20070782
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00858364
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	07 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate non-inferiority of overall survival (OS) when comparing subjects on darbeopetin alfa treated to a hemoglobin ceiling of 12.0 g/dL to subjects treated with placebo.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material was submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form was to be received by Amgen before recruitment of subjects into the study and shipment of investigational product.

The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy:

Participants were receiving cyclic chemotherapy for the treatment of NSCLC.

Evidence for comparator: -

Actual start date of recruitment	17 July 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	94 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Greece: 53
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Luxembourg: 2
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Bulgaria: 34
Country: Number of subjects enrolled	Czech Republic: 90

Country: Number of subjects enrolled	Poland: 61
Country: Number of subjects enrolled	Romania: 51
Country: Number of subjects enrolled	Russian Federation: 118
Country: Number of subjects enrolled	Serbia: 41
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Ukraine: 279
Country: Number of subjects enrolled	Argentina: 27
Country: Number of subjects enrolled	Brazil: 173
Country: Number of subjects enrolled	Chile: 64
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Mexico: 39
Country: Number of subjects enrolled	Philippines: 143
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	India: 509
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 292
Country: Number of subjects enrolled	China: 372
Country: Number of subjects enrolled	Japan: 16
Worldwide total number of subjects	2549
EEA total number of subjects	390

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)	1496
From 65 to 84 years	1039
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 371 centers in Europe, Latin America, Asia, India, North America, Israel, and South Africa.

Pre-assignment

Screening details:

Eligible subjects were randomized to darbepoetin alfa or placebo in a 2:1 ratio. Randomization was stratified by histology (squamous vs other), screening hemoglobin (< 10.0 g/dL vs ≥ 10.0 g/dL), and geographic region.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously once every 3 weeks

Arm title	Darbepoetin alfa
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Arm description:

Participants received darbepoetin alfa 500 µg once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Darbepoetin alfa
Investigational medicinal product code	
Other name	Aranesp®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously once every 3 weeks

Number of subjects in period 1	Placebo	Darbepoetin alfa
Started	846	1703
Received Study Drug	837	1681
Completed	642	1246
Not completed	204	457
Consent withdrawn by subject	44	118
Administrative decision	3	2
Protocol Deviation	-	2
Other	9	17
Adverse event	5	2
Participants still on-study	114	247
Ineligibility determined	1	10
Lost to follow-up	24	54
Missing	1	1
Noncompliance	3	4

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.	
Reporting group title	Darbepoetin alfa
Reporting group description:	
Participants received darbepoetin alfa 500 µg once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.	

Reporting group values	Placebo	Darbepoetin alfa	Total
Number of subjects	846	1703	2549
Age Categorical			
Units: Subjects			
18 - 64 years	482	1014	1496
65 - 74 years	287	547	834
75 - 84 years	71	134	205
≥ 85 years	6	8	14
Age Continuous			
Units: years			
arithmetic mean	62.2	61.6	
standard deviation	± 9.9	± 9.8	-
Gender Categorical			
Units: Subjects			
Female	281	585	866
Male	565	1118	1683
Race			
Units: Subjects			
White or Caucasian	404	808	1212
Black or African American	27	46	73
Asian	357	741	1098
Japanese	7	12	19
Native Hawaiian or Other Pacific Islander	1	0	1
Aborigine	0	1	1
Other	5	14	19
Hispanic	45	81	126
Geographic Region			
Stratification factor at the time of randomization. Data are reported for the primary analysis set (all randomized and consented subjects with NSCLC who received at least 1 dose of investigational product).			
Units: Subjects			
Western Europe, Israel and South Africa	54	108	162
Central and Eastern Europe	220	451	671
Latin America and Asia	166	337	503
India	168	339	507
North America	99	192	291

China	123	243	366
Japan	6	10	16
Participants not in primary analysis set	10	23	33
Histology			
Stratification factor at the time of randomization. Data are reported for the primary analysis set.			
Units: Subjects			
Squamous	289	589	878
Non-squamous	547	1091	1638
Participants not in primary analysis set	10	23	33
Screening Hemoglobin			
Stratification factor at the time of randomization. Data are reported for the primary analysis set.			
Units: Subjects			
< 10 g/dL	433	870	1303
≥ 10 g/dL	403	810	1213
Participants not in primary analysis set	10	23	33

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received placebo once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.	
Reporting group title	Darbepoetin alfa
Reporting group description: Participants received darbepoetin alfa 500 µg once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.	

Primary: Overall survival (OS)

End point title	Overall survival (OS)
End point description: Overall survival (OS) was defined as the time from randomization to the date of death due to any cause. Participants were censored on the date of last contact (ie, the date the participant was last known to be alive) if they were not known to have died. The analysis was conducted in the primary analysis set which consisted of all randomized and consented participants with non-small cell lung cancer who received at least one dose of study drug.	
End point type	Primary
End point timeframe: From randomization until death or end of study; a maximum follow-up time was 93.6 months.	

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	836	1680		
Units: months				
median (confidence interval 95%)	9.260 (8.250 to 10.020)	9.460 (8.900 to 10.120)		

Statistical analyses

Statistical analysis title	Primary Analysis of overall Survival
Statistical analysis description: The primary analysis used the Cox Proportional Hazard Model stratified by the randomization stratification factors (geographic region, histology, and screening hemoglobin), with treatment group as the only covariate. A hazard ratio < 1.0 indicates a lower risk of death for Darbepoetin Alfa relative to Placebo.	
Comparison groups	Placebo v Darbepoetin alfa

Number of subjects included in analysis	2516
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.01

Notes:

[1] - Non-inferiority was declared if the upper confidence limit for the hazard ratio (darbepoetin alfa to placebo) was less than 1.15 using a 1-sided significance level of 0.025.

Statistical analysis title	Sensitivity Analysis - Unstratified Model
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Statistical analysis description:

As a sensitivity analysis, an unstratified Cox Proportional Hazard Model with treatment group as the only covariate was conducted. A hazard ratio < 1.0 indicates a lower risk of death for darbepoetin alfa relative to placebo.

Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2516
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1

Notes:

[2] - Non-inferiority was declared if the upper confidence limit for the hazard ratio (darbepoetin alfa to placebo) was less than 1.15 using a 1-sided significance level of 0.025.

Statistical analysis title	Superiority Analysis (Stratified)
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2516
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.07 ^[4]
Method	Stratified log-rank test

Notes:

[3] - If non-inferiority was demonstrated for both OS and PFS and superiority was demonstrated for the transfusion endpoint, superiority was then tested for both OS and PFS using the Hochberg procedure to adjust for multiplicity.

[4] - Stratified by the randomization stratification factors (geographic region, histology, screening hemoglobin).

Statistical analysis title	Superiority Analysis (Unstratified)
Comparison groups	Placebo v Darbepoetin alfa

Number of subjects included in analysis	2516
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 ^[5]
Method	Logrank

Notes:

[5] - Unstratified log rank test

Statistical analysis title	OS Adjusted for Cross-in
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Statistical analysis description:

To evaluate the potential effect of cross-in (participants in the placebo group who began treatment with an erythropoiesis-stimulating agent (ESA) at any point after randomization), a sensitivity analysis was conducted that included ESA use as a time-dependent covariate in a Cox regression model stratified by the randomization stratification factors (geographic region, histology, and screening hemoglobin).

Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2516
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.02

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
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End point description:

Progression-free survival was defined as the time from randomization to the date of radiographic disease progression or death from any cause, whichever event occurred first. Participants without either event were censored on the date of their last disease assessment. Disease progression was based on the investigator's assessment of scans using the version of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The analysis was conducted in the radiographic endpoint primary analysis set which included all participants in the primary analysis set who did not have disease progression prior to randomization.

End point type	Secondary
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End point timeframe:

From randomization until disease progression or death; maximum time on follow-up was 87.23 months.

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	819	1638		
Units: months				
median (confidence interval 95%)	4.340 (4.170 to 4.700)	4.800 (4.370 to 5.320)		

Statistical analyses

Statistical analysis title	Primary Analysis of Progression-free Survival
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Statistical analysis description:

The primary analysis of PFS used a Cox Proportional Hazard Model stratified by the randomization stratification factors (geographic region, histology, and screening hemoglobin), with treatment group as the only covariate.

A hazard ratio < 1.0 indicates a lower risk of death or progression for darbepoetin alfa relative to placebo.

Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2457
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[6]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.04

Notes:

[6] - If non-inferiority was declared for OS, non-inferiority would be declared for PFS if the upper confidence limit for the hazard ratio was less than 1.15 using a 1-sided significance level of 0.025.

Statistical analysis title	Sensitivity Analysis - Unstratified Model
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Statistical analysis description:

As a sensitivity analysis, an unstratified Cox Proportional Hazard Model with treatment group as the only covariate was conducted.

A hazard ratio < 1.0 indicates a lower risk of death or progression for darbepoetin alfa relative to placebo.

Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2457
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.04

Notes:

[7] - If non-inferiority was declared for OS, non-inferiority would be declared for PFS if the upper confidence limit for the hazard ratio was less than 1.15 using a 1-sided significance level of 0.025.

Statistical analysis title	Superiority Analysis (Stratified)
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Statistical analysis description:

If non-inferiority was demonstrated for both OS and PFS and superiority was demonstrated for the

transfusion endpoint, superiority was then tested for both OS and PFS using the Hochberg procedure to adjust for multiplicity.

Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 ^[8]
Method	Stratified log-rank test

Notes:

[8] - Stratified by the randomization stratification factors (geographic region, histology, screening hemoglobin).

Statistical analysis title	Superiority Analysis (Unstratified)
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27 ^[9]
Method	Logrank

Notes:

[9] - Unstratified log rank test

Statistical analysis title	PFS Adjusted for Cross-in
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Statistical analysis description:

To evaluate the potential effect of cross-in (participants in the placebo group who began treatment with an erythropoiesis-stimulating agent (ESA) at any point after randomization), a sensitivity analysis was conducted that included ESA use as a time-dependent covariate in a Cox regression model stratified by the randomization stratification factors (geographic region, histology, and screening hemoglobin).

Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2457
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.05

Secondary: Percentage of Participants with a Red Blood Cell Transfusion or Hemoglobin \leq 8.0 g/dL From Week 5 to End of the Efficacy Treatment Period

End point title	Percentage of Participants with a Red Blood Cell Transfusion or Hemoglobin \leq 8.0 g/dL From Week 5 to End of the Efficacy Treatment Period
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End point description:

Any red blood cell (RBC) transfusion (packed RBCs or whole blood) given or a hemoglobin \geq 8.0 g/dL on or after study day 29 until the EOETP, inclusive.

The analysis was conducted in primary analysis set participants who were on study as of day 29.

End point type	Secondary
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End point timeframe:

Week 5 (day 29) to end of the efficacy treatment period (EOETP; defined as 21 days after either the last dose of study drug or the last dose of chemotherapy, whichever was later); median (range) duration of dosing was 10 (1 to 106) weeks in both groups.

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	764	1517		
Units: percentage of participants				
number (not applicable)	29.2	22.5		

Statistical analyses

Statistical analysis title	Analysis of Transfusion or Hemoglobin \leq 8.0 g/dL
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Statistical analysis description:

The primary analysis of the incidence of a transfusion or hemoglobin \leq 8.0 g/dL from day 29 to EOETP was based on the Cochran-Mantel-Haenszel method to test for treatment group differences while adjusting for the randomization stratification factors (geographic region, histology, and screening hemoglobin).

An odds ratio < 1.0 indicates a lower event rate for darbepoetin alfa relative to placebo.

Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2281
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.704
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.573
upper limit	0.864

Notes:

[10] - If non-inferiority was declared for OS and PFS, superiority would be declared for the transfusion endpoint if the p-value from a two-sided test of significance using the Cochran-Mantel-Haenszel method was less than 0.05 in favor of the darbepoetin alfa group.

Statistical analysis title	Sensitivity Analysis - Logistic Regression
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Statistical analysis description:

As a sensitivity analysis a logistic regression analysis was conducted, stratified by the randomization stratification factors (geographic region, histology, screening hemoglobin). An odds ratio < 1.0 indicates a lower event rate for darbepoetin alfa relative to placebo.

Comparison groups	Placebo v Darbepoetin alfa
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Number of subjects included in analysis	2281
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.705
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.574
upper limit	0.866

Secondary: Number of Participants with Adverse Events of Special Interest

End point title	Number of Participants with Adverse Events of Special Interest
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End point description:

Adverse events of interest for darbepoetin alfa, based on clinical data in anemic patients with cancer to date, included the following categories: antibody-mediated pure red cell aplasia (PRCA), cardiac failure, central nervous system vascular disorders, convulsions, embolic and thrombotic events, hypersensitivity, hypertension, ischemic heart disease, malignancies, and severe cutaneous adverse reactions. Lack of efficacy and medication errors were also evaluated.

The analysis was conducted in all randomized and consented participants who received at least 1 dose of study drug. Four participants in the placebo group received at least 1 dose of darbepoetin alfa during the study and were included in the darbepoetin alfa group for safety analyses.

End point type	Secondary
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End point timeframe:

From first dose of study drug until 30 days after last dose; the median (range) duration of treatment was 10 (1 to 106) weeks in both groups.

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	833	1685		
Units: participants				
Any adverse events of interest	157	369		
Antibody-mediated pure red cell aplasia	20	51		
Cardiac failure	7	12		
Central nervous system vascular disorders	8	25		
Convulsions	8	9		
Embolic and thrombotic events	34	89		
Embolic and thrombotic events, arterial	6	19		
Embolic and thrombotic events, venous	23	51		
Embolic and thrombotic events, unspecified/mixed	10	26		
Hypersensitivity	75	178		
Hypertension	26	41		
Ischaemic heart disease	9	23		
Lack of efficacy/effect	0	0		

Malignancies	16	38		
Medication errors	0	1		
Severe cutaneous adverse reactions	11	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Objective Tumor Response

End point title	Percentage of Participants with an Objective Tumor Response
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End point description:

Objective response was defined as the incidence of a complete or partial response at any time during the study. Response was determined by the investigator's assessment of the scans using RECIST version 1.0 or 1.1 depending on the timing of enrollment.

The analysis was conducted in the radiographic endpoint primary analysis set which included all participants in the primary analysis set who did not have disease progression prior to randomization.

End point type	Secondary
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End point timeframe:

Day 1 to end of the efficacy treatment period (EOETP; defined as 21 days after either the last dose of study drug or the last dose of chemotherapy, whichever was later); median (range) duration of dosing was 10 (1 to 106) weeks in both groups.

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	819	1638		
Units: percentage of participants				
number (not applicable)	32.6	36.2		

Statistical analyses

Statistical analysis title	Stratified Analysis of Objective Response
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2457
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.076 ^[11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.983
upper limit	1.401

Notes:

[11] - Cochran-Mantel-Haenszel method adjusted for the randomization stratification factors (geographic region, histology, screening hemoglobin).

Statistical analysis title	Unstratified Analysis of Objective Response
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2457
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.078 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.982
upper limit	1.401

Notes:

[12] - Unstratified analysis

Secondary: Number of Participants who Developed Neutralizing Antibodies to Darbepoetin Alfa

End point title	Number of Participants who Developed Neutralizing Antibodies to Darbepoetin Alfa
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End point description:

Developing antibody incidence was defined as neutralizing antibody positive postbaseline with a negative or no result at baseline.

The analysis was conducted in all randomized and consented participants who received at least one dose of study drug and with a postbaseline result.

End point type	Secondary
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End point timeframe:

Baseline and end of the efficacy treatment period (EOETP; defined as 21 days after either the last dose of study drug or the last dose of chemotherapy, whichever was later. the median (range) duration of treatment was 10 (1 to 106) weeks in both groups.

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	803	1606		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Red Blood Cell Transfusion or Hemoglobin \leq 8.0 g/dL From Week 1 to End of the Efficacy Treatment Period

End point title	Percentage of Participants with a Red Blood Cell Transfusion or Hemoglobin \leq 8.0 g/dL From Week 1 to End of the Efficacy Treatment Period
End point description: Any red blood cell (RBC) transfusion (packed RBCs or whole blood) given or a hemoglobin \leq 8.0 g/dL on or after study day 1 until the EOETP, inclusive. The analysis was conducted in the primary analysis set.	
End point type	Secondary
End point timeframe: Week 1 to end of the efficacy treatment period (EOETP; defined as 21 days after either the last dose of study drug or the last dose of chemotherapy, whichever was later); the median (range) duration of treatment was 10 (1 to 106) weeks in both groups.	

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	836	1680		
Units: percentage of participants				
number (not applicable)	29.7	24.2		

Statistical analyses

Statistical analysis title	Stratified Analysis
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2516
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 ^[13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.741
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.901

Notes:

[13] - Cochran-Mantel-Haenszel method adjusted for the randomization stratification factors (geographic region, histology, screening hemoglobin).

Statistical analysis title	Unstratified Analysis
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	2516
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.758

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.913

Secondary: Change from Baseline in Hemoglobin to End of Efficacy Treatment Period

End point title	Change from Baseline in Hemoglobin to End of Efficacy Treatment Period
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End point description:

Post-baseline hemoglobin values within 28 days after a RBC transfusion were not be used in the calculation of change.

The analysis was conducted in the primary analysis set with available baseline and at least 1 postbaseline value; if the EOETP value was missing, the last available postbaseline value was used.

End point type	Secondary
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End point timeframe:

Baseline and end of the efficacy treatment period (EOETP; defined as 21 days after either the last dose of study drug or the last dose of chemotherapy, whichever was later); the median (range) duration of treatment was 10 (1 to 106) weeks in both groups.

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	633	1344		
Units: g/dL				
arithmetic mean (standard deviation)	-0.11 (± 1.71)	0.50 (± 1.81)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days after last dose; the median (range) duration of treatment was 10 (1 to 106) weeks in both groups.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received placebo once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.

Reporting group title	Darbepoetin Alfa
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Reporting group description:

Participants received darbepoetin alfa 500 µg once every 3 weeks (Q3W) administered subcutaneously until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.

Serious adverse events	Placebo	Darbepoetin Alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	259 / 833 (31.09%)	524 / 1685 (31.10%)	
number of deaths (all causes)	657	1273	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage IV			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Lung neoplasm malignant			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant pleural effusion			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to adrenals			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to bone			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-small cell lung cancer			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Tumour associated fever			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 833 (0.36%)	11 / 1685 (0.65%)	
occurrences causally related to treatment / all	1 / 3	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	6 / 833 (0.72%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Peripheral artery stenosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose ulceration			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular occlusion			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroidectomy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 833 (0.84%)	11 / 1685 (0.65%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 2	
Chest pain			
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	9 / 833 (1.08%)	12 / 1685 (0.71%)	
occurrences causally related to treatment / all	0 / 9	1 / 12	
deaths causally related to treatment / all	0 / 9	1 / 12	
Disease progression			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Fatigue			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Inflammation			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 833 (0.48%)	7 / 1685 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 4	0 / 7	
Non-cardiac chest pain			
subjects affected / exposed	0 / 833 (0.00%)	5 / 1685 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organ failure			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 833 (0.36%)	15 / 1685 (0.89%)	
occurrences causally related to treatment / all	1 / 4	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sudden death			
subjects affected / exposed	8 / 833 (0.96%)	12 / 1685 (0.71%)	
occurrences causally related to treatment / all	1 / 8	0 / 12	
deaths causally related to treatment / all	1 / 8	0 / 12	
Swelling			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (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 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion associated graft versus host disease			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 833 (0.24%)	9 / 1685 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 6	
Aspiration			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial haemorrhage			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	

Bronchitis chronic			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	1 / 833 (0.12%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	26 / 833 (3.12%)	31 / 1685 (1.84%)	
occurrences causally related to treatment / all	0 / 34	1 / 33	
deaths causally related to treatment / all	0 / 12	0 / 11	
Dyspnoea exertional			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 833 (0.36%)	14 / 1685 (0.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 6	
Hypoxia			

subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Painful respiration			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	12 / 833 (1.44%)	6 / 1685 (0.36%)	
occurrences causally related to treatment / all	1 / 16	0 / 6	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pneumonitis			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 833 (0.72%)	20 / 1685 (1.19%)	
occurrences causally related to treatment / all	2 / 8	9 / 22	
deaths causally related to treatment / all	1 / 3	3 / 11	
Pulmonary haemorrhage			
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pulmonary hypertension			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory depression			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory failure			

subjects affected / exposed	13 / 833 (1.56%)	24 / 1685 (1.42%)	
occurrences causally related to treatment / all	1 / 14	2 / 29	
deaths causally related to treatment / all	1 / 9	1 / 21	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			

subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood albumin abnormal			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ejection fraction decreased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin abnormal			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Platelet count decreased			
subjects affected / exposed	6 / 833 (0.72%)	6 / 1685 (0.36%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella test positive			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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			
Fall			
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Laceration			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root injury lumbar			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation dysphagia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			

subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
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	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	1 / 833 (0.12%)	0 / 1685 (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 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Acute myocardial infarction			
subjects affected / exposed	3 / 833 (0.36%)	5 / 1685 (0.30%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 3	
Angina pectoris			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	3 / 833 (0.36%)	8 / 1685 (0.47%)	
occurrences causally related to treatment / all	0 / 3	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 833 (0.24%)	7 / 1685 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 7	
Cardiac failure			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	7 / 833 (0.84%)	9 / 1685 (0.53%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 7	0 / 8	
Cardio-respiratory distress			

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiogenic shock			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 833 (0.12%)	5 / 1685 (0.30%)	
occurrences causally related to treatment / all	0 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nodal arrhythmia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sinus node dysfunction			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebral ischaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	1 / 833 (0.12%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cognitive disorder			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic neuropathy			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			

subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Presyncope			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Somnolence			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombotic stroke			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	46 / 833 (5.52%)	57 / 1685 (3.38%)	
occurrences causally related to treatment / all	2 / 60	1 / 65	
deaths causally related to treatment / all	1 / 2	0 / 1	
Bicytopenia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	8 / 833 (0.96%)	20 / 1685 (1.19%)	
occurrences causally related to treatment / all	0 / 10	0 / 23	
deaths causally related to treatment / all	0 / 1	0 / 2	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 833 (0.84%)	14 / 1685 (0.83%)	
occurrences causally related to treatment / all	0 / 7	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	2 / 833 (0.24%)	7 / 1685 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	6 / 833 (0.72%)	17 / 1685 (1.01%)	
occurrences causally related to treatment / all	0 / 6	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	4 / 833 (0.48%)	9 / 1685 (0.53%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sideroblastic anaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	16 / 833 (1.92%)	28 / 1685 (1.66%)	
occurrences causally related to treatment / all	0 / 20	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 833 (0.00%)	12 / 1685 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 833 (0.96%)	12 / 1685 (0.71%)	
occurrences causally related to treatment / all	1 / 8	1 / 14	
deaths causally related to treatment / all	0 / 1	0 / 3	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysphagia			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces discoloured			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (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	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Incarcerated inguinal hernia			

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising colitis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 833 (0.24%)	9 / 1685 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Peau d'orange			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	4 / 833 (0.48%)	12 / 1685 (0.71%)	
occurrences causally related to treatment / all	1 / 4	1 / 14	
deaths causally related to treatment / all	0 / 0	0 / 4	
Azotaemia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (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	2 / 833 (0.24%)	5 / 1685 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			

subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesical fistula			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic nodular goitre			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 833 (0.36%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	4 / 833 (0.48%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (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	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	3 / 833 (0.36%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 833 (0.24%)	7 / 1685 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung abscess			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	7 / 833 (0.84%)	13 / 1685 (0.77%)	
occurrences causally related to treatment / all	0 / 8	0 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (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	20 / 833 (2.40%)	44 / 1685 (2.61%)	
occurrences causally related to treatment / all	0 / 26	0 / 56	
deaths causally related to treatment / all	0 / 5	0 / 9	
Pneumonia bacterial			
subjects affected / exposed	1 / 833 (0.12%)	6 / 1685 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	4 / 833 (0.48%)	6 / 1685 (0.36%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	9 / 833 (1.08%)	15 / 1685 (0.89%)	
occurrences causally related to treatment / all	0 / 11	0 / 22	
deaths causally related to treatment / all	0 / 4	0 / 9	
Septic encephalopathy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
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	1 / 833 (0.12%)	3 / 1685 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	
Staphylococcal infection			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection viral			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 833 (0.48%)	6 / 1685 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 833 (0.12%)	7 / 1685 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	5 / 833 (0.60%)	6 / 1685 (0.36%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	4 / 833 (0.48%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 833 (0.00%)	5 / 1685 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 833 (0.36%)	2 / 1685 (0.12%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
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: 0 %

Non-serious adverse events	Placebo	Darbepoetin Alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	674 / 833 (80.91%)	1319 / 1685 (78.28%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 833 (0.12%)	8 / 1685 (0.47%)	
occurrences (all)	1	8	
Malignant pleural effusion			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Metastases to central nervous system			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Paraneoplastic syndrome			
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)	
occurrences (all)	2	0	
Tumour haemorrhage			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Tumour pain			
subjects affected / exposed	2 / 833 (0.24%)	6 / 1685 (0.36%)	
occurrences (all)	2	6	
Uterine leiomyoma			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Vascular disorders			
Angiopathy			

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Arterial disorder		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Arteriosclerosis		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Deep vein thrombosis		
subjects affected / exposed	7 / 833 (0.84%)	8 / 1685 (0.47%)
occurrences (all)	7	8
Diastolic hypertension		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Embolism		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Extremity necrosis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Flushing		
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)
occurrences (all)	0	4
Haematoma		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	2	2
Haemorrhage		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Hot flush		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	4	1
Hypertension		
subjects affected / exposed	21 / 833 (2.52%)	35 / 1685 (2.08%)
occurrences (all)	32	43
Hypotension		

subjects affected / exposed	6 / 833 (0.72%)	11 / 1685 (0.65%)
occurrences (all)	6	15
Intermittent claudication		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Orthostatic hypotension		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Pallor		
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)
occurrences (all)	2	3
Pelvic venous thrombosis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Peripheral artery occlusion		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Peripheral artery thrombosis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Peripheral venous disease		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Phlebitis		
subjects affected / exposed	1 / 833 (0.12%)	5 / 1685 (0.30%)
occurrences (all)	1	5
Phlebitis superficial		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Superior vena cava syndrome		
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)
occurrences (all)	2	3
Thrombophlebitis		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	4
Thrombophlebitis superficial		

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	0 / 833 (0.00%)	5 / 1685 (0.30%)	
occurrences (all)	0	5	
Varicose vein			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Vena cava thrombosis			
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)	
occurrences (all)	2	0	
Vascular insufficiency			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Constipation prophylaxis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Joint arthroplasty			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Leg amputation			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Pneumonolysis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Reduction of increased intracranial pressure			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Adverse drug reaction		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Asthenia		
subjects affected / exposed	92 / 833 (11.04%)	158 / 1685 (9.38%)
occurrences (all)	111	200
Axillary pain		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Catheter site haemorrhage		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Catheter site pain		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	4
Chest discomfort		
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)
occurrences (all)	4	6
Chest pain		
subjects affected / exposed	30 / 833 (3.60%)	52 / 1685 (3.09%)
occurrences (all)	39	60
Chills		
subjects affected / exposed	5 / 833 (0.60%)	9 / 1685 (0.53%)
occurrences (all)	5	9
Complication associated with device		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Extravasation		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Face oedema		
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)
occurrences (all)	3	5
Facial pain		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1

Fatigue		
subjects affected / exposed	69 / 833 (8.28%)	117 / 1685 (6.94%)
occurrences (all)	96	154
Feeling abnormal		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Feeling cold		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Gait disturbance		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	4
General physical health deterioration		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Generalised oedema		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Gravitational oedema		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hyperthermia		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Implant site pain		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Inflammation		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	3
Influenza like illness		
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)
occurrences (all)	2	3
Infusion site extravasation		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1

Injection site haematoma		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Injection site phlebitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Injection site reaction		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Local swelling		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Localised oedema		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	2	2
Malaise		
subjects affected / exposed	6 / 833 (0.72%)	14 / 1685 (0.83%)
occurrences (all)	6	16
Mass		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Mucosal inflammation		
subjects affected / exposed	8 / 833 (0.96%)	7 / 1685 (0.42%)
occurrences (all)	9	9
Mucous membrane disorder		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Non-cardiac chest pain		
subjects affected / exposed	7 / 833 (0.84%)	23 / 1685 (1.36%)
occurrences (all)	8	24
Oedema		
subjects affected / exposed	7 / 833 (0.84%)	10 / 1685 (0.59%)
occurrences (all)	7	11
Oedema peripheral		
subjects affected / exposed	30 / 833 (3.60%)	50 / 1685 (2.97%)
occurrences (all)	39	61

Pain			
subjects affected / exposed	18 / 833 (2.16%)	41 / 1685 (2.43%)	
occurrences (all)	20	49	
Performance status decreased			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Peripheral swelling			
subjects affected / exposed	5 / 833 (0.60%)	5 / 1685 (0.30%)	
occurrences (all)	5	6	
Pyrexia			
subjects affected / exposed	57 / 833 (6.84%)	110 / 1685 (6.53%)	
occurrences (all)	77	136	
Temperature intolerance			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences (all)	0	3	
Vessel puncture site pain			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Vessel puncture site swelling			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Contrast media allergy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Drug hypersensitivity			
subjects affected / exposed	5 / 833 (0.60%)	2 / 1685 (0.12%)	
occurrences (all)	5	3	
Hypersensitivity			
subjects affected / exposed	1 / 833 (0.12%)	8 / 1685 (0.47%)	
occurrences (all)	1	8	
Immune system disorder			

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Immunodeficiency			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Iodine allergy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Seasonal allergy			
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)	
occurrences (all)	1	3	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	2	
Breast mass			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Breast pain			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	3	0	
Breast swelling			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	3 / 833 (0.36%)	0 / 1685 (0.00%)	
occurrences (all)	3	0	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Prostatitis			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Scrotal oedema			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Vaginal haemorrhage			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Vulvovaginal pruritus			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Allergic respiratory symptom			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Apnoea			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	2	
Aspiration			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Asthma			
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)	
occurrences (all)	2	3	
Atelectasis			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	2	
Bronchial haemorrhage			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Bronchial hyperreactivity			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Bronchial obstruction			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Bronchiectasis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Bronchitis chronic		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Bronchospasm		
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)
occurrences (all)	2	5
Bronchostenosis		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Chronic obstructive pulmonary disease		
subjects affected / exposed	1 / 833 (0.12%)	9 / 1685 (0.53%)
occurrences (all)	1	9
Cough		
subjects affected / exposed	52 / 833 (6.24%)	147 / 1685 (8.72%)
occurrences (all)	56	170
Dry throat		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Dysphonia		
subjects affected / exposed	4 / 833 (0.48%)	12 / 1685 (0.71%)
occurrences (all)	4	12
Dyspnoea		
subjects affected / exposed	60 / 833 (7.20%)	111 / 1685 (6.59%)
occurrences (all)	76	138
Dyspnoea at rest		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Dyspnoea exertional		
subjects affected / exposed	8 / 833 (0.96%)	21 / 1685 (1.25%)
occurrences (all)	9	23

Epistaxis		
subjects affected / exposed	11 / 833 (1.32%)	31 / 1685 (1.84%)
occurrences (all)	11	38
Haemoptysis		
subjects affected / exposed	24 / 833 (2.88%)	42 / 1685 (2.49%)
occurrences (all)	30	55
Hiccups		
subjects affected / exposed	1 / 833 (0.12%)	7 / 1685 (0.42%)
occurrences (all)	1	7
Hypopnoea		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hypoxia		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	2	3
Laryngeal inflammation		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Laryngeal pain		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Lung infiltration		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Nasal congestion		
subjects affected / exposed	3 / 833 (0.36%)	5 / 1685 (0.30%)
occurrences (all)	3	5
Nasal dryness		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Nasal mucosal ulcer		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Oropharyngeal pain		
subjects affected / exposed	7 / 833 (0.84%)	15 / 1685 (0.89%)
occurrences (all)	7	15

Orthopnoea		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Paranasal sinus hypersecretion		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Pharyngeal inflammation		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Pleural effusion		
subjects affected / exposed	4 / 833 (0.48%)	8 / 1685 (0.47%)
occurrences (all)	13	9
Pleurisy		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Pleuritic pain		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	3
Pneumonitis		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	1
Pneumothorax		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Productive cough		
subjects affected / exposed	15 / 833 (1.80%)	31 / 1685 (1.84%)
occurrences (all)	16	35
Pulmonary arterial hypertension		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Pulmonary congestion		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Pulmonary embolism		
subjects affected / exposed	2 / 833 (0.24%)	7 / 1685 (0.42%)
occurrences (all)	2	7

Pulmonary haemorrhage		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Pulmonary mass		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Pulmonary oedema		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Respiratory disorder		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Respiratory distress		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Respiratory failure		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Respiratory tract congestion		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Respiratory tract haemorrhage		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Rhinitis allergic		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	1
Rhinorrhoea		
subjects affected / exposed	3 / 833 (0.36%)	6 / 1685 (0.36%)
occurrences (all)	5	7
Sinus congestion		
subjects affected / exposed	1 / 833 (0.12%)	6 / 1685 (0.36%)
occurrences (all)	1	6
Sinus disorder		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0

Sleep apnoea syndrome subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Sneezing subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 2	1 / 1685 (0.06%) 1	
Sputum discoloured subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Sputum retention subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	1 / 1685 (0.06%) 1	
Tachypnoea subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	1 / 1685 (0.06%) 1	
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	3 / 1685 (0.18%) 3	
Wheezing subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	4 / 1685 (0.24%) 4	
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Anxiety subjects affected / exposed occurrences (all)	9 / 833 (1.08%) 9	18 / 1685 (1.07%) 18	
Anxiety disorder subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Anxiety disorder due to a general medical condition			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Confusional state		
subjects affected / exposed	4 / 833 (0.48%)	6 / 1685 (0.36%)
occurrences (all)	5	7
Delirium		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Depressed mood		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Depression		
subjects affected / exposed	8 / 833 (0.96%)	11 / 1685 (0.65%)
occurrences (all)	8	11
Dysphoria		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Flight of ideas		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hallucination		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hyposomnia		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	3
Initial insomnia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Insomnia		
subjects affected / exposed	22 / 833 (2.64%)	41 / 1685 (2.43%)
occurrences (all)	26	45
Insomnia related to another mental condition		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1

Mental disorder			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Mental status changes			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	3	
Mood swings			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Organic brain syndrome			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	3 / 833 (0.36%)	1 / 1685 (0.06%)	
occurrences (all)	4	1	
Tic			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Product issues			
Device leakage			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	2	1	
Chronic hepatic failure			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences (all)	0	4	
Drug-induced liver injury			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Gallbladder polyp			

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Hepatic cyst		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Hepatic failure		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hepatic function abnormal		
subjects affected / exposed	4 / 833 (0.48%)	9 / 1685 (0.53%)
occurrences (all)	5	10
Hepatic lesion		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Hepatic pain		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Hepatic steatosis		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Hepatotoxicity		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Hyperbilirubinaemia		
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)
occurrences (all)	2	2
Hyperplastic cholecystopathy		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Liver disorder		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Liver injury		
subjects affected / exposed	3 / 833 (0.36%)	4 / 1685 (0.24%)
occurrences (all)	3	5
Ocular icterus		

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	2	
Alanine aminotransferase decreased			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	3	
Alanine aminotransferase increased			
subjects affected / exposed	26 / 833 (3.12%)	43 / 1685 (2.55%)	
occurrences (all)	47	57	
Albumin CSF decreased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Alpha hydroxybutyrate dehydrogenase increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Antineutrophil cytoplasmic antibody decreased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	2	
Aspartate aminotransferase decreased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 833 (2.52%)	38 / 1685 (2.26%)	
occurrences (all)	34	51	
Aspiration pleural cavity			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Biopsy pleura			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Blood albumin decreased			

subjects affected / exposed	5 / 833 (0.60%)	7 / 1685 (0.42%)
occurrences (all)	6	7
Blood alkaline phosphatase increased		
subjects affected / exposed	7 / 833 (0.84%)	20 / 1685 (1.19%)
occurrences (all)	9	24
Blood bicarbonate decreased		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Blood bicarbonate increased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Blood bilirubin increased		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	8
Blood bilirubin unconjugated increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Blood calcitonin increased		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Blood calcium decreased		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	2
Blood chloride decreased		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Blood chloride increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Blood cholesterol increased		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Blood creatine		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1

Blood creatine abnormal subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	2 / 1685 (0.12%) 3
Blood creatine increased subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	6 / 1685 (0.36%) 7
Blood creatine phosphokinase MB increased subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Blood creatinine subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	16 / 833 (1.92%) 19	27 / 1685 (1.60%) 43
Blood glucose increased subjects affected / exposed occurrences (all)	5 / 833 (0.60%) 7	6 / 1685 (0.36%) 11
Blood iron abnormal subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Blood iron decreased subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	3 / 1685 (0.18%) 3
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	8 / 833 (0.96%) 8	13 / 1685 (0.77%) 15
Blood potassium decreased subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	6 / 1685 (0.36%) 8
Blood pressure increased subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 4	2 / 1685 (0.12%) 3
Blood pressure systolic increased		

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Blood testosterone decreased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Blood thyroid stimulating hormone decreased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Blood triglycerides increased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Blood urea decreased		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Blood urea increased		
subjects affected / exposed	6 / 833 (0.72%)	10 / 1685 (0.59%)
occurrences (all)	8	10
Blood uric acid increased		
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)
occurrences (all)	2	4
Body temperature increased		
subjects affected / exposed	3 / 833 (0.36%)	1 / 1685 (0.06%)
occurrences (all)	4	1
Brain natriuretic peptide increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Breath sounds abnormal		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	1
C-reactive protein increased		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Creatinine renal clearance decreased		
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)
occurrences (all)	3	5

Creatinine renal clearance increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Eastern Cooperative Oncology Group performance status worsened		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	5
Electrocardiogram QT prolonged		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Fibrin D dimer increased		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Fibrin degradation products increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Gamma-glutamyltransferase		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Gamma-glutamyltransferase decreased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Gamma-glutamyltransferase increased		
subjects affected / exposed	10 / 833 (1.20%)	22 / 1685 (1.31%)
occurrences (all)	15	33
Gastric pH decreased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
General physical condition abnormal		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Globulins decreased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Glomerular filtration rate decreased		

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Glucose tolerance decreased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Glucose urine present		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Glycosylated haemoglobin increased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Granulocyte count decreased		
subjects affected / exposed	2 / 833 (0.24%)	9 / 1685 (0.53%)
occurrences (all)	6	15
Haematocrit decreased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Haemoglobin decreased		
subjects affected / exposed	10 / 833 (1.20%)	8 / 1685 (0.47%)
occurrences (all)	15	12
Heart rate increased		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	2
Hepatic enzyme increased		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Human epidermal growth factor receptor decreased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
International normalised ratio increased		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	4	1
Iron binding capacity total decreased		

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Iron binding capacity unsaturated decreased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Laboratory test abnormal		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Liver function test abnormal		
subjects affected / exposed	1 / 833 (0.12%)	10 / 1685 (0.59%)
occurrences (all)	1	13
Liver function test increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Lymphocyte count abnormal		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Lymphocyte count decreased		
subjects affected / exposed	5 / 833 (0.60%)	15 / 1685 (0.89%)
occurrences (all)	11	33
Lymphocyte count increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	3
Mean cell volume increased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Monocyte percentage increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Myoglobin blood increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Neutrophil count		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1

Neutrophil count abnormal subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 4	1 / 1685 (0.06%) 2
Neutrophil count decreased subjects affected / exposed occurrences (all)	47 / 833 (5.64%) 107	95 / 1685 (5.64%) 249
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	5 / 1685 (0.30%) 6
Neutrophil percentage increased subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	2 / 1685 (0.12%) 2
PCO2 decreased subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Platelet adhesiveness decreased subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0
Platelet adhesiveness increased subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Platelet count abnormal subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 2
Platelet count decreased subjects affected / exposed occurrences (all)	66 / 833 (7.92%) 126	130 / 1685 (7.72%) 282
Protein total decreased subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	2 / 1685 (0.12%) 2
Platelet count increased subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	3 / 1685 (0.18%) 4
Protein total increased subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0

Protein urine present		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Respiratory rate decreased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Serum ferritin decreased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Serum ferritin increased		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Transaminases increased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Troponin I increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Troponin increased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Urine output decreased		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Vitamin D decreased		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Weight decreased		
subjects affected / exposed	24 / 833 (2.88%)	53 / 1685 (3.15%)
occurrences (all)	26	59
Weight increased		
subjects affected / exposed	4 / 833 (0.48%)	4 / 1685 (0.24%)
occurrences (all)	4	4
White blood cell count		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	3	1

White blood cell count decreased subjects affected / exposed occurrences (all)	64 / 833 (7.68%) 197	138 / 1685 (8.19%) 407	
White blood cell count increased subjects affected / exposed occurrences (all)	3 / 833 (0.36%) 3	7 / 1685 (0.42%) 9	
White blood cells urine positive subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Injury, poisoning and procedural complications			
Airway complication of anaesthesia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Animal scratch subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Ankle fracture subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Arthropod bite subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Chemical poisoning subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Clavicle fracture subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Concussion subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Contusion subjects affected / exposed occurrences (all)	5 / 833 (0.60%) 5	6 / 1685 (0.36%) 6	
Fall			

subjects affected / exposed	3 / 833 (0.36%)	7 / 1685 (0.42%)
occurrences (all)	3	7
Fracture		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Humerus fracture		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Infusion related reaction		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Laceration		
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)
occurrences (all)	2	3
Limb injury		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Lumbar vertebral fracture		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Overdose		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Poisoning		
subjects affected / exposed	4 / 833 (0.48%)	4 / 1685 (0.24%)
occurrences (all)	5	4
Post procedural fistula		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Procedural pain		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Radiation oesophagitis		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Radiation pneumonitis		

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Radiation skin injury			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Rib fracture			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	2	0	
Skin abrasion			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Spinal compression fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Toxicity to various agents			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Wound complication			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Acute coronary syndrome subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	1 / 1685 (0.06%) 1
Angina pectoris subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	3 / 1685 (0.18%) 3
Angina unstable subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0
Arrhythmia subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	2 / 1685 (0.12%) 2
Arrhythmia supraventricular subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Arteriosclerosis coronary artery subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	2 / 1685 (0.12%) 4
Atrial tachycardia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	3 / 1685 (0.18%) 3
Cardiac discomfort subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Cardiac disorder subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Cardiac failure subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	1 / 1685 (0.06%) 1
Cardiac failure congestive subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1

Cardiomyopathy		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Congestive cardiomyopathy		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Cyanosis		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Metabolic cardiomyopathy		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Myocardial infarction		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Myocardial ischaemia		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Palpitations		
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)
occurrences (all)	3	4
Pericardial effusion		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Pericarditis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Sinus arrhythmia		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Sinus tachycardia		
subjects affected / exposed	1 / 833 (0.12%)	5 / 1685 (0.30%)
occurrences (all)	1	5
Supraventricular extrasystoles		
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)
occurrences (all)	2	3

Supraventricular tachycardia subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Tachycardia subjects affected / exposed occurrences (all)	7 / 833 (0.84%) 8	10 / 1685 (0.59%) 10	
Nervous system disorders			
Amnesia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	2 / 1685 (0.12%) 2	
Anaesthesia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Aphasia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Aphonia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Ataxia subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	5 / 1685 (0.30%) 5	
Burning sensation subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	2 / 1685 (0.12%) 2	
Central nervous system lesion subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Central pain syndrome subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Cerebral atrophy subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	2 / 1685 (0.12%) 2	
Cerebral infarction			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Cerebral ischaemia		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Cerebrovascular disorder		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Cervical radiculopathy		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Cognitive disorder		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Diabetic neuropathy		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Dizziness		
subjects affected / exposed	24 / 833 (2.88%)	58 / 1685 (3.44%)
occurrences (all)	26	67
Dizziness postural		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Dysarthria		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Dysgeusia		
subjects affected / exposed	2 / 833 (0.24%)	7 / 1685 (0.42%)
occurrences (all)	2	7
Dyskinesia		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Encephalopathy		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Epilepsy		

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Facial paralysis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Head discomfort		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Headache		
subjects affected / exposed	18 / 833 (2.16%)	55 / 1685 (3.26%)
occurrences (all)	20	61
Hemiparesis		
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)
occurrences (all)	2	4
Hemiplegia		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Hypoaesthesia		
subjects affected / exposed	13 / 833 (1.56%)	21 / 1685 (1.25%)
occurrences (all)	16	23
Hypogeusia		
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)
occurrences (all)	2	2
Intellectual disability		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Intercostal neuralgia		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	5
Loss of consciousness		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Migraine		

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Monoparesis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Nervous system disorder		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Neuralgia		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	3
Neuropathy peripheral		
subjects affected / exposed	40 / 833 (4.80%)	57 / 1685 (3.38%)
occurrences (all)	51	69
Paraesthesia		
subjects affected / exposed	14 / 833 (1.68%)	26 / 1685 (1.54%)
occurrences (all)	18	36
Peripheral motor neuropathy		
subjects affected / exposed	3 / 833 (0.36%)	4 / 1685 (0.24%)
occurrences (all)	3	8
Peripheral sensory neuropathy		
subjects affected / exposed	21 / 833 (2.52%)	39 / 1685 (2.31%)
occurrences (all)	30	57
Polyneuropathy		
subjects affected / exposed	5 / 833 (0.60%)	6 / 1685 (0.36%)
occurrences (all)	6	22
Poor quality sleep		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Presyncope		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Psychomotor hyperactivity		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Sciatica		

subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	3 / 833 (0.36%)	4 / 1685 (0.24%)	
occurrences (all)	3	5	
Sensory disturbance			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)	
occurrences (all)	1	4	
Syncope			
subjects affected / exposed	3 / 833 (0.36%)	10 / 1685 (0.59%)	
occurrences (all)	3	10	
Tremor			
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Anaemia			
subjects affected / exposed	244 / 833 (29.29%)	451 / 1685 (26.77%)	
occurrences (all)	503	899	
Anaemia megaloblastic			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Bandaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Bicytopenia			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Bone marrow failure		
subjects affected / exposed	16 / 833 (1.92%)	39 / 1685 (2.31%)
occurrences (all)	31	76
Disseminated intravascular coagulation		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Erythropenia		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	3	0
Febrile neutropenia		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	4
Granulocytopenia		
subjects affected / exposed	3 / 833 (0.36%)	11 / 1685 (0.65%)
occurrences (all)	19	21
Haematotoxicity		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Haemolytic anaemia		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Hypercoagulation		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Increased tendency to bruise		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Iron deficiency anaemia		
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)
occurrences (all)	0	4
Leukocytosis		
subjects affected / exposed	5 / 833 (0.60%)	11 / 1685 (0.65%)
occurrences (all)	5	11

Leukopenia		
subjects affected / exposed	40 / 833 (4.80%)	101 / 1685 (5.99%)
occurrences (all)	86	220
Lymph node pain		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Lymphadenitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Lymphadenopathy		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Lymphopenia		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	5	1
Neutropenia		
subjects affected / exposed	79 / 833 (9.48%)	202 / 1685 (11.99%)
occurrences (all)	175	387
Neutrophilia		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Pancytopenia		
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)
occurrences (all)	2	5
Platelet disorder		
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)
occurrences (all)	2	6
Platelet production decreased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Thrombocytopenia		
subjects affected / exposed	66 / 833 (7.92%)	156 / 1685 (9.26%)
occurrences (all)	141	330
Thrombocytopenia neonatal		

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Thrombocytosis			
subjects affected / exposed	1 / 833 (0.12%)	7 / 1685 (0.42%)	
occurrences (all)	2	8	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Hypoacusis			
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)	
occurrences (all)	0	4	
Otorrhoea			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	4 / 833 (0.48%)	3 / 1685 (0.18%)	
occurrences (all)	4	3	
Vertigo			
subjects affected / exposed	4 / 833 (0.48%)	5 / 1685 (0.30%)	
occurrences (all)	5	5	
Eye disorders			
Asthenopia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Blindness			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Blindness unilateral			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Cataract			

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Conjunctival haemorrhage		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Conjunctival pallor		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Diplopia		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Dry eye		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	5
Eye disorder		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Eye irritation		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Eye pain		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Eyelid margin crusting		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Eyelid oedema		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	4
Glaucoma		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Keratitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Lacrimation increased		

subjects affected / exposed occurrences (all)	5 / 833 (0.60%) 5	7 / 1685 (0.42%) 7	
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Photophobia subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	2 / 1685 (0.12%) 2	
Pupils unequal subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Ulcerative keratitis subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	3 / 833 (0.36%) 3	3 / 1685 (0.18%) 3	
Visual impairment subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	3 / 833 (0.36%) 3	6 / 1685 (0.36%) 7	
Abdominal distension subjects affected / exposed occurrences (all)	8 / 833 (0.96%) 8	9 / 1685 (0.53%) 11	
Abdominal pain subjects affected / exposed occurrences (all)	18 / 833 (2.16%) 24	50 / 1685 (2.97%) 57	
Abdominal pain lower subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	5 / 1685 (0.30%) 5	
Abdominal pain upper subjects affected / exposed occurrences (all)	15 / 833 (1.80%) 17	17 / 1685 (1.01%) 21	

Abdominal tenderness		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Acute abdomen		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Anal inflammation		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Ascites		
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)
occurrences (all)	2	2
Chronic gastritis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Constipation		
subjects affected / exposed	56 / 833 (6.72%)	106 / 1685 (6.29%)
occurrences (all)	71	121
Dental caries		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Diarrhoea		
subjects affected / exposed	46 / 833 (5.52%)	106 / 1685 (6.29%)
occurrences (all)	58	127
Diverticulum intestinal		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Dry mouth		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Duodenitis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Dyspepsia		
subjects affected / exposed	5 / 833 (0.60%)	12 / 1685 (0.71%)
occurrences (all)	5	13

Dysphagia		
subjects affected / exposed	5 / 833 (0.60%)	16 / 1685 (0.95%)
occurrences (all)	5	17
Enteritis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Epigastric discomfort		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	6
Faeces hard		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Flatulence		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	4
Gastric polyps		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Gastric ulcer		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Gastritis		
subjects affected / exposed	5 / 833 (0.60%)	11 / 1685 (0.65%)
occurrences (all)	5	11
Gastrointestinal disorder		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	2
Gastrointestinal haemorrhage		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 833 (0.24%)	6 / 1685 (0.36%)
occurrences (all)	2	6
Gingival swelling		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3

Glossitis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Glossodynia		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Haematemesis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Haematochezia		
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)
occurrences (all)	3	2
Haemorrhoidal haemorrhage		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	1
Haemorrhoids		
subjects affected / exposed	3 / 833 (0.36%)	1 / 1685 (0.06%)
occurrences (all)	3	1
Hyperchlorhydria		
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)
occurrences (all)	0	3
Ileus		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Inguinal hernia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Intestinal haemorrhage		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Irritable bowel syndrome		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Lip dry		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1

Lip swelling			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Melaena			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	3 / 833 (0.36%)	7 / 1685 (0.42%)	
occurrences (all)	3	7	
Nausea			
subjects affected / exposed	101 / 833 (12.12%)	187 / 1685 (11.10%)	
occurrences (all)	163	270	
Odynophagia			
subjects affected / exposed	1 / 833 (0.12%)	5 / 1685 (0.30%)	
occurrences (all)	1	6	
Oesophageal stenosis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Oesophagitis			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences (all)	2	2	
Oral disorder			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	3	
Rectal haemorrhage			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	2	
Rectal ulcer			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Regurgitation			

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Retching			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	3	
Small intestinal obstruction			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	6 / 833 (0.72%)	20 / 1685 (1.19%)	
occurrences (all)	7	22	
Tooth loss			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	57 / 833 (6.84%)	118 / 1685 (7.00%)	
occurrences (all)	73	164	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	2	
Actinic keratosis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	70 / 833 (8.40%)	125 / 1685 (7.42%)	
occurrences (all)	85	147	
Cold sweat			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	4 / 833 (0.48%)	4 / 1685 (0.24%)	
occurrences (all)	4	4	

Dermatitis		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Dermatitis acneiform		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Dermatitis allergic		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Dermatitis bullous		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Drug eruption		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Dry skin		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	4
Ecchymosis		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	4
Eczema		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	2
Erythema		
subjects affected / exposed	5 / 833 (0.60%)	4 / 1685 (0.24%)
occurrences (all)	8	4
Haemorrhage subcutaneous		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Hand dermatitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hyperhidrosis		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	4

Ingrowing nail		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Nail discolouration		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Nail disorder		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Night sweats		
subjects affected / exposed	3 / 833 (0.36%)	2 / 1685 (0.12%)
occurrences (all)	3	2
Pain of skin		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Palmar erythema		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Petechiae		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	4
Photosensitivity reaction		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Pigmentation disorder		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Plantar erythema		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Pruritus		

subjects affected / exposed	3 / 833 (0.36%)	22 / 1685 (1.31%)
occurrences (all)	3	25
Pruritus allergic		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Pruritus generalised		
subjects affected / exposed	3 / 833 (0.36%)	1 / 1685 (0.06%)
occurrences (all)	3	1
Purpura		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Rash		
subjects affected / exposed	14 / 833 (1.68%)	25 / 1685 (1.48%)
occurrences (all)	17	31
Rash erythematous		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Rash generalised		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Rash maculo-papular		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Rash pruritic		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Skin discolouration		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Skin disorder		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Skin erosion		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Skin exfoliation		

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	2	
Skin fissures			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Skin mass			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Skin odour abnormal			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	2	
Subcutaneous emphysema			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	3 / 833 (0.36%)	2 / 1685 (0.12%)	
occurrences (all)	3	2	
Urticaria			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Xeroderma			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 833 (0.36%)	5 / 1685 (0.30%)	
occurrences (all)	5	5	
Anuria			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	

Bladder dilatation		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Calculus bladder		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Chronic kidney disease		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Dysuria		
subjects affected / exposed	1 / 833 (0.12%)	11 / 1685 (0.65%)
occurrences (all)	1	12
Glycosuria		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Haematuria		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Nephrolithiasis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Nephropathy		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Nocturia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Oliguria		
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)
occurrences (all)	0	4
Pollakiuria		
subjects affected / exposed	3 / 833 (0.36%)	2 / 1685 (0.12%)
occurrences (all)	3	2
Proteinuria		
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)
occurrences (all)	2	2

Renal failure subjects affected / exposed occurrences (all)	5 / 833 (0.60%) 5	5 / 1685 (0.30%) 6	
Renal impairment subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	4 / 1685 (0.24%) 4	
Renal pain subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	3 / 1685 (0.18%) 3	
Urinary hesitation subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	1 / 1685 (0.06%) 1	
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	4 / 1685 (0.24%) 4	
Urinary retention subjects affected / exposed occurrences (all)	3 / 833 (0.36%) 3	1 / 1685 (0.06%) 1	
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Hypercalcaemia of malignancy subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	1 / 1685 (0.06%) 1	
Thyroid dysfunction in pregnancy subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Arthralgia			

subjects affected / exposed	21 / 833 (2.52%)	32 / 1685 (1.90%)
occurrences (all)	23	39
Back pain		
subjects affected / exposed	35 / 833 (4.20%)	65 / 1685 (3.86%)
occurrences (all)	39	81
Bone formation increased		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Bursitis		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	2
Bone pain		
subjects affected / exposed	10 / 833 (1.20%)	30 / 1685 (1.78%)
occurrences (all)	11	58
Coccydynia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Connective tissue disorder		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Exostosis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Fistula		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Flank pain		
subjects affected / exposed	1 / 833 (0.12%)	5 / 1685 (0.30%)
occurrences (all)	1	5
Gouty arthritis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hypercreatinaemia		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	3
Joint range of motion decreased		

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Joint swelling		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	1
Limb discomfort		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Muscle fatigue		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Muscle spasms		
subjects affected / exposed	5 / 833 (0.60%)	6 / 1685 (0.36%)
occurrences (all)	5	6
Muscle twitching		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Muscular weakness		
subjects affected / exposed	9 / 833 (1.08%)	12 / 1685 (0.71%)
occurrences (all)	9	13
Musculoskeletal chest pain		
subjects affected / exposed	8 / 833 (0.96%)	17 / 1685 (1.01%)
occurrences (all)	9	24
Musculoskeletal discomfort		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Musculoskeletal pain		
subjects affected / exposed	12 / 833 (1.44%)	25 / 1685 (1.48%)
occurrences (all)	12	28
Musculoskeletal stiffness		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Myalgia		
subjects affected / exposed	12 / 833 (1.44%)	26 / 1685 (1.54%)
occurrences (all)	19	34
Neck pain		

subjects affected / exposed	4 / 833 (0.48%)	7 / 1685 (0.42%)	
occurrences (all)	5	7	
Osteolysis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Osteoporosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	22 / 833 (2.64%)	57 / 1685 (3.38%)	
occurrences (all)	32	69	
Pain in jaw			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	2	
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Pathological fracture			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Rhabdomyolysis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	1 / 833 (0.12%)	5 / 1685 (0.30%)	
occurrences (all)	1	8	
Synovial cyst			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Trismus			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abdominal wall infection			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	

Alveolar osteitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Amoebiasis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Anorectal cellulitis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Bacterial infection		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Balanoposthitis infective		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Bronchiolitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Bronchitis		
subjects affected / exposed	7 / 833 (0.84%)	18 / 1685 (1.07%)
occurrences (all)	7	20
Bronchitis bacterial		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Candida infection		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Catheter site cellulitis		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Cellulitis		
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)
occurrences (all)	2	7
Chikungunya virus infection		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0

Clostridium difficile colitis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Conjunctivitis		
subjects affected / exposed	3 / 833 (0.36%)	4 / 1685 (0.24%)
occurrences (all)	3	4
Cystitis		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Device related infection		
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)
occurrences (all)	0	4
Erysipelas		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Eye infection		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Febrile infection		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Folliculitis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Fungal infection		
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)
occurrences (all)	3	2
Fungal skin infection		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Furuncle		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Gastroenteritis		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	3

Gastroenteritis viral		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Gastrointestinal infection		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hepatitis B		
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)
occurrences (all)	2	2
Herpes dermatitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Herpes simplex		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Herpes virus infection		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	3 / 833 (0.36%)	7 / 1685 (0.42%)
occurrences (all)	3	7
Infected bite		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Infection		
subjects affected / exposed	3 / 833 (0.36%)	4 / 1685 (0.24%)
occurrences (all)	3	4
Influenza		
subjects affected / exposed	5 / 833 (0.60%)	8 / 1685 (0.47%)
occurrences (all)	6	8
Kidney infection		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Localised infection		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0

Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	6 / 1685 (0.36%) 7
Lung infection subjects affected / exposed occurrences (all)	6 / 833 (0.72%) 8	12 / 1685 (0.71%) 13
Mastoiditis subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	2 / 1685 (0.12%) 2
Meningoencephalitis bacterial subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Mucosal infection subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	1 / 1685 (0.06%) 1
Oesophageal candidiasis subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Onychomycosis subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 2	7 / 1685 (0.42%) 7
Oral fungal infection subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	1 / 1685 (0.06%) 1
Oral herpes subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	3 / 1685 (0.18%) 3
Oral infection subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1

Orchitis		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Oropharyngeal candidiasis		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Paronychia		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Penile infection		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	3 / 833 (0.36%)	3 / 1685 (0.18%)
occurrences (all)	3	3
Pneumonia		
subjects affected / exposed	13 / 833 (1.56%)	26 / 1685 (1.54%)
occurrences (all)	13	27
Pneumonia bacterial		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Post procedural infection		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	3	0
Rash pustular		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Respiratory tract infection		
subjects affected / exposed	3 / 833 (0.36%)	9 / 1685 (0.53%)
occurrences (all)	3	10
Respiratory tract infection viral		
subjects affected / exposed	5 / 833 (0.60%)	5 / 1685 (0.30%)
occurrences (all)	6	5
Rhinitis		
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)
occurrences (all)	2	3

Sepsis		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Sinusitis		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	5
Skin infection		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Sputum purulent		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Staphylococcal infection		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	2
Strongyloidiasis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Tinea cruris		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Tonsillitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Tooth infection		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Tracheitis		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Tracheobronchitis		
subjects affected / exposed	3 / 833 (0.36%)	2 / 1685 (0.12%)
occurrences (all)	3	2
Upper respiratory tract infection		
subjects affected / exposed	14 / 833 (1.68%)	33 / 1685 (1.96%)
occurrences (all)	19	35

Urinary tract infection subjects affected / exposed occurrences (all)	14 / 833 (1.68%) 15	27 / 1685 (1.60%) 32	
Urinary tract infection fungal subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Viral infection subjects affected / exposed occurrences (all)	2 / 833 (0.24%) 3	1 / 1685 (0.06%) 1	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 833 (0.72%) 6	8 / 1685 (0.47%) 9	
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Wound infection subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Metabolism and nutrition disorders			
Acidosis subjects affected / exposed occurrences (all)	0 / 833 (0.00%) 0	1 / 1685 (0.06%) 1	
Cachexia subjects affected / exposed occurrences (all)	1 / 833 (0.12%) 1	0 / 1685 (0.00%) 0	
Decreased appetite subjects affected / exposed occurrences (all)	63 / 833 (7.56%) 78	134 / 1685 (7.95%) 160	
Dehydration subjects affected / exposed occurrences (all)	14 / 833 (1.68%) 15	37 / 1685 (2.20%) 50	
Diabetes mellitus subjects affected / exposed occurrences (all)	4 / 833 (0.48%) 5	1 / 1685 (0.06%) 1	
Diabetes mellitus inadequate control			

subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Dyslipidaemia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Electrolyte imbalance		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Fluid retention		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Glucose tolerance impaired		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Gout		
subjects affected / exposed	2 / 833 (0.24%)	0 / 1685 (0.00%)
occurrences (all)	2	0
Hypercalcaemia		
subjects affected / exposed	5 / 833 (0.60%)	4 / 1685 (0.24%)
occurrences (all)	5	4
Hyperchloraemia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hypercholesterolaemia		
subjects affected / exposed	3 / 833 (0.36%)	1 / 1685 (0.06%)
occurrences (all)	3	1
Hypercreatininaemia		
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)
occurrences (all)	2	6
Hyperglycaemia		
subjects affected / exposed	14 / 833 (1.68%)	32 / 1685 (1.90%)
occurrences (all)	18	54
Hyperkalaemia		
subjects affected / exposed	1 / 833 (0.12%)	7 / 1685 (0.42%)
occurrences (all)	1	8
Hyperlipidaemia		

subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hypernatraemia		
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Hyperphosphataemia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Hypertriglyceridaemia		
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)
occurrences (all)	1	6
Hyperuricaemia		
subjects affected / exposed	2 / 833 (0.24%)	8 / 1685 (0.47%)
occurrences (all)	3	11
Hypoalbuminaemia		
subjects affected / exposed	16 / 833 (1.92%)	47 / 1685 (2.79%)
occurrences (all)	27	65
Hypocalcaemia		
subjects affected / exposed	11 / 833 (1.32%)	25 / 1685 (1.48%)
occurrences (all)	19	36
Hypochloraemia		
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)
occurrences (all)	2	1
Hypoglycaemia		
subjects affected / exposed	4 / 833 (0.48%)	1 / 1685 (0.06%)
occurrences (all)	4	1
Hypokalaemia		
subjects affected / exposed	36 / 833 (4.32%)	53 / 1685 (3.15%)
occurrences (all)	51	71
Hypomagnesaemia		
subjects affected / exposed	10 / 833 (1.20%)	9 / 1685 (0.53%)
occurrences (all)	12	12
Hyponatraemia		
subjects affected / exposed	12 / 833 (1.44%)	25 / 1685 (1.48%)
occurrences (all)	19	33
Hypophagia		

subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)
occurrences (all)	1	2
Hypoproteinaemia		
subjects affected / exposed	11 / 833 (1.32%)	9 / 1685 (0.53%)
occurrences (all)	15	10
Hypophosphataemia		
subjects affected / exposed	3 / 833 (0.36%)	0 / 1685 (0.00%)
occurrences (all)	5	0
Hypovolaemia		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Iron deficiency		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Malnutrition		
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)
occurrences (all)	1	4
Iron overload		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Marasmus		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Metabolic disorder		
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)
occurrences (all)	1	0
Protein deficiency		
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)
occurrences (all)	0	2
Tetany		
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)
occurrences (all)	0	1
Type 2 diabetes mellitus		
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)
occurrences (all)	1	1
Vitamin D deficiency		

subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Weight loss poor			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2009	The following revisions were made based on regulatory feedback: <ul style="list-style-type: none">- Further rationale was provided for the definition of noninferiority (upper limit = 1.15).- The definition of a nonresponder was changed from a subject whose week 10 hemoglobin dropped by > 0.5 g/dL from week 1 or who had a RBC transfusion within 21 days before week 10 to a subject who, after study day 35, received 2 transfusions \geq 21 days and \leq 42 days apart.- The end of investigational product administration was changed to the next study visit after the last dose of chemotherapy for consistency with updated product labeling.- The study title was changed to remove "to a hemoglobin ceiling of 12.0 g/dL."- An end of efficacy treatment period definition was added.- The statistical section was revised to clarify the inclusion of fatal events after the 2700th event but before the termination date in the primary analysis.- ANC was replaced with WBC in the Other Analyses section, as ANC is derived and could be missing or inconsistently reported.- Assessment of suspected bone metastases was updated to allow for the use of MRI, CT, or PET/CT in addition to bone scans for the initial assessment.
22 March 2009	The duration of investigational product administration was clarified (end of treatment within 3 weeks after the last dose of chemotherapy or upon determination of disease progression, whichever occurred first).
25 May 2010	The effect of maintenance therapy on subject eligibility and investigational product administration was clarified. Subject eligibility was updated to change stage IIIb with malignant pleural effusion to stage IV in eligibility criteria, consistent with current medical classification of NSCLC. The eligibility criteria were updated to clarify the inclusion of subjects with newly diagnosed stage IV NSCLC and the exclusion of subjects with recurrent disease to reduce possibly heterogeneity in expected OS. Modified RECIST 1.0 was replaced with modified RECIST 1.1 to align with current clinical research practice.
13 November 2012	Serious adverse event reporting requirements were changed from 1 business day to 24 hours in accordance with updates for the European Medicines Agency guidance. Testing frequencies for total iron-binding capacity, C-reactive protein, and soluble transferrin saturation were corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported