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

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 darbepoetin 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

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

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

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)

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

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

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

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)

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

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 ≤ 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 ≤ 8.0 g/dL From Week 5 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 ≥ 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

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 ≤ 8.0 g/dL

Statistical analysis description:

The primary analysis of the incidence of a transfusion or hemoglobin ≤ 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

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

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

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

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

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

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

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

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 ≤ 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 ≤ 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 ≤ 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

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

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

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.

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	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Sneezing			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	2	1	
Sputum discoloured			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Sputum retention			
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences (all)	2	1	
Tachypnoea			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences (all)	0	3	
Wheezing			
subjects affected / exposed	2 / 833 (0.24%)	4 / 1685 (0.24%)	
occurrences (all)	2	4	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	9 / 833 (1.08%)	18 / 1685 (1.07%)	
occurrences (all)	9	18	
Anxiety disorder			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	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	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	3	
Blood creatine increased			
subjects affected / exposed	0 / 833 (0.00%)	6 / 1685 (0.36%)	
occurrences (all)	0	7	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Blood creatinine			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	16 / 833 (1.92%)	27 / 1685 (1.60%)	
occurrences (all)	19	43	
Blood glucose increased			
subjects affected / exposed	5 / 833 (0.60%)	6 / 1685 (0.36%)	
occurrences (all)	7	11	
Blood iron abnormal			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Blood iron decreased			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences (all)	0	3	
Blood lactate dehydrogenase increased			
subjects affected / exposed	8 / 833 (0.96%)	13 / 1685 (0.77%)	
occurrences (all)	8	15	
Blood potassium decreased			
subjects affected / exposed	2 / 833 (0.24%)	6 / 1685 (0.36%)	
occurrences (all)	2	8	
Blood pressure increased			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences (all)	4	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	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	4	2	
Neutrophil count decreased			
subjects affected / exposed	47 / 833 (5.64%)	95 / 1685 (5.64%)	
occurrences (all)	107	249	
Neutrophil count increased			
subjects affected / exposed	0 / 833 (0.00%)	5 / 1685 (0.30%)	
occurrences (all)	0	6	
Neutrophil percentage increased			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	2	
PCO2 decreased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Platelet adhesiveness decreased			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Platelet adhesiveness increased			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Platelet count abnormal			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	2	
Platelet count decreased			
subjects affected / exposed	66 / 833 (7.92%)	130 / 1685 (7.72%)	
occurrences (all)	126	282	
Protein total decreased			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	2	
Platelet count increased			
subjects affected / exposed	2 / 833 (0.24%)	3 / 1685 (0.18%)	
occurrences (all)	2	4	
Protein total increased			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	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	64 / 833 (7.68%)	138 / 1685 (8.19%)	
occurrences (all)	197	407	
White blood cell count increased			
subjects affected / exposed	3 / 833 (0.36%)	7 / 1685 (0.42%)	
occurrences (all)	3	9	
White blood cells urine positive			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Airway complication of anaesthesia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Animal scratch			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Ankle fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Arthropod bite			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Chemical poisoning			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Clavicle fracture			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Concussion			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	5 / 833 (0.60%)	6 / 1685 (0.36%)	
occurrences (all)	5	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	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Angina pectoris			
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)	
occurrences (all)	1	3	
Angina unstable			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Arrhythmia			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences (all)	2	2	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	2 / 833 (0.24%)	2 / 1685 (0.12%)	
occurrences (all)	2	4	
Atrial tachycardia			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences (all)	0	3	
Cardiac discomfort			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Cardiac disorder			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Cardiac failure			
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences (all)	2	1	
Cardiac failure congestive			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	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	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	7 / 833 (0.84%)	10 / 1685 (0.59%)	
occurrences (all)	8	10	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	2	
Anaesthesia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Aphasia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Aphonia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Ataxia			
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)	
occurrences (all)	2	5	
Burning sensation			
subjects affected / exposed	1 / 833 (0.12%)	2 / 1685 (0.12%)	
occurrences (all)	1	2	
Central nervous system lesion			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Central pain syndrome			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Cerebral atrophy			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	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	5 / 833 (0.60%)	7 / 1685 (0.42%)	
occurrences (all)	5	7	
Ocular hyperaemia			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	2	
Pupils unequal			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Ulcerative keratitis			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	3 / 833 (0.36%)	3 / 1685 (0.18%)	
occurrences (all)	3	3	
Visual impairment			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 833 (0.36%)	6 / 1685 (0.36%)	
occurrences (all)	3	7	
Abdominal distension			
subjects affected / exposed	8 / 833 (0.96%)	9 / 1685 (0.53%)	
occurrences (all)	8	11	
Abdominal pain			
subjects affected / exposed	18 / 833 (2.16%)	50 / 1685 (2.97%)	
occurrences (all)	24	57	
Abdominal pain lower			
subjects affected / exposed	2 / 833 (0.24%)	5 / 1685 (0.30%)	
occurrences (all)	2	5	
Abdominal pain upper			
subjects affected / exposed	15 / 833 (1.80%)	17 / 1685 (1.01%)	
occurrences (all)	17	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	5 / 833 (0.60%)	5 / 1685 (0.30%)	
occurrences (all)	5	6	
Renal impairment			
subjects affected / exposed	1 / 833 (0.12%)	4 / 1685 (0.24%)	
occurrences (all)	1	4	
Renal pain			
subjects affected / exposed	0 / 833 (0.00%)	3 / 1685 (0.18%)	
occurrences (all)	0	3	
Urinary hesitation			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Urinary incontinence			
subjects affected / exposed	0 / 833 (0.00%)	4 / 1685 (0.24%)	
occurrences (all)	0	4	
Urinary retention			
subjects affected / exposed	3 / 833 (0.36%)	1 / 1685 (0.06%)	
occurrences (all)	3	1	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Hyperthyroidism			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Thyroid dysfunction in pregnancy			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	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	1 / 833 (0.12%)	6 / 1685 (0.36%)	
occurrences (all)	1	7	
Lung infection			
subjects affected / exposed	6 / 833 (0.72%)	12 / 1685 (0.71%)	
occurrences (all)	8	13	
Mastoiditis			
subjects affected / exposed	0 / 833 (0.00%)	2 / 1685 (0.12%)	
occurrences (all)	0	2	
Meningoencephalitis bacterial			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Mucosal infection			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Oesophageal candidiasis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	2 / 833 (0.24%)	7 / 1685 (0.42%)	
occurrences (all)	2	7	
Oral fungal infection			
subjects affected / exposed	1 / 833 (0.12%)	1 / 1685 (0.06%)	
occurrences (all)	1	1	
Oral herpes			
subjects affected / exposed	1 / 833 (0.12%)	3 / 1685 (0.18%)	
occurrences (all)	1	3	
Oral infection			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	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	14 / 833 (1.68%)	27 / 1685 (1.60%)	
occurrences (all)	15	32	
Urinary tract infection fungal			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	2 / 833 (0.24%)	1 / 1685 (0.06%)	
occurrences (all)	3	1	
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 833 (0.72%)	8 / 1685 (0.47%)	
occurrences (all)	6	9	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 833 (0.00%)	1 / 1685 (0.06%)	
occurrences (all)	0	1	
Cachexia			
subjects affected / exposed	1 / 833 (0.12%)	0 / 1685 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	63 / 833 (7.56%)	134 / 1685 (7.95%)	
occurrences (all)	78	160	
Dehydration			
subjects affected / exposed	14 / 833 (1.68%)	37 / 1685 (2.20%)	
occurrences (all)	15	50	
Diabetes mellitus			
subjects affected / exposed	4 / 833 (0.48%)	1 / 1685 (0.06%)	
occurrences (all)	5	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: - 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 ≥ 21 days and ≤ 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