Clinical trial results:
A Randomized, Multicenter, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone vs. Lenalidomide and Dexamethasone in Subjects with Relapsed Multiple Myeloma

Summary

EudraCT number	2009-016839-35
Trial protocol	ES GB BE NL CZ DE AT BG FR HU SE GR IT
Global end of trial date	05 December 2017

Results information

Result version number	v1 (current)
This version publication date	19 December 2018
First version publication date	19 December 2018

Trial information

Trial identification

Sponsor protocol code	PX-171-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01080391
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen Study No.: 20130395

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	05 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare progression-free survival (PFS) in subjects with relapsed multiple myeloma receiving carfilzomib, Revlimid (lenalidomide), and dexamethasone (CRd) versus subjects receiving Revlimid (lenalidomide) and dexamethasone (Rd) in a randomized, open-label, multicenter setting.

Protection of trial subjects:

The study was conducted in accordance with United States (US) Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP).
The protocol, protocol amendments, protocol clarification letters, informed consent forms (ICFs), subject dosing diaries, advertisements, and health-related quality of life (HRQL) questionnaires were reviewed and approved by each study center's Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
Written informed consent was obtained from all potential subjects (or legal representatives in the event the subject was unable to sign) prior to any study-specific procedures being conducted. During the informed consent process, the purpose and investigational nature of the study was explained to the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Bulgaria: 57
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	Czech Republic: 78
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Greece: 37
Country: Number of subjects enrolled	Hungary: 79
Country: Number of subjects enrolled	Israel: 31
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Netherlands: 3

Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Serbia: 20
Country: Number of subjects enrolled	Spain: 68
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 130
Worldwide total number of subjects	792
EEA total number of subjects	522

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)	399
From 65 to 84 years	383
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 14 July 2010 to 15 March 2012. The primary analysis was conducted using a data cut-off date of 16 June 2014 and the final safety analysis after last subject last visit date (05 December 2017).

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio to one of two treatment groups. Randomization was stratified by β2 microglobulin level (< vs. ≥ 2.5 mg/L), prior bortezomib exposure (no vs. yes), and prior lenalidomide exposure (no vs. yes).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide and Dexamethasone (Rd)

Arm description:

Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Lenalidomide 25 mg was administered orally on days 1 to 21 and dexamethasone 40 mg was administered orally or intravenously on days 1, 8, 15, and 22.

Arm type	Active comparator
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

40 mg orally or IV on days 1, 8, 15, 22

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25 mg orally on days 1-21

Arm title	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

Arm description:

Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Carfilzomib 20 mg/m² was administered intravenously (IV) on days 1 and 2 of cycle 1, then escalated to 27 mg/m² on Days 8, 9, 15, and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15, and 16 of cycle 2 through cycle 12 and then from cycle 13 through cycle 18, 27 mg/m² on days 1, 2, 15, and 16. Lenalidomide 25 mg was administered orally on days 1 to 21 of every cycle. Dexamethasone 40 mg was administered orally or IV on days 1, 8, 15, and 22 of every cycle.

Arm type	Experimental

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
20 mg/m², 27 mg/m² intravenously

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:
40 mg orally or IV on days 1, 8, 15, 22

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
25 mg orally on days 1-21

Number of subjects in period 1	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)
Started	396	396
Treated	389	392
Completed	389	392
Not completed	7	4
Randomized but not treated	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide and Dexamethasone (Rd)
Reporting group description:	
Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Lenalidomide 25 mg was administered orally on days 1 to 21 and dexamethasone 40 mg was administered orally or intravenously on days 1, 8, 15, and 22.	
Reporting group title	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)
Reporting group description:	
Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Carfilzomib 20 mg/m² was administered intravenously (IV) on days 1 and 2 of cycle 1, then escalated to 27 mg/m² on Days 8, 9, 15, and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15, and 16 of cycle 2 through cycle 12 and then from cycle 13 through cycle 18, 27 mg/m² on days 1, 2, 15, and 16. Lenalidomide 25 mg was administered orally on days 1 to 21 of every cycle. Dexamethasone 40 mg was administered orally or IV on days 1, 8, 15, and 22 of every cycle.	

Reporting group values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)	Total
Number of subjects	396	396	792
Age categorical Units: Subjects			
Adults (18-64 years)	211	188	399
From 65-84 years	179	204	383
85 years and over	6	4	10
Age Continuous Units: years			
arithmetic mean	64.5	63.3	
standard deviation	± 9.04	± 9.21	-
Sex: Female, Male Units: Subjects			
Female	164	181	345
Male	232	215	447
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian/Native Hawaiian or Pacific Islander	3	1	4
Black or African American	11	12	23
White	377	377	754
Other	4	6	10
Serum β2 Microglobulin Units: Subjects			
< 2.5 mg/L	77	77	154
≥ 2.5 mg/L	319	319	638
Prior Bortezomib Exposure Units: Subjects			
Yes	261	261	522
No	135	135	270
Prior Lenalidomide Exposure			

Units: Subjects			
Yes	78	80	158
No	318	316	634

End points

End points reporting groups

Reporting group title	Lenalidomide and Dexamethasone (Rd)

Reporting group description:

Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Lenalidomide 25 mg was administered orally on days 1 to 21 and dexamethasone 40 mg was administered orally or intravenously on days 1, 8, 15, and 22.

Reporting group title	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

Reporting group description:

Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Carfilzomib 20 mg/m² was administered intravenously (IV) on days 1 and 2 of cycle 1, then escalated to 27 mg/m² on Days 8, 9, 15, and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15, and 16 of cycle 2 through cycle 12 and then from cycle 13 through cycle 18, 27 mg/m² on days 1, 2, 15, and 16. Lenalidomide 25 mg was administered orally on days 1 to 21 of every cycle. Dexamethasone 40 mg was administered orally or IV on days 1, 8, 15, and 22 of every cycle.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

Kaplan-Meier estimate of median time from randomization to progressive disease (PD) or all-cause death. PD was assessed using International Myeloma Working Group-Uniform Response Criteria (IMWG-URC). One or more conditions were required to meet PD: 2 consecutive rising serum or urine M-protein from central lab; documented new bone lesion(s) or soft tissue plasmacytoma(s) or increased size of existing bone lesion(s) or plasmacytoma(s); or confirmed hypercalcemia due solely to plasma cell proliferative disorder (local lab greater than 11.5 mg/dL on 2 separate occasions). Censoring conditions (censoring dates) were: no post-baseline disease assessment (DA) (randomization date); started non-protocol systemic anticancer treatment before PD or death (last DA date before such treatment); died or had PD after more than 1 missed DA (last DA date without PD before the first missed visit); or were alive and without documentation of PD, including lost to follow-up without PD (last DA date).

End point type	Primary

End point timeframe:

From randomization through the data cutoff date of 16 June 2014. Median follow-up time was approximately 31 months.

End point values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: months				
median (confidence interval 95%)	17.6 (15.0 to 20.6)	26.3 (23.3 to 30.5)		

Statistical analyses

Statistical analysis title	Analysis of Progression-free Survival
Comparison groups	Lenalidomide and Dexamethasone (Rd) v Carfilzomib, Lenalidomide, and Dexamethasone (CRd)
Number of subjects included in analysis	792
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.834

Notes:

[1] - The stopping boundary for this analysis was 0.0127 based on 1-sided significance level (O'Brien-Fleming with Lan-DeMets spending function).
[2] - Analysis was stratified by β2 microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes).

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the duration from randomization to death due to any cause. Participants who were still alive were censored at the date when the participant was last known to be alive or the data cutoff date, whichever occurred earlier.

End point type	Secondary

End point timeframe:

From randomization through the data cutoff date of 28 April 2017 for the final analysis of overall survival; median follow up time was 67.1 months in each treatment group.

End point values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: months				
median (confidence interval 95%)	40.4 (33.6 to 44.4)	48.3 (42.4 to 52.8)		

Statistical analyses

Statistical analysis title	Analysis of Overall Survival

Statistical analysis description:

The final analysis of OS was to be performed after 510 deaths occur. A total of 510 deaths would provide 85% power to detect, with a 1-sided significance level of 0.025, a hazard ratio of 0.765 corresponding to a 23.5% reduction in risk for death for CRd versus Rd (39.2 vs. 30.0 months, respectively).

Comparison groups	Lenalidomide and Dexamethasone (Rd) v Carfilzomib, Lenalidomide, and Dexamethasone (CRd)
Number of subjects included in analysis	792
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0045 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.794
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.667
upper limit	0.945

Notes:

[3] - The stopping boundary for this analysis was 0.0231 based on 1-sided significance level (O'Brien-Fleming with Lan-DeMets spending function).
[4] - Analysis was stratified by β2 microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes).

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall response rate is defined as the percentage of participants who achieved either a confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as their best response based on the Independent Review Committee (IRC) assessed response outcome. Response was determined using the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC).

End point type	Secondary

End point timeframe:

From randomization through the data cutoff date of 16 June 2014. Median follow-up time was approximately 31 months.

End point values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: percentage of participants				
number (confidence interval 95%)	66.7 (61.8 to 71.3)	87.1 (83.4 to 90.3)		

Statistical analyses

Statistical analysis title	Analysis of Overall Response Rate
Comparison groups	Lenalidomide and Dexamethasone (Rd) v Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

Number of subjects included in analysis	792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Cochran-Mantel Haenszel chi-square test
Parameter estimate	Odds ratio (OR)
Point estimate	3.472
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.411
upper limit	5.001

Notes:

[5] - Cochran-Mantel Haenszel chi-square test with β2 macroglobulin level, prior bortezomib, and prior lenalidomide as stratification factors.

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate was defined as the percentage of participants who achieved a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), or stable disease (SD) lasting ≥ 8 weeks according to International Myeloma Working Group - Uniform Response Criteria (IMWG-URC) (MR was determined using European Group for Blood and Marrow Transplantation criteria).

End point type	Secondary

End point timeframe:

From randomization through the data cutoff date of 16 June 2014. Median follow-up time was approximately 31 months.

End point values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: percentage of participants				
number (confidence interval 95%)	87.1 (83.4 to 90.3)	92.7 (89.7 to 95.0)		

Statistical analyses

Statistical analysis title	Analysis of Disease Control Rate
Comparison groups	Lenalidomide and Dexamethasone (Rd) v Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

Number of subjects included in analysis	792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044 [6]
Method	Cochran-Mantel Haenszel chi-square test
Parameter estimate	Odds ratio (OR)
Point estimate	1.897
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	3.08

Notes:

[6] - Cochran-Mantel Haenszel chi-square test with β2 macroglobulin level, prior bortezomib, and prior lenalidomide as stratification factors.

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR) was calculated for participants who achieved a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR). Duration of response was defined as the time in months from the initial start of response (PR or better) to the earlier of documented progressive disease (PD) or death due to any cause. Participants who had not progressed or died were censored according to the censoring rules defined previously for PFS.

End point type	Secondary

End point timeframe:

From randomization through the data cutoff date of 16 June 2014. Longest follow-up time was approximately 42 months.

End point values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	345		
Units: months				
median (confidence interval 95%)	21.2 (16.7 to 25.8)	28.6 (24.9 to 31.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control

End point title	Duration of Disease Control

End point description:

Duration of disease control (DDC) was calculated for participants who achieved disease control. DDC was defined as the time in months from randomization to the earlier of documented progressive disease

(PD) or death due to any cause. Participants who had not progressed or died were censored according to the censoring rules defined previously for PFS.

End point type	Secondary

End point timeframe:

From randomization through the data cutoff date of 16 June 2014. Longest follow-up time was approximately 46 months.

End point values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	367		
Units: months				
median (confidence interval 95%)	18.9 (16.6 to 22.2)	28.7 (24.4 to 31.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Core Module (QLQ-C30) Global Health Status/Quality of Life Scores

End point title	Quality of Life Core Module (QLQ-C30) Global Health Status/Quality of Life Scores

End point description:

Health-related quality of life was assessed with the use of the European Organization for Research and Treatment of Cancer Quality of Life Core Module (QLQ-C30) questionnaire, a validated instrument in multiple myeloma patients. Scores range from 0 to 100, with higher scores indicating better health related quality of life.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (Baseline), Day 1 of Cycles 3, 6, 12, 18

End point values	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	367	375		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (Baseline)	58.1 (± 21.7)	58.3 (± 21.7)		
Cycle 3, Day 1 (N = 334, 356)	56.8 (± 19.4)	59.9 (± 20.4)		
Cycle 6, Day 1 (N = 284, 326)	58.9 (± 19.7)	62.5 (± 20.1)		
Cycle 12, Day 1 (N = 212, 255)	57.3 (± 19.7)	62.7 (± 19.6)		

Cycle 18, Day 1 (N = 147, 226)	59.9 (± 18.8)	64.3 (± 19.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug to 30 days after the last dose or initiation of new anticancer therapy, whichever occurred first. Median treatment duration was 57 and 88 weeks in each treatment group respectively, with a maximum of 338 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Lenalidomide and Dexamethasone (Rd)

Reporting group description:

Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Lenalidomide 25 mg was administered orally on days 1 to 21 and dexamethasone 40 mg was administered orally or intravenously on days 1, 8, 15, and 22.

Reporting group title	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

Reporting group description:

Participants received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity. Carfilzomib 20 mg/m² was administered intravenously (IV) on days 1 and 2 of cycle 1, then escalated to 27 mg/m² on Days 8, 9, 15, and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15, and 16 of cycle 2 through cycle 12 and then from cycle 13 through cycle 18, 27 mg/m² on days 1, 2, 15, and 16. Lenalidomide 25 mg was administered orally on days 1 to 21 of every cycle. Dexamethasone 40 mg was administered orally or IV on days 1, 8, 15, and 22 of every cycle.

Serious adverse events	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)	
Total subjects affected by serious adverse events			
subjects affected / exposed	221 / 389 (56.81%)	256 / 392 (65.31%)	
number of deaths (all causes)	266	247	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	2 / 389 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B precursor type acute leukaemia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	4 / 389 (1.03%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	3 / 5	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal neoplasm			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of pleura			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelodysplastic syndrome			
subjects affected / exposed	4 / 389 (1.03%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatic neoplasm			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasma cell myeloma			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasmacytoma			
subjects affected / exposed	1 / 389 (0.26%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	3 / 389 (0.77%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 389 (0.26%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	6 / 389 (1.54%)	9 / 392 (2.30%)	
occurrences causally related to treatment / all	6 / 6	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 389 (0.77%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (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	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 389 (0.00%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 389 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Disease progression			
subjects affected / exposed	8 / 389 (2.06%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 6	0 / 2	
Drowning			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 389 (1.03%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Influenza like illness			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 389 (0.26%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 389 (0.00%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	12 / 389 (3.08%)	15 / 392 (3.83%)	
occurrences causally related to treatment / all	7 / 15	6 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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 respiratory distress syndrome			
subjects affected / exposed	0 / 389 (0.00%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Alveolitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 389 (0.26%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 389 (0.77%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eosinophilic pneumonia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngospasm			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	4 / 389 (1.03%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (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	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural fibrosis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	8 / 389 (2.06%)	12 / 392 (3.06%)	
occurrences causally related to treatment / all	7 / 8	10 / 15	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 389 (0.00%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 389 (1.03%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
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 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac stress test abnormal			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			

subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoclonal immunoglobulin present			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus test positive			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcus test positive			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral test positive			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 389 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	3 / 389 (0.77%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder injury			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	3 / 389 (0.77%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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	2 / 389 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal compression fracture			

subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic injury			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Traumatic fracture			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 389 (0.26%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	4 / 389 (1.03%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	8 / 389 (2.06%)	9 / 392 (2.30%)	
occurrences causally related to treatment / all	4 / 8	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 389 (0.26%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 2	
Cardiac asthma			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 389 (0.77%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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	3 / 389 (0.77%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	2 / 4	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			

subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular failure			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 389 (0.77%)	6 / 392 (1.53%)	
occurrences causally related to treatment / all	1 / 3	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 3	
Myocardial ischaemia			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyotrophic lateral sclerosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral cyst			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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	10 / 389 (2.57%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	4 / 11	3 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Headache			

subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myxoedema coma			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	3 / 389 (0.77%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 389 (0.51%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 389 (0.77%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 389 (2.57%)	8 / 392 (2.04%)	
occurrences causally related to treatment / all	7 / 13	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (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	4 / 389 (1.03%)	8 / 392 (2.04%)	
occurrences causally related to treatment / all	3 / 4	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 389 (1.29%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	4 / 5	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet disorder			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 389 (1.03%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	2 / 5	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	1 / 389 (0.26%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract nuclear			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract subcapsular			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia obstructive			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 389 (0.77%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	9 / 389 (2.31%)	7 / 392 (1.79%)	
occurrences causally related to treatment / all	4 / 10	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum oesophageal			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (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	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	3 / 389 (0.77%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 389 (0.26%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis toxic			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute generalised exanthematous pustulosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	1 / 389 (0.26%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 389 (1.03%)	8 / 392 (2.04%)	
occurrences causally related to treatment / all	1 / 4	3 / 8	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (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	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral prolapse			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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	4 / 389 (1.03%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone pain			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crystal arthropathy			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture pain			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	2 / 389 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	3 / 389 (0.77%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 389 (0.26%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	11 / 389 (2.83%)	9 / 392 (2.30%)	
occurrences causally related to treatment / all	3 / 11	1 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site cellulitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 389 (1.03%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis C			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 389 (0.00%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 389 (0.26%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterocolitis bacterial			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			

subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	5 / 389 (1.29%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infection			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 389 (0.51%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis bacterial			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 389 (0.77%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 389 (0.26%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis bacterial			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	52 / 389 (13.37%)	67 / 392 (17.09%)	
occurrences causally related to treatment / all	22 / 64	29 / 77	
deaths causally related to treatment / all	0 / 3	2 / 6	
Pneumonia bacterial			

subjects affected / exposed	3 / 389 (0.77%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative abscess			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	8 / 389 (2.06%)	16 / 392 (4.08%)	
occurrences causally related to treatment / all	5 / 10	4 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	2 / 389 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 389 (1.29%)	7 / 392 (1.79%)	
occurrences causally related to treatment / all	2 / 6	3 / 7	
deaths causally related to treatment / all	1 / 3	1 / 3	
Sepsis syndrome			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
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	4 / 389 (1.03%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	2 / 4	3 / 4	
deaths causally related to treatment / all	1 / 2	0 / 1	
Sinusitis			
subjects affected / exposed	2 / 389 (0.51%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site abscess			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular abscess			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 389 (0.00%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	2 / 389 (0.51%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	1 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 389 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 389 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 389 (0.77%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 389 (0.00%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			

subjects affected / exposed	0 / 389 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 389 (0.26%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 389 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mineral deficiency			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 389 (0.00%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 389 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lenalidomide and Dexamethasone (Rd)	Carfilzomib, Lenalidomide, and Dexamethasone (CRd)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	358 / 389 (92.03%)	370 / 392 (94.39%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	11 / 389 (2.83%)	21 / 392 (5.36%)	
occurrences (all)	11	23	
Hypertension			
subjects affected / exposed	30 / 389 (7.71%)	62 / 392 (15.82%)	
occurrences (all)	50	110	
Hypotension			
subjects affected / exposed	22 / 389 (5.66%)	26 / 392 (6.63%)	
occurrences (all)	25	34	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	57 / 389 (14.65%)	72 / 392 (18.37%)	
occurrences (all)	104	134	
Chills			
subjects affected / exposed	9 / 389 (2.31%)	26 / 392 (6.63%)	
occurrences (all)	9	29	
Fatigue			
subjects affected / exposed	124 / 389 (31.88%)	132 / 392 (33.67%)	
occurrences (all)	244	307	
Oedema peripheral			
subjects affected / exposed	66 / 389 (16.97%)	78 / 392 (19.90%)	
occurrences (all)	116	143	
Peripheral swelling			
subjects affected / exposed	21 / 389 (5.40%)	21 / 392 (5.36%)	
occurrences (all)	28	29	
Pyrexia			
subjects affected / exposed	80 / 389 (20.57%)	110 / 392 (28.06%)	
occurrences (all)	126	194	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	70 / 389 (17.99%)	116 / 392 (29.59%)	
occurrences (all)	103	203	
Dyspnoea			
subjects affected / exposed	59 / 389 (15.17%)	76 / 392 (19.39%)	
occurrences (all)	105	119	
Dyspnoea exertional			
subjects affected / exposed	19 / 389 (4.88%)	23 / 392 (5.87%)	
occurrences (all)	23	28	
Epistaxis			
subjects affected / exposed	17 / 389 (4.37%)	20 / 392 (5.10%)	
occurrences (all)	21	28	
Oropharyngeal pain			
subjects affected / exposed	22 / 389 (5.66%)	28 / 392 (7.14%)	
occurrences (all)	28	30	
Productive cough			
subjects affected / exposed	12 / 389 (3.08%)	21 / 392 (5.36%)	
occurrences (all)	17	28	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	17 / 389 (4.37%)	33 / 392 (8.42%)	
occurrences (all)	22	40	
Insomnia			
subjects affected / exposed	65 / 389 (16.71%)	81 / 392 (20.66%)	
occurrences (all)	92	121	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 389 (3.86%)	21 / 392 (5.36%)	
occurrences (all)	26	37	
Blood creatinine increased			
subjects affected / exposed	21 / 389 (5.40%)	27 / 392 (6.89%)	
occurrences (all)	36	60	
Neutrophil count decreased			
subjects affected / exposed	22 / 389 (5.66%)	21 / 392 (5.36%)	
occurrences (all)	81	89	
Weight decreased			

subjects affected / exposed	20 / 389 (5.14%)	14 / 392 (3.57%)	
occurrences (all)	23	21	
Nervous system disorders			
Dizziness			
subjects affected / exposed	45 / 389 (11.57%)	54 / 392 (13.78%)	
occurrences (all)	78	78	
Dysgeusia			
subjects affected / exposed	21 / 389 (5.40%)	14 / 392 (3.57%)	
occurrences (all)	23	16	
Headache			
subjects affected / exposed	32 / 389 (8.23%)	56 / 392 (14.29%)	
occurrences (all)	46	95	
Neuropathy peripheral			
subjects affected / exposed	28 / 389 (7.20%)	34 / 392 (8.67%)	
occurrences (all)	47	56	
Paraesthesia			
subjects affected / exposed	23 / 389 (5.91%)	27 / 392 (6.89%)	
occurrences (all)	30	38	
Peripheral sensory neuropathy			
subjects affected / exposed	27 / 389 (6.94%)	25 / 392 (6.38%)	
occurrences (all)	42	44	
Tremor			
subjects affected / exposed	32 / 389 (8.23%)	28 / 392 (7.14%)	
occurrences (all)	51	32	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	154 / 389 (39.59%)	166 / 392 (42.35%)	
occurrences (all)	434	562	
Leukopenia			
subjects affected / exposed	22 / 389 (5.66%)	33 / 392 (8.42%)	
occurrences (all)	59	61	
Neutropenia			
subjects affected / exposed	133 / 389 (34.19%)	157 / 392 (40.05%)	
occurrences (all)	523	633	
Thrombocytopenia			

subjects affected / exposed	94 / 389 (24.16%)	115 / 392 (29.34%)	
occurrences (all)	288	580	
Eye disorders			
Cataract			
subjects affected / exposed	36 / 389 (9.25%)	39 / 392 (9.95%)	
occurrences (all)	44	48	
Vision blurred			
subjects affected / exposed	15 / 389 (3.86%)	24 / 392 (6.12%)	
occurrences (all)	19	24	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 389 (6.94%)	32 / 392 (8.16%)	
occurrences (all)	38	63	
Abdominal pain upper			
subjects affected / exposed	12 / 389 (3.08%)	28 / 392 (7.14%)	
occurrences (all)	23	36	
Constipation			
subjects affected / exposed	69 / 389 (17.74%)	81 / 392 (20.66%)	
occurrences (all)	95	127	
Diarrhoea			
subjects affected / exposed	143 / 389 (36.76%)	170 / 392 (43.37%)	
occurrences (all)	344	385	
Dyspepsia			
subjects affected / exposed	22 / 389 (5.66%)	24 / 392 (6.12%)	
occurrences (all)	23	27	
Nausea			
subjects affected / exposed	57 / 389 (14.65%)	82 / 392 (20.92%)	
occurrences (all)	82	135	
Toothache			
subjects affected / exposed	12 / 389 (3.08%)	20 / 392 (5.10%)	
occurrences (all)	13	22	
Vomiting			
subjects affected / exposed	34 / 389 (8.74%)	49 / 392 (12.50%)	
occurrences (all)	51	80	
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	13 / 389 (3.34%)	30 / 392 (7.65%)	
occurrences (all)	17	40	
Hyperhidrosis			
subjects affected / exposed	18 / 389 (4.63%)	28 / 392 (7.14%)	
occurrences (all)	22	34	
Pruritus			
subjects affected / exposed	16 / 389 (4.11%)	31 / 392 (7.91%)	
occurrences (all)	21	37	
Rash			
subjects affected / exposed	59 / 389 (15.17%)	50 / 392 (12.76%)	
occurrences (all)	68	74	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	57 / 389 (14.65%)	57 / 392 (14.54%)	
occurrences (all)	80	76	
Back pain			
subjects affected / exposed	81 / 389 (20.82%)	73 / 392 (18.62%)	
occurrences (all)	116	102	
Bone pain			
subjects affected / exposed	36 / 389 (9.25%)	39 / 392 (9.95%)	
occurrences (all)	52	54	
Muscle spasms			
subjects affected / exposed	82 / 389 (21.08%)	106 / 392 (27.04%)	
occurrences (all)	134	209	
Muscular weakness			
subjects affected / exposed	24 / 389 (6.17%)	28 / 392 (7.14%)	
occurrences (all)	32	32	
Musculoskeletal chest pain			
subjects affected / exposed	29 / 389 (7.46%)	26 / 392 (6.63%)	
occurrences (all)	38	31	
Musculoskeletal pain			
subjects affected / exposed	36 / 389 (9.25%)	25 / 392 (6.38%)	
occurrences (all)	47	30	
Myalgia			

subjects affected / exposed	22 / 389 (5.66%)	25 / 392 (6.38%)	
occurrences (all)	24	30	
Pain in extremity			
subjects affected / exposed	42 / 389 (10.80%)	48 / 392 (12.24%)	
occurrences (all)	57	79	
Infections and infestations			
Bronchitis			
subjects affected / exposed	56 / 389 (14.40%)	75 / 392 (19.13%)	
occurrences (all)	111	123	
Influenza			
subjects affected / exposed	14 / 389 (3.60%)	26 / 392 (6.63%)	
occurrences (all)	20	34	
Nasopharyngitis			
subjects affected / exposed	65 / 389 (16.71%)	87 / 392 (22.19%)	
occurrences (all)	131	182	
Pneumonia			
subjects affected / exposed	29 / 389 (7.46%)	45 / 392 (11.48%)	
occurrences (all)	39	51	
Respiratory tract infection			
subjects affected / exposed	39 / 389 (10.03%)	41 / 392 (10.46%)	
occurrences (all)	63	81	
Sinusitis			
subjects affected / exposed	18 / 389 (4.63%)	24 / 392 (6.12%)	
occurrences (all)	24	35	
Upper respiratory tract infection			
subjects affected / exposed	81 / 389 (20.82%)	115 / 392 (29.34%)	
occurrences (all)	123	269	
Urinary tract infection			
subjects affected / exposed	21 / 389 (5.40%)	36 / 392 (9.18%)	
occurrences (all)	33	50	
Viral infection			
subjects affected / exposed	11 / 389 (2.83%)	28 / 392 (7.14%)	
occurrences (all)	20	40	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	35 / 389 (9.00%)	47 / 392 (11.99%)	
occurrences (all)	47	70	
Hyperglycaemia			
subjects affected / exposed	39 / 389 (10.03%)	48 / 392 (12.24%)	
occurrences (all)	82	122	
Hyperuricaemia			
subjects affected / exposed	11 / 389 (2.83%)	22 / 392 (5.61%)	
occurrences (all)	12	25	
Hypocalcaemia			
subjects affected / exposed	49 / 389 (12.60%)	65 / 392 (16.58%)	
occurrences (all)	104	196	
Hypokalaemia			
subjects affected / exposed	58 / 389 (14.91%)	114 / 392 (29.08%)	
occurrences (all)	135	298	
Hypomagnesaemia			
subjects affected / exposed	29 / 389 (7.46%)	40 / 392 (10.20%)	
occurrences (all)	69	137	
Hypophosphataemia			
subjects affected / exposed	33 / 389 (8.48%)	57 / 392 (14.54%)	
occurrences (all)	100	250	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2010	• Per FDA feedback, amended text to emphasize the importance of confirming progression by 2 measurements of serum or urine M-protein. Also permitted 10% additional enrollment to help achieve 526 progression events.
22 April 2010	• Updated lenalidomide REMS requirements: o Included requirement for RevAssist program (US participants) for access to lenalidomide. o Language was also added to describe the lenalidomide requirements for subjects in ex-US countries, including RevAid for access to lenalidomide in Canada and a Pregnancy Risk Minimization Plan for Celgene trials.
03 May 2010	Minor administrative amendment consisting of the following: • Addressed FDA request that OS be listed as the first secondary endpoint. • Reordered secondary endpoints. • Made changes to protocol synopsis, statistical methods, and efficacy analysis to clarify disease outcome grading by investigator to be consistent with text in body of the protocol.
04 March 2011	• The window provided for Inclusion Criterion 2 to demonstrate measurable disease by central laboratory analyses was increased from within 14 days prior to randomization to within 21 days prior to randomization to account for the challenge in logistics of trans-country sample shipment followed by analysis and review. • Additional changes included: o Refined the technique for measuring soft tissue plasmacytomas from a simple unidirectional to bidirectional measurements. o Defined the "measurability" of any given soft tissue plasmacytoma and amended progression criteria accordingly. o Clarified definition for females of childbearing potential (for all countries except Canada) and pregnancy test requirements. o Clarified that MR was defined per EBMT criteria. o Clarified inclusion criterion for measurement of serum IgA. o Clarified that, for PK assessment, lenalidomide should be taken a minimum of 2 hours (instead of 4 hours) after the carfilzomib dose.
19 December 2011	• Prespecified sample size adjustment from700 subjects to approximately 780 subjects following the first interim analysis review by an IDMC. • Additional changes included: o Clarified that, regardless of SPEP and UPEP results at screening, both tests were required to confirm VGPR and CR. o Clarified that MDS was considered a malignant disease within the context of the exclusion criteria. o Clarified definition of measureable disease for assessment of progression and response in subjects with IgA myeloma.
05 November 2014	• clarified procedures conducted before and after the primary analysis since the primary endpoint of progression-free survival was reached; in particular, that central laboratory analysis of subject samples were no longer performed updated the medical monitor for the study • updated the approval process for amendments • updated the secondary and exploratory endpoints to be consistent with the statistical analysis plan, which was finalized before the primary analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported